Janssen Research & Development*

Clinical Protocol

Protocol Title
A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis

QUASAR

Short Title
A Study of the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis

Protocol CNTO1959UCO3001; Phase 2b/3
AMENDMENT 3

CNTO 1959 (guselkumab)

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US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	12 September 2022
Amendment 2	03 August 2021
Amendment 1	08 January 2020
Original Protocol	29 May 2019

Amendment 3 (12 September 2022)

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CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	
CCI [redacted]	[redacted]	
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Section Number and Name	Description of Change	Brief Rationale
CCI		
CCI		

Section Number and Name	Description of Change	Brief Rationale
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1.1. Synopsis

A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis

Protocol number: CNTO1959UCO3001

EudraCT Number: 2018-004002-25

IND Number: 140330

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

OVERVIEW OF PROTOCOL

The Phase 2b/3 clinical development program for guselkumab in ulcerative colitis (UC) is designed to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active UC. Under this single protocol (CNTO1959UCO3001), there are 3 separate studies:

- Induction Study 1 (Phase 2b Induction Dose-ranging Study)
- Induction Study 2 (Phase 3 Induction Study)
- Maintenance Study (Phase 3 Maintenance Study)

Participants who complete the Maintenance Study and who may benefit from continued study intervention, in the opinion of the investigator, will have the opportunity to participate in the long-term extension (LTE) of the Maintenance Study and receive up to approximately another 4 years of treatment.

OBJECTIVES AND ENDPOINTS

Induction Study 1 (Phase 2b Induction Dose-ranging Study)

Objectives

Primary Objectives

The primary objectives of this study are, in participants with moderately to severely active UC:

- To evaluate the efficacy of guselkumab as induction therapy.
- To evaluate the safety of guselkumab as induction therapy.
- To evaluate the dose-response of guselkumab to inform induction dose selection for the Phase 3 induction study.

Secondary Objectives

The secondary objectives of this study are, in participants with moderately to severely active UC:

- To evaluate the impact of guselkumab on health-related quality of life (HRQoL) and health economics outcome measures.

- To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of guselkumab therapy, including changes in C-reactive protein (CRP) and fecal calprotectin.

Endpoints

All endpoints will evaluate the efficacy of guselkumab versus placebo, in participants with moderately to severely active UC.

Primary Endpoint

The primary endpoint in this study is clinical response at Induction Week 12 (Week I-12).

Major Secondary Endpoints

- Clinical remission at Week I-12.
- Symptomatic remission at Week I-12.
- Endoscopic healing at Week I-12.
- Histologic-endoscopic mucosal healing at Week I-12.
- Endoscopic normalization at Week I-12.

Hypothesis

The primary hypothesis is that guselkumab is superior to placebo in inducing clinical response at Week I-12 in participants with moderately to severely active UC.

Induction Study 2 (Phase 3 Induction Study)

Objectives

Primary Objectives

The primary objectives of this study are, in participants with moderately to severely active UC:

- To evaluate the efficacy of guselkumab as induction therapy.
- To evaluate the safety of guselkumab as induction therapy.

Secondary Objectives

The secondary objectives of this study are, in participants with moderately to severely active UC:

- To evaluate the impact of guselkumab on HRQoL and health economics outcome measures.
- To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin.

Endpoints

All endpoints will evaluate the efficacy of guselkumab versus placebo, in participants with moderately to severely active UC.

Primary Endpoint

The primary endpoint in this study is clinical remission at Week I-12.

Major Secondary Endpoints

- Symptomatic remission at Week I-12.

- Endoscopic healing at Week I-12.
- Clinical response at Week I-12.
- Symptomatic remission at Week I-4.
- Inflammatory Bowel Disease Questionnaire (IBDQ) remission at Week I-12.
- Histologic-endoscopic mucosal healing at Week I-12.
- Fatigue response at Week I-12.
- Symptomatic remission at Week I-2.
- Endoscopic normalization at Week I-12.

Note: The final ordering of the major secondary endpoints will be provided in the Statistical Analysis Plan (SAP) for this study.

Hypotheses

The primary hypothesis is that guselkumab is superior to placebo in inducing clinical remission at Week I-12 in participants with moderately to severely active UC.

Hypotheses for major secondary endpoints in participants with moderately to severely active UC are listed below:

- Guselkumab is superior to placebo in inducing symptomatic remission at Week I-12.
- Guselkumab is superior to placebo in inducing endoscopic healing at Week I-12.
- Guselkumab is superior to placebo in inducing clinical response at Week I-12.
- Guselkumab is superior to placebo in inducing symptomatic remission at Week I-4.
- Guselkumab is superior to placebo in inducing IBDQ remission at Week I-12.
- Guselkumab is superior to placebo in inducing histologic-endoscopic mucosal healing at Week I-12.
- Guselkumab is superior to placebo in inducing fatigue response at Week I-12.
- Guselkumab is superior to placebo in inducing symptomatic remission at Week I-2.
- Guselkumab is superior to placebo in inducing endoscopic normalization at Week I-12.

Maintenance Study (Phase 3 Maintenance Study)

Objectives

Primary Objectives

The primary objectives of this study are, in participants with moderately to severely active UC who were induced into clinical response with guselkumab:

- To evaluate the efficacy of maintenance regimens of guselkumab.
- To evaluate the safety of maintenance regimens of guselkumab.

Secondary Objectives

The secondary objectives of this study are, in participants with moderately to severely active UC who were induced into clinical response with guselkumab:

- To evaluate the impact of guselkumab on HRQoL and health economics outcome measures.

- To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin.

Endpoints

All endpoints will evaluate the efficacy of guselkumab versus placebo, in participants with moderately to severely active UC who were in clinical response after 12 weeks of guselkumab intravenous (IV) induction therapy.

Primary Endpoint

The primary endpoint in this study is clinical remission at Maintenance Week 44 (Week M-44).

Major Secondary Endpoints

- Symptomatic remission at Week M-44.
- Endoscopic healing at Week M-44.
- Corticosteroid-free (ie, not requiring any treatment with corticosteroids for at least 8 weeks prior) clinical remission at Week M-44.
- Clinical response at Week M-44.
- Histologic-endoscopic mucosal healing at Week M-44.
- IBDQ remission at Week M-44.
- Fatigue response at Week M-44.
- Clinical remission at Week M-44 among the participants who had achieved clinical remission at maintenance baseline (ie, maintenance of clinical remission at M-44).
- Endoscopic normalization at Week M-44.

Note: The final ordering of the major secondary endpoints will be provided in the SAP for this study.

Hypotheses

The primary hypothesis is that guselkumab maintenance therapy is superior to placebo in achieving clinical remission at Week M-44 in participants with moderately to severely active UC who were induced into clinical response with guselkumab.

Hypotheses for major secondary endpoints in participants with moderately to severely active UC who were induced into clinical response with guselkumab are listed below:

- Guselkumab maintenance therapy is superior to placebo in achieving symptomatic remission at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving endoscopic healing at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving corticosteroid-free clinical remission at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in maintaining clinical response through Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving histologic-endoscopic mucosal healing at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving IBDQ remission at Week M-44.

- Guselkumab maintenance therapy is superior to placebo in achieving fatigue response at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving endoscopic normalization at Week M-44.

The hypothesis for the major secondary endpoint in participants with moderately to severely active UC who were induced into clinical remission with guselkumab is listed below:

- Guselkumab maintenance therapy is superior to placebo in maintaining clinical remission through Week M-44.

OVERALL DESIGN

All 3 studies (Induction Study 1, Induction Study 2, Maintenance Study) under this single protocol will be randomized, double-blind, placebo-controlled, parallel-group, multicenter studies to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active UC. The induction studies (Induction Study 1 and Induction Study 2) will target participants 18 years of age or older with moderately to severely active UC who have demonstrated an inadequate response or failure to tolerate conventional (ie, 6-mercaptopurine [6-MP], azathioprine [AZA], or corticosteroids) or advanced therapy (ADT; ie, tumor necrosis factor alpha [TNFα] antagonists, vedolizumab, or tofacitinib). Participants who had an inadequate response or failure to tolerate advanced therapy (ADT-Failure) will comprise a minimum of approximately 40% and a maximum of approximately 50% of the population for the following: 1) the first 150 participants randomized in Induction Study 1 for the interim analysis and induction dose decision; and 2) the total population of Induction Study 2. The Maintenance Study is a randomized withdrawal study targeting participants with moderately to severely active UC who have demonstrated a clinical response to guselkumab treatment in either Induction Study 1 or Induction Study 2.

Overall, the program will evaluate guselkumab treatment through at least 56 weeks of induction and maintenance therapy. Participants who complete the safety and efficacy evaluations (including the required endoscopy procedure) at Week M-44 of the Maintenance Study and who may benefit from continued study intervention, in the opinion of the investigator, will have the opportunity to participate in the LTE of the Maintenance Study for up to approximately an additional 4 years of treatment to evaluate the efficacy and safety of long-term maintenance treatment.

All UC-specific medical therapies (ie, oral 5-aminosalicylic (5-ASA) compounds, oral corticosteroids, 6-MP, AZA, or methotrexate [MTX]) must be maintained at a stable dose through to the end of the induction studies and can only be discontinued or reduced in dose if investigator judgment requires it because of toxicity or medical necessity. The initiation or increase in dose of UC-specific therapies (or any restricted/prohibited medication or therapy) during Induction Study 1 or Induction Study 2 will prohibit a participant from entering the Maintenance Study.

For participants who are receiving oral corticosteroids on entry in the Maintenance Study, the investigator must begin tapering the daily dose of corticosteroids at Week M-0. Other UC-specific medical therapies (ie, oral 5-ASA compounds, 6-MP, AZA, or MTX) must be maintained at stable doses through Week M-44 unless investigator judgment requires that the therapy be discontinued, or the dose reduced because of toxicity or medical necessity. Tapering of the daily dose of corticosteroids may be paused for participants meeting clinical flare criteria. Participants meeting criteria for loss of clinical response during the Maintenance Study will be eligible for a single blinded dose adjustment as described in the protocol.

During Induction Study 1, an interim analysis of the first 150 randomized participants who have completed the Week I-12 visit or have terminated study participation prior to Week I-12 will be performed. The purpose of this interim analysis is to select a single induction dose for confirmatory evaluation in the Phase 3 induction study (Induction Study 2). A Dose Selection Committee, composed of sponsor management representatives from Clinical, Safety, Biostatistics, and Clinical Pharmacology, who are not associated with study conduct, will be responsible for selecting the induction dose of guselkumab to be evaluated in

Induction Study 2. While the data from the first 150 randomized participants is being evaluated, participants will continue to be enrolled in Induction Study 1, up to a maximum of 390 participants. Once the induction dose selection has occurred, participants will begin randomization into Induction Study 2.

Efficacy, safety, PK, immunogenicity, and biomarkers will be assessed at time points indicated in the appropriate Schedule of Activities (SoA).

An external, independent Data Monitoring Committee (DMC), with defined roles and responsibilities as governed by a DMC charter, will assess the safety of participants across the 3 studies.

End of Study

For each of the 3 studies conducted under this protocol, the study is considered completed when the last participant completes the last scheduled study assessment as shown in the SoA for that study, or if a decision has been made by the sponsor not to pursue an indication in UC. For each study, the final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

NUMBER OF PARTICIPANTS

The overall CNTO1959UCO3001 Phase 2b/3 protocol will enroll a target of approximately 950 randomized participants with a modified Mayo score of 5 to 9 (1000 randomized participants with a modified Mayo score of 4 included).

INTERVENTION GROUPS AND DURATION

At Weeks I-12 and/or I-24 of Induction Study 1 and Induction Study 2, participants will be evaluated for clinical response. Eligibility for the Maintenance Study will be determined by the participant's clinical response status.

Induction Study 1 (Phase 2b Induction Dose-ranging Study)

From Week I-0 Through Week I-12

In Induction Study 1, participants will be randomized to 1 of 3 study intervention groups as described below. Participants will remain on their assigned study intervention through Week I-12.

- **Guselkumab 400 mg IV:** Participants will receive guselkumab 400 mg IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).
- **Guselkumab 200 mg IV:** Participants will receive guselkumab 200 mg IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).
- **Placebo:** Participants will receive placebo IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).

From Week I-12 Through Week I-24

Guselkumab

For participants who received 3 IV guselkumab doses (400 mg or 200 mg), subsequent study intervention will be based on clinical response status at Week I-12 as follows:

- Guselkumab clinical responders at Week I-12: Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg subcutaneously (SC) every 4 weeks (q4w), guselkumab 100 mg SC every 8 weeks (q8w), or placebo.

- Guselkumab clinical nonresponders at Week I-12: Participants will receive guselkumab 200 mg SC at Weeks I-12, I-16, and I-20. Placebo IV will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-24 (ie, guselkumab 24-Week responders): Participants will enter the Maintenance Study and will receive guselkumab 200 mg SC q4w.
- Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

Placebo

For participants who received 3 IV placebo doses, subsequent study intervention will be based on clinical response status at Week I-12 as follows:

- Placebo clinical responders at Week I-12: Participants will enter the Maintenance Study and receive placebo SC q4w.
- Placebo clinical nonresponders at Week I-12: Participants will receive guselkumab 200 mg IV at Weeks I-12, I-16, and I-20. Placebo SC will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-24 (ie, placebo crossover responders): Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg q8w, or placebo.
- Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

Induction Study 2 (Phase 3 Induction Study)

In Induction Study 2, participants will be randomized to 1 of 2 study intervention groups as described below. Participants will remain on their assigned study intervention through Week I-12.

Guselkumab Induction Dose Regimen

Selection of the Phase 3 guselkumab induction dose for Induction Study 2 will be based on an interim analysis of Induction Study 1. The participants will receive study intervention at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).

At Week I-12, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-12: Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg q8w, or placebo.
- Guselkumab clinical nonresponders at Week I-12: Participants will receive guselkumab 200 mg SC at Weeks I-12, I-16, and I-20. Placebo IV will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-24 (ie, guselkumab 24-Week responders): Participants will enter the Maintenance Study and will receive guselkumab 200 mg SC q4w.
- Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

Placebo

Participants will receive placebo IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).

At Week I-12, subsequent study intervention will be based on clinical response status as follows:

- Placebo clinical responders at Week I-12: Participants will enter the Maintenance Study and receive placebo SC q4w.
- Placebo clinical nonresponders at Week I-12: Participants will receive the Phase 3 guselkumab induction IV dose at Weeks I-12, I-16, and I-20. Placebo SC will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-24 (ie, placebo crossover responders): Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg q8w, or placebo.
- Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

Maintenance Study (Phase 3 Maintenance Study)

In the Maintenance Study, the randomized population will include guselkumab clinical responders at Week I-12 and placebo crossover responders at Week I-24 from Induction Study 1 or Induction Study 2. These participants will be rerandomized to 1 of 3 study intervention groups as described below.

- **Guselkumab 200 mg SC q4w**: Participants will receive guselkumab 200 mg SC q4w starting at Week M-0 through Week M-44.
- **Guselkumab 100 mg SC q8w**: Participants will receive guselkumab 100 mg SC q8w starting at Week M-4 through Week M-44. Placebo SC will also be administered at alternate visits to maintain the blind.
- **Placebo:** Participants will receive placebo SC q4w starting at Week M-0 through Week M-44.

Participants will remain on their assigned study intervention through Week M-44. Participants who subsequently meet criteria for loss of clinical response will be eligible for a single blinded dose adjustment as described in the protocol. The primary analysis population for the Maintenance Study will be based on randomized participants with a modified Mayo score of 5 to 9 at induction baseline.

In the Maintenance Study, the nonrandomized population will consist of guselkumab 24-Week responders and placebo responders at Week I-12. Guselkumab 24-Week responders will receive guselkumab 200 mg SC q4w starting at Week M-0 through Week M-44. Induction placebo responders at Week I-12 will receive placebo SC q4w starting at Week M-0 through Week M-44. These populations are not eligible for dose adjustment.

EFFICACY EVALUATIONS

Efficacy evaluations for all 3 studies include the following:

- Mayo score and Partial Mayo score.
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS).
- Inflammatory PD markers including CRP and fecal calprotectin.
- Patient-reported outcome measures to assess HRQoL outcomes and fatigue (ie, IBDQ, Patient-Reported Outcomes Measurement Information System [PROMIS]-29, and PROMIS Fatigue 7-item Short Form [7a]), Patient's Global Impression of Change [PGIC] of Severity of UC [Induction

Study 1 and Induction Study 2 only], Patient's Global Impression of Severity [PGIS] of UC, and 5-level EuroQol five dimensions instrument [EQ-5D-5L]).

- Extraintestinal manifestations.

PHARMACOKINETIC EVALUATIONS

Serum samples will be analyzed to determine concentrations of guselkumab using validated, specific, and sensitive immunoassay methods by or under the supervision of the sponsor.

IMMUNOGENICITY EVALUATIONS

Serum samples will be screened for antibodies binding to guselkumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of guselkumab.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab treatment and/or UC. Assessments will include the evaluation of relevant biomarkers in serum, whole blood, stool, and colonic biopsy samples (where local regulations permit).

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary where local regulations permit. Participation in pharmacogenomic research is optional.

MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS EVALUATIONS

Medical resource utilization, all medical encounters including UC-related emergency department visits, hospitalizations, and surgeries, will be collected in this study. The Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH) will also be utilized to evaluate work productivity.

SAFETY EVALUATIONS

Key safety assessments include adverse events (AEs), clinical laboratory tests (hematology and chemistry), vital signs and physical examinations, a screening electrocardiogram, suicidality assessment, monitoring for hypersensitivity reactions, AEs temporally associated with infusion, injection-site reactions, and early detection of active tuberculosis.

STATISTICAL METHODS

The primary analysis population for all 3 studies will be based on randomized and treated participants with a modified Mayo score of 5 to 9 at induction baseline.

Sample Size Determination

Induction Study 1 (Phase 2b Induction Dose-ranging Study)

Sample sizes were determined by the power to detect a significant difference in clinical response at Week I-12 (primary endpoint) between each guselkumab group and the placebo group using a 2-sided chi-square test with 0.05 significance level. Based on the data from the Phase 3 ustekinumab (anti-IL-12/23 mAb) UC CNTO1275UCO3001 program (a clinical program conducted by the sponsor in a very similar target population [ie, participants with moderately to severely active UC who had failed or were intolerant to biologic or conventional therapies]) and mirikizumab (another anti-IL-23 mAb) Phase 2 UC study, the

clinical response rates are assumed to be 30% for placebo and 60% for each of the guselkumab doses in this study.

The planned sample size (150 participants total or 50 per treatment group) for the interim analysis is considered sufficient as it provides at least 80% power to detect a treatment difference between any guselkumab group and placebo based on the current assumptions on clinical response rate and is consistent with past Phase 2 dose-ranging studies in UC.

Since Induction Study 1 also serves as a feeder study for the Phase 3 Maintenance Study and thus will keep enrolling until an induction dose decision is made for Induction Study 2, the sample size for Induction Study 1 is not fixed. However, it is estimated that when the induction dose decision is made from the interim analysis, there will be approximately 390 participants (130 per treatment group) randomized in Induction Study 1. Therefore, 130 participants in each of the 2 guselkumab groups and 130 participants in placebo will provide an overall power of >90% for the primary endpoint of clinical response at Week I-12 for each guselkumab group compared to placebo, based on the assumptions above.

Induction Study 2 (Phase 3 Induction Study)

Sample sizes were determined by the power to detect a significant difference in clinical remission at Week I-12 (primary endpoint) between the guselkumab group and the placebo group using a 2-sided chi-square test with a 0.05 significance level. The study is sized such that the guselkumab therapy achieves ≥90% power for the primary endpoint compared with placebo.

Based on the data from the ustekinumab CNTO1275UCO3001 UC program and the mirikizumab Phase 2 UC study, the clinical remission rates at Week I-12 are assumed to be 8-10% for placebo and 20-24% for the selected guselkumab dose for this study. Assuming 8% clinical remission in the placebo group and 20% in the guselkumab group, 175 participants per group (350 participants in total) will provide statistical power of 90% for comparison of guselkumab versus placebo at a significance level of 0.05 (2-sided). However, to provide a sufficient number of participants for the primary analysis population in the Maintenance Study, the sample size for Induction Study 2 was increased to at least 560 randomized participants with a modified Mayo score of 5 to 9 and the randomization allocation was slightly skewed to guselkumab (3:2) to generate a sufficient number of guselkumab clinical responders. In addition, a sample size of 560 randomized participants with a modified Mayo score of 5 to 9 also provides sufficient power for the majority of the major secondary endpoints.

Maintenance Study (Phase 3 Maintenance Study)

A multiplicity-controlled testing procedure, starting with the high guselkumab dose group (200 mg SC q4w), will be used to control the overall Type-I error rate at the 0.05 level (2-sided) over the primary and major secondary endpoints. As such, sample size/power calculations were based on the chi-square test to detect a significant difference between participants receiving SC guselkumab 200 mg q4w and those receiving placebo. Based on the data from the ustekinumab CNTO1275UCO3001 UC program, the clinical remission rates are assumed to be 25% for placebo and 45% for each of the guselkumab doses. Based on these assumptions, 118 participants in each group (354 participants in total) will provide statistical power of 90% at a significance level of 0.05 (2-sided).

The number of participants in the primary analysis population of the Maintenance Study will depend on the number of randomized participants with a modified Mayo score of 5 to 9 at induction baseline from the following 2 groups of the induction studies:

- Group A: participants in clinical response to IV guselkumab at Week I-12 of either Induction Study 1 or Induction Study 2
- Group B: participants who were not in clinical response to IV placebo induction at Week I-12 of either Induction Study 1 or Induction Study 2 but were in clinical response at Week I-24 after receiving IV guselkumab at Weeks I-12, I-16, and I-20.

Based on the assumptions in Induction Study 1, the average clinical response rate to guselkumab IV induction is 60%, thus the 2 induction studies will result in approximately 484 participants in the primary analysis population of the Maintenance Study. However, the average clinical response rate to guselkumab IV induction could range from 50% to 65%. With 596 participants with a modified Mayo score of 5 to 9 expected to receive guselkumab and 354 participants with a modified Mayo score of 5 to 9 expected to receive placebo at Week I-0, the number of participants in the primary analysis population of the Maintenance Study could range from 404 to 525. The expected enrollment in the primary analysis population of the Maintenance Study is 484 participants, which is over the required sample size of 354. The targeted number was increased because the maintenance study is intended to power at >90% for the majority of the major secondary endpoints based on the primary analysis population.

Statistical Analyses for Induction Study 1 (Phase 2b Induction Dose-ranging Study)

Primary Endpoint Analysis

For testing of the primary endpoint, the efficacy of each guselkumab group versus placebo will be compared. For all statistical comparisons of the primary endpoint, a Cochran-Mantel-Haenszel (CMH) test (2-sided) stratified by ADT-Failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No) will be used. A step-up multiple testing procedure will be used to control the Type-I error at a 2-sided 0.05 significance level over the comparisons for the primary endpoint. The study will be considered positive if at least 1 guselkumab group is significantly different from the placebo group for the primary endpoint.

Major Secondary Endpoint Analyses

For testing of the major secondary endpoints, the efficacy of each guselkumab group versus placebo will be compared. For all statistical comparisons of the major secondary endpoints, a CMH test (2-sided) stratified by ADT-Failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No) will be used.

The study is not being powered to detect treatment differences between guselkumab and placebo for these major secondary endpoints. These endpoints will not be multiplicity-controlled for analysis purposes, and all p-values will be considered nominal.

Statistical Analyses for Induction Study 2 (Phase 3 Induction Study)

Primary Endpoint Analysis

For testing of the primary endpoint, the efficacy of the guselkumab group versus placebo will be compared. A CMH test (2-sided) stratified by ADT-Failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No) will be used. The comparison between guselkumab and placebo will be controlled at the 2-sided 0.05 significance level. The study will be considered positive if the guselkumab group is significantly different from the placebo group for the primary endpoint.

Major Secondary Endpoint Analyses

For testing of the major secondary endpoints, the efficacy of the guselkumab group versus placebo will be compared. For all statistical comparisons of the major secondary endpoints, a CMH test (2-sided) stratified by ADT-Failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No) will be used.

A fixed sequence testing procedure will be used to control for multiplicity over the primary and major secondary endpoints. That is, the major secondary endpoints will be tested at the 2-sided 0.05 significance level after the test on the primary endpoint. However, if an endpoint is not significant, all subsequent tests in the hierarchy will be considered not to be significant, and the p-values associated with those tests will be considered to be nominal. The testing order of these major secondary endpoints will be specified in the SAP.

Statistical Analyses for Maintenance Study (Phase 3 Maintenance Study)

Primary Endpoint Analysis

For testing of the primary endpoint, the efficacy of each guselkumab group versus placebo will be compared. For all statistical comparisons of the primary endpoint, a CMH test (2-sided) stratified by clinical remission status at maintenance baseline (Yes/No) and induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover [guselkumab 200 mg], and placebo crossover [guselkumab 400 mg, if chosen as the Phase 3 guselkumab induction dose]) will be used. A multiplicity-controlled testing procedure to control the Type-I error at a 2-sided 0.05 significance level over the primary and major secondary endpoints is briefly described below and will be described in further detail in the SAP. As part of this testing procedure, a fixed sequence testing procedure will be used where the guselkumab 200 mg SC q4w group for the primary endpoint will be tested first. The study will be considered positive if the guselkumab 200 mg SC q4w group is significantly different from the placebo group for the primary endpoint.

Major Secondary Endpoint Analyses

For testing of the major secondary endpoints, the efficacy of each guselkumab group versus placebo will be compared. For all statistical comparisons of the major secondary endpoints (except for clinical remission at Week M-44 among the participants who had achieved clinical remission at maintenance baseline), a CMH test (2-sided) stratified by clinical remission status at maintenance baseline (Yes/No) and induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover [guselkumab 200 mg], and placebo crossover [guselkumab 400 mg, if chosen as the Phase 3 guselkumab induction dose]) will be used. For clinical remission at Week M-44 among the participants who had achieved clinical remission at maintenance baseline, a CMH test (2-sided) stratified by induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover [guselkumab 200 mg], and placebo crossover [guselkumab 400 mg, if chosen as the Phase 3 guselkumab induction dose]) will be used.

Type I error control for Rest of World (ie, countries/territories outside the United States): A fixed sequence testing procedure will be employed to control the overall Type 1 error rate over the primary and all major secondary efficacy analyses at the 2-sided 0.05 significance level within a guselkumab dose group. For this procedure, a fixed sequence testing procedure will be used for the primary endpoint, with the higher dose group being tested first. Following this, the major secondary endpoints will be tested in a hierarchical manner for that dose group that is significant for the primary endpoint and the testing order will be specified in the SAP. A major secondary endpoint for a guselkumab dose group will be considered significant only if both the previous endpoints in the hierarchy and current endpoint test positive at the 2 sided 0.05 level of significance. If an endpoint is not significant, all subsequent tests in the hierarchy will be considered not to be significant. Nominal p-values will be reported for all analyses that are not multiplicity controlled.

Type I error control in the United States: A different multiplicity-controlled testing procedure to strongly control the Type-I error rate at the 2-sided 0.05 significance level will be used for submission for the United States and will be specified in the SAP.

Safety Analyses

Safety data, including but not limited to, AEs, serious adverse events, infections, AEs temporally associated with infusion, injection-site reactions, changes in laboratory parameters (hematology and chemistry), and suicidal ideation and behavior will be summarized. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. The verbatim terms used in the electronic case report form by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities.

Other Analyses

Pharmacokinetic Analyses

Serum guselkumab concentration over time will be summarized for each treatment group using descriptive statistics. Population PK modeling may be conducted when appropriate. If these population PK analyses are conducted, the results of these analyses will be presented in a separate report.

Immunogenicity Analyses

The incidence and titers of antibodies to guselkumab will be summarized for all participants who receive at least 1 dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab (ie, participants with at least 1 sample obtained after their first dose of guselkumab). The incidence of neutralizing antibodies to guselkumab will be summarized for participants who are positive for antibodies to guselkumab and have samples evaluable for neutralizing antibodies to guselkumab.

Biomarkers Analyses

Changes in serum protein analytes, whole blood RNA, and colonic biopsy RNA obtained over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select biomarkers and response to treatment will be explored. Results of serum, whole blood analyses, stool, and colonic biopsy analyses will be reported in separate technical reports.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum concentrations of guselkumab and the efficacy measures and/or relevant PD endpoints may be explored graphically when appropriate. If any visual trend is observed, additional analysis may be conducted if deemed necessary.

Pharmacogenomic Analyses

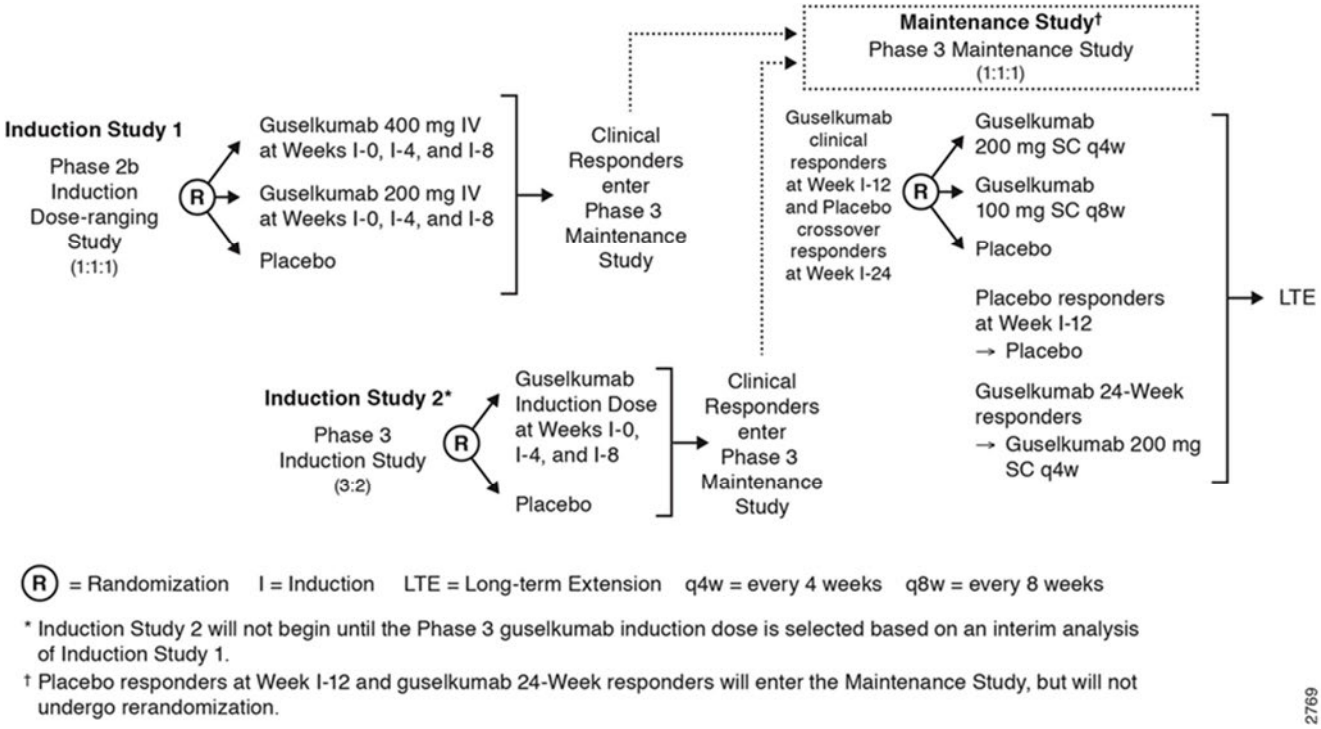
Genetic (DNA) analyses will be conducted only in participants who sign the consent form to participate in the pharmacogenomic substudy. These analyses are considered exploratory and will be summarized in a separate technical report.

Medical Resource Utilization and Health Economics Analyses

Medical resource utilization and health economics will be descriptively summarized by intervention group.

1.2. Schema

Figure 1: Overview of the CNTO1959UCO3001 Phase 2b/3 Study Design



1.3. Schedule of Activities

1.3.1. Induction Study 1 (Phase 2b Induction Dose-ranging Study) and Induction Study 2 (Phase 3 Induction Study)

Table 1: Screening and Week I-0 to Week I-24 of Induction Study 1 and Induction Study 2

Phase	Screening	Treatment							Early Term[b,c]	Safety F/U[c,g]	Notes
Week	Within 8 weeks	I-0	I-4	I-8	I-12[e,f]	I-16[e]	I-20[e]	I-24[e,f]			
Study Procedures[a,b,c,d]											
Screening/Administrative											
Informed consent (ICF)	X										Must be signed before first study related activity.
ICF for Optional Genetic Research	X										ICF for participants consenting to participate in the optional pharmacogenomic substudy.
Review medical history requirements	X										
Inclusion/exclusion criteria	X	X									
Demographics	X										
Review prestudy therapy	X										Prestudy therapies administered up to 30 days before the first dose of study intervention must be recorded on the eCRF.
Review preplanned surgery/procedure(s)	X										
QuantiFERON TB® (or T SPOT® for sites in Japan) test	X										All participants will undergo QuantiFERON® TB (or T SPOT® for sites in Japan) testing. If the QuantiFERON® TB test is not approved/registered in the country/territory in which this protocol is being conducted or the tuberculin skin test is mandated by local health authorities, a negative tuberculin skin test result is also required. In Ukraine, while the QuantiFERON® TB test is not approved/registered, it is accepted, and a tuberculin skin test is not required.
HBV and HCV testing	X										For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti HBc) and/or surface antibody (anti HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines. Additional details are provided in Appendix 7 (Section 10.7; Hepatitis B Virus (HBV) Screening with HBV DNA Testing).
HIV test	X										

Table 1: Screening and Week I-0 to Week I-24 of Induction Study 1 and Induction Study 2											
Phase	**Screening**	**Treatment**							**Early Term[b,c]**	**Safety F/U[c,g]**	**Notes**
Week	**Within 8 weeks**	**I-0**	**I-4**	**I-8**	**I-12[e,f]**	**I-16[e]**	**I-20[e]**	**I-24[e,f]**			
Study Procedures[a,b,c,d]											
Chest radiograph	X										Chest radiograph (posterior anterior and lateral views, or per country/territory regulations where applicable) must be obtained within 12 weeks before the Week I 0 visit. Note: A chest CT scan is also acceptable if obtained instead of a chest radiograph outside of the protocol.
Stool for enteric pathogens	X										Stool studies for enteric pathogens may be performed at either the central or local laboratory and must include a stool culture and *Clostridium difficile* toxin assay. These tests must be performed during screening or have been performed during the current episode of disease exacerbation (as long as the stool studies were performed within 4 months before the first dose of study intervention). Additional testing (eg, ova and parasites or Escherichia coli O157:H7 assessments) may be performed at the investigator's clinical discretion. A positive test result for *Clostridium difficile* infection may be presumed in the setting of positive enzyme immunoassay screening for glutamate dehydrogenase antigen and toxins A or B. A negative result may be presumed if both enzyme immunoassays are negative. Confirmation nucleic acid amplification testing will be performed by polymerase chain reaction if the results are discordant.
Training on Mayo diary completion	X	X									Participants should be instructed to bring their diaries to each study visit for review.
Study Intervention Administration											
Randomization		X									
Administer study intervention		X	X	X	X*	X*	X*				* Participants who are not in clinical response at Week I 12 will receive guselkumab (and placebo to maintain the blind) at Weeks I 12, I 16, and I 20. For the Week I 12, I 16, and I 20 visits, the IV study intervention should be administered first. The SC study intervention should be administered approximately 30 minutes after the IV study intervention infusion is complete.

Table 1: Screening and Week I-0 to Week I-24 of Induction Study 1 and Induction Study 2

Phase	Screening	Treatment							Early Term[b,c]	Safety F/U[c,g]	Notes
Week	Within 8 weeks	I-0	I-4	I-8	I-12[e,f]	I-16[e]	I-20[e]	I-24[e,f]			
Study Procedures[a,b,c,d]											
Efficacy Evaluations											
Endoscopy[#]	X†				X			X	X		# Endoscopy findings will be assessed by the investigator (ie, local endoscopist) during the procedure and a video of the endoscopy must be submitted to the central reader. † The screening endoscopy should be performed within 2 weeks before the Week I 0 visit. The interval from the endoscopy procedure to the availability of the Mayo endoscopy subscore as assessed by the central reader is approximately 4 days; therefore, the screening endoscopy should be performed at least 4 days before the baseline (Week I 0) visit. The Mayo endoscopy subscore assessed by the central reader will be used to determine eligibility (ie, Mayo endoscopy subscore ≥2) and to calculate the baseline modified Mayo score. A full colonoscopy will replace a sigmoidoscopy if screening for polyps or dysplasia is required. Per exclusion criterion 9, adenomatous colonic polyps present on screening endoscopy must be removed. At least 48 hours should elapse between a colonoscopy with polypectomy and the Week I 0 visit. Local pathology results from the screening endoscopy should be available and reviewed before the first dose of study intervention.
Mayo score		X			X			X	X		
Partial Mayo score	X		X	X		X	X				
Extraintestinal manifestations	X	X	X	X	X	X	X	X	X		
Patient-reported Outcomes											
IBDQ		X			X			X	X		
PROMIS 29		X			X			X	X		
PROMIS Fatigue Short Form 7a		X			X			X	X		
PGIC					X			X	X		
PGIS		X			X			X	X		
EQ 5D 5L		X			X			X	X		
Health Economics											
WPAI GH		X			X			X	X		
Review of all medical encounters including UC related emergency department visits, hospitalizations, and surgeries	X	X	X	X	X	X	X	X	X	X	

Table 1: Screening and Week I-0 to Week I-24 of Induction Study 1 and Induction Study 2

Phase	Screening	Treatment							Early Term[b,c]	Safety F/U[c,g]	Notes
Week	Within 8 weeks	I-0	I-4	I-8	I-12[e,f]	I-16[e]	I-20[e]	I-24[e,f]			
Study Procedures[a,b,c,d]											
Safety Assessments											
Physical examination	X				X			X	X	X	
12 lead ECG	X										
TB evaluation/other infection assessment	X	X	X	X	X	X	X	X	X	X	If TB is suspected at any time, a chest radiograph (or chest CT scan if obtained instead of a chest radiograph outside of the protocol) and QuantiFERON® TB (or T SPOT® for sites in Japan) test should be performed. In countries/territories where the QuantiFERON® TB test is not registered/approved, or the tuberculin skin test is mandated by local health authorities, TB skin testing should also be performed. Note: In Ukraine, while the QuantiFERON® TB test is not approved/registered, it is accepted, and a tuberculin skin test is not required.
Vital signs	X	X	X	X	X	X	X	X	X	X	Temperature, pulse/heart rate, respiratory rate, and blood pressure. At a study intervention administration visit, vital signs should be obtained before, approximately every 30 minutes during, and twice (at approximately 30 minute intervals) after completion of the IV infusion(s), or before and approximately 30 minutes after the SC injection, or if the participant reports any symptoms.
Weight	X	X			X			X	X	X	
Height	X										
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	A urine pregnancy test must be performed at screening and before any study intervention administration for women of childbearing potential.
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	
AE review	X	X	X	X	X	X	X	X	X	X	
C SSRS	X	X	X	X	X	X	X	X	X		At the screening visit, the C SSRS should be completed as the first assessment after signing informed consent and before any other tests, procedures, or other consultations. For subsequent visits, the C SSRS should be completed after all PROs and before any other tests, procedures, or other consultations.
Study intervention injection site evaluation (only for participants who receive study intervention at I 12, I 16, and I 20 visits)					X	X	X				An injection site reaction is any adverse reaction at any SC study intervention injection site. Injection sites will be evaluated for reactions and any injection site reaction should be recorded as an adverse event.
Clinical Laboratory Tests											
Hematology and chemistry	X	X	X	X	X	X	X	X	X		
CRP		X	X	X	X	X	X	X	X		

Table 1: Screening and Week I-0 to Week I-24 of Induction Study 1 and Induction Study 2

Phase	Screening	Treatment							Early Term[b,c]	Safety F/U[c,g]	Notes
Week	Within 8 weeks	I-0	I-4	I-8	I-12[e,f]	I-16[e]	I-20[e]	I-24[e,f]			
Study Procedures[a,b,c,d]											
Fecal calprotectin		X	X		X			X	X		At visits also requiring endoscopy, stool samples should be collected prior to the initiation of endoscopy bowel preparations. Refer to the At Home Stool Collection Manual for collection instructions.
Pharmacokinetics/Immunogenicity											
Serum guselkumab concentration		X	X	X	X	X	X	X	X	X	For all visits where study intervention will be administered, 1 blood sample should be collected prior to the start of study intervention administration for evaluation of serum concentrations and/or antibodies to study intervention. In addition, for IV infusion related visits, another blood draw should be taken approximately 60 minutes after the completion of the IV infusion for serum concentration measurement. For visits where participants will receive both SC injection and IV infusion (Weeks I 12, I 16, and I 20), 1 blood sample for evaluation of serum concentrations and/or antibodies to study intervention should be collected first, followed by the IV infusion. Subcutaneous injection should follow 30 minutes after the completion of the IV infusion, and another blood draw should be taken approximately 60 minutes after the completion of the IV infusion for serum concentration measurement. For clinical responders at the I 12 or I 24 visit, samples for evaluation of serum concentrations and antibodies should be collected at the time of study IP administration, M 0 timepoint, using the I 12/I 24 sample collection kit. All reasonable attempts should be made to collect samples at the scheduled timepoints and record the actual dates and times of PK sample collections.
Antibodies to guselkumab		X	X	X	X			X	X	X	
Random guselkumab concentration (population PK sample)			X								One random blood sample for serum guselkumab concentration should be drawn at any time from the day following the Week I 0 study intervention administration to 1 day before the Week I 12 visit. This sample should not be drawn on or within 1 day of a scheduled visit during this time period (ie, Weeks I 0, I 4, I 8, and I 12). All reasonable attempts should be made to record the actual date and time of PK sample collection.

Table 1: Screening and Week I-0 to Week I-24 of Induction Study 1 and Induction Study 2

Phase	Screening	Treatment							Early Term[b,c]	Safety F/U[c,g]	Notes
Week	Within 8 weeks	I-0	I-4	I-8	I-12[e,f]	I-16[e]	I-20[e]	I-24[e,f]			
Study Procedures[a,b,c,d]											
Pharmacodynamics and Biomarkers (where local regulations permit)											
Biopsy (RNA, histology, single cell isolation)	X				X			X	X		Colonic biopsy samples will be collected from all participants during endoscopy for histologic assessment and RNA transcriptomic analysis. Pre defined sites will collect adjacent biopsy samples to support exploratory single cell isolation and analyses.
Whole blood PBMC isolation	X				X			X	X		Whole blood samples will be collected for PBMC isolation from a subset of participants that provide biopsy samples for single cell analyses at selected sites. Whole blood (PBMC) samples should be collected within ±2 days of the endoscopy visit.
Serum biomarkers		X	X		X			X	X		Serum biomarkers will be measured in all participants to evaluate the effects of study intervention on inflammatory proteins associated with UC, including cytokines associated with the IL 23 pathway.
Whole blood (RNA)		X	X		X			X	X		Whole blood (RNA) will be measured in all participants to evaluate the molecular effects of study intervention in UC.
Fecal biomarkers		X	X		X			X	X		Fecal biomarkers may be used for evaluation of changes in inflammatory proteins or microbiome composition. At visits also requiring endoscopy, stool samples should be collected prior to the initiation of endoscopy bowel preparations. Refer to the At Home Stool Collection Manual for detailed instructions.
Genetic and Epigenetic (DNA) Evaluations											
Whole blood (DNA)		X									Whole blood for genetic analyses will be collected (where local regulations permit) only from participants who sign a separate ICF to participate in the optional pharmacogenomic substudy. The pharmacogenomic (DNA) sample should be collected at the specified time point; however, if necessary, it may be collected later without constituting a protocol deviation.

Abbreviations: AE adverse event; CRP C reactive protein; C SSRS Columbia Suicide Severity Rating Scale; DNA deoxyribonucleic acid; Early Term early termination (visit); ECG electrocardiogram; eCRF electronic case report form; EQ 5D 5L 5 level EuroQol five dimensions instrument (includes the EQ 5D descriptive system [EQ 5D] and the EQ visual analog scale [EQ VAS]); F/U follow up; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; I induction; IBDQ Inflammatory Bowel Disease Questionnaire; IV intravenous; PBMC peripheral blood mononuclear cell; PK pharmacokinetic; PGIC Patient's Global Impression of Change (of Severity of UC); PGIS Patient's Global Impression of Severity; PRO patient reported outcome; PROMIS 29 Patient Reported Outcomes Measurement Information System; RNA ribonucleic acid; SC subcutaneous; TB tuberculosis; UC ulcerative colitis; WPAI GH Work Productivity and Activity Impairment Questionnaire General Health.

Table 1: Screening and Week I-0 to Week I-24 of Induction Study 1 and Induction Study 2

Phase	Screening	Treatment							Early Term[b,c]	Safety F/U[c,g]	Notes
Week	Within 8 weeks	I-0	I-4	I-8	I-12[e,f]	I-16[e]	I-20[e]	I-24[e,f]			
Study Procedures[a,b,c,d]											

a. Screening should occur within 8 weeks before the Week I 0 visit. Visit dates are based on the participant's induction randomization date; visit windows are as follows:
Week I 4, I 8, I 16, and I 20 visits: day of the scheduled visit **±4 days**.
Week I 12 and I 24 visits: day of the scheduled visit **±3 days**.

b. Participants who discontinue study intervention or terminate study participation should undergo procedures described for an Early Termination visit at the time of discontinuation or termination of study participation.

c. Participants who terminate their study participation at the Week I 12 visit should complete the Week I 12 assessments at the time of termination. Participants who terminate their study participation at the Week I 24 visit should complete the Week I 24 assessments at the time of termination. Participants who terminate their study participation prior to the Week I 12 visit, or after the Week I 12 visit but prior to the Week I 24 visit, should complete early termination assessments at the time of termination.

d. All assessments are to be completed before study intervention administration, unless otherwise specified. It is recommended that PRO assessments be completed first.

e. Only participants who are not in clinical response at Week I 12 will have Week I 16, I 20, and I 24 visits. Participants who are not in clinical response at Week I 24 will not receive further study intervention and should have a safety follow up visit approximately 12 weeks after their last dose of study intervention.

f. Participants who are in clinical response at Week I 12 or Week I 24 will enter the Maintenance Study. These participants may complete the Week M 0 assessments and dosing at the Week I 12 or Week I 24 visit or at a separate Week M 0 visit within the acceptable visit window as specified in Table 2.

g. Participants who do not enter the Maintenance Study (and have not terminated study participation) should have a safety follow up visit approximately 12 weeks after their last dose of study intervention.

1.3.2. Maintenance Study (Phase 3)

Table 2: Week M-0 to Week M-44 of Maintenance Study

Week	M-0[h]	M-4	M-8[b]	M-12[b]	M-16[b]	M-20[b]	M-24[b]	M-28[b]	M-32[b]	M-36	M-40	M-44[u]	Early Term[c]	Safety F/U[d]
Study Procedures[a,b]														
Administrative														
Study eligibility[e]	X													
Study Intervention Administration														
Randomization[f]	X													
Study intervention administration[g]	X	X	X	X	X	X	X	X	X	X	X			
Efficacy Assessments														
Endoscopy[i,v]												X	X	
Mayo score												X	X	
Partial Mayo score		X	X	X	X	X	X	X	X	X	X	X		
Extraintestinal manifestations		X	X	X	X	X	X	X	X	X	X	X	X	
Patient-reported Outcomes														
IBDQ								X				X	X	
PROMIS 29								X				X	X	
PROMIS Fatigue Short Form 7a								X				X	X	
PGIS								X				X	X	
EQ 5D 5L								X				X	X	
Health Economics														
WPAI GH								X				X	X	
Review of all medical encounters including UC related emergency department visits, hospitalizations and surgeries	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments														
Physical examination												X	X	X
TB evaluation[j] /other infection assessment	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[k]	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[l]	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review including review of corticosteroid tapering (if applicable)	X[w, x]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE review	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	X
C SSRS[m]	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	

Table 2: Week M-0 to Week M-44 of Maintenance Study

Week	M-0[h]	M-4	M-8[b]	M-12[b]	M-16[b]	M-20[b]	M-24[b]	M-28[b]	M-32[b]	M-36	M-40	M-44[u]	Early Term[c]	Safety F/U[d]
Study Procedures[a,b]														
Study intervention injection site evaluation[n]	X	X	X	X	X	X	X	X	X	X	X			
Clinical Laboratory Assessments														
Hematology and chemistry		X	X	X		X		X		X		X	X	
CRP		X		X		X		X		X		X	X	
Fecal calprotectin[v]								X				X	X	
Pharmacokinetics/Immunogenicity														
Serum guselkumab concentration[o]		X	X	X		X		X		X		X	X	X
Antibodies to guselkumab		X		X		X		X		X		X	X	X
Pharmacodynamics and Biomarkers (where local regulations permit)														
Biopsy (RNA, histology, single cell isolation)[p]												X	X	
Whole blood PBMC isolation[q]												X	X	
Serum biomarkers[r]								X				X	X	
Whole blood (RNA)[s]								X				X	X	
Fecal biomarkers[t,v]								X				X	X	

Abbreviations: AE adverse event; CRP C reactive protein; C SSRS Columbia Suicide Severity Rating Scale; Early Term early study termination visit; EQ 5D 5L 5 level EuroQol five dimensions instrument (includes the EQ 5D descriptive system [EQ 5D] and the EQ visual analog scale [EQ VAS]); F/U follow up; I induction; IBDQ Inflammatory Bowel Disease Questionnaire; LTE long term extension; M maintenance; PBMC peripheral blood mononuclear cell; PGIS Patient's Global Impression of Severity; PRO patient reported outcome; PROMIS 29 Patient Reported Outcomes Measurement Information System; RNA ribonucleic acid; SC subcutaneous; TB tuberculosis; WPAI GH Work Productivity and Activity Impairment Questionnaire General Health; UC ulcerative colitis.

a. Except for the Week M 0 visit, the visit window for each visit is ±10 days. Visit dates are based on the participant's Week M 0 visit date. The Week M 0 visit (ie, Week 0 visit for the Maintenance Study) should occur within 4 days after the Week I 12 visit (or the Week I 24 visit for participants who were not in clinical response at Week I 12 but were in clinical response at Week I 24). At the investigator's discretion, the Week M 0 visit window may be extended to 8 days to allow for any local pathology result turnaround, or appropriate treatment of and/or recovery from nonserious infections (eg, acute upper respiratory tract infection, simple urinary tract infection).
b. Participants in clinical flare for the first time prior to Week M 32 should complete all visit assessments indicated for the Week M 44 visit (including an endoscopy, which need only be a sigmoidoscopy) at the time of clinical flare during their scheduled visit or at any unscheduled visit. Participants with a subsequent clinical flare should complete all assessments indicated for the visit at which the clinical flare occurred.
c. Participants who discontinue study intervention or terminate study participation should undergo procedures described for an Early Termination visit.
d. Participants who discontinue study intervention (but have not terminated study participation) or who do not enter the LTE should have a safety follow up visit approximately 12 weeks after their last dose of study intervention.
e. Participants who were in clinical response at Week I 12 or Week I 24 from Induction Study 1 or Induction Study 2 will be eligible to enter the Maintenance Study. Participants who initiated or increased the dose of a UC specific medication (or restricted or prohibited medications, as defined in the protocol) during the induction studies are prohibited from entering the Maintenance Study.

Table 2: Week M-0 to Week M-44 of Maintenance Study

Week	M-0[h]	M-4	M-8[b]	M-12[b]	M-16[b]	M-20[b]	M-24[b]	M-28[b]	M-32[b]	M-36	M-40	M-44[u]	Early Term[c]	Safety F/U[d]
Study Procedures[a,b]														

f. Only guselkumab clinical responders at Week I 12 and placebo crossover responders at Week I 24 will be rerandomized in the Maintenance Study. Guselkumab 24 Week responders and induction placebo responders at Week I 12 will enter the Maintenance study but will not be rerandomized.
g. All assessments are to be completed before study intervention administration, unless otherwise specified. It is recommended that PRO assessments be completed first.
h. For all assessments not marked at this visit, data from the study assessments performed at the Week I 12 visit (for participants in clinical response at Week I 12) or at the Week I 24 visit (for participants who were not in clinical response at Week I 12 but were in clinical response at Week I 24) will be used for the Week M 0 visit.
i. A participant who meets the criteria for clinical flare for the first time prior to Week M 32 should undergo an endoscopy (which need only be a flexible sigmoidoscopy) to determine loss of clinical response based on the modified Mayo score (Section 4.1.3.1).
j. If TB is suspected at any time during the study, a chest radiograph and QuantiFERON TB® (or T SPOT® for sites in Japan) test should be performed. In countries/territories where the QuantiFERON TB® test is not registered/approved, TB skin testing should also be performed (recommended but not required for study centers in Ukraine if tuberculin is not available).
k. Temperature, pulse/heart rate, respiratory rate, and blood pressure. At a study intervention administration visit, vital signs should be obtained before and approximately 30 minutes after SC injection, or if the participant reports any symptoms.
l. A urine pregnancy test must be performed before any study intervention administration for women of childbearing potential.
m. The C SSRS should be completed after all PROs and before any other tests, procedures, or other consultations to prevent influencing participant perceptions.
n. An injection site reaction is any adverse reaction at any SC study intervention injection site. Injection sites will be evaluated for reactions and any injection site reaction should be recorded as an adverse event.
o. Predose samples should be collected at all dosing visits before study intervention administration. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual dates and times of sample collections.
p. Colonic biopsy samples will be collected from all participants during endoscopy for histologic assessment and RNA transcriptomic analysis. Pre defined sites will collect adjacent biopsy samples to support exploratory single cell isolation and analyses.
q. Whole blood samples will be collected for PBMC isolation from a subset of participants that provide biopsy samples for single cell analyses at selected sites. Whole blood (PBMC) samples should be collected within ±3 days of the endoscopy visit.
r. Serum biomarkers will be measured in all participants to evaluate the effects of study intervention on inflammatory proteins associated with UC, including cytokines associated with the IL 23 pathway.
s. Whole blood (RNA) will be measured in all participants to evaluate the molecular effects of study intervention in UC.
t. Fecal biomarkers may be used for evaluation of changes in inflammatory proteins or microbiome composition.
u. Participants who complete the safety and efficacy evaluations (including the required endoscopy procedure) at maintenance Week M 44 and who may benefit from continued study intervention, in the opinion of the investigator, will have the opportunity to participate in the LTE of the Maintenance Study.
v. At visits also requiring endoscopy, stool samples should be collected prior to the initiation of endoscopy bowel preparations. Refer to the At Home Stool Collection Manual for detailed instructions.
w. Should be completed if the Week M 0 visit is completed on a day other than that of the Week I 12 visit or Week I 24 visit.
x. Corticosteroid tapering must begin at M 0 for all participants receiving corticosteroids at baseline. Refer to Section 6.5.1 for guidance and requirements for corticosteroid use.

1.3.3. Long-term Extension of the Maintenance Study

Table 3: Long-term Extension for Eligible Participants Who Have Completed the Maintenance Study

Study Procedures [a,b]	Every 4 weeks [c]	Every 8 weeks [c,v]	Every 16 weeks [c,s]	Every 24 weeks [d,e]	Every 48 weeks [e,w]	Final Efficacy Visit [f]	Final Safety Visit [g]
Study Intervention Administration							
Administer study intervention[o]	X						
Efficacy Assessments							
Endoscopy					X	X[r]	
Mayo score					X	X[r]	
Partial Mayo score		X					
Extraintestinal manifestations					X	X	
Patient-reported Outcomes							
IBDQ				X		X	
PROMIS Fatigue Short Form 7a				X		X	
PROMIS 29				X		X	
Health Economics							
WPAI GH				X		X	
Review of all medical encounters including UC related emergency department visits, hospitalizations, and surgeries	X[q]					X	X
Safety Assessments							
Physical examination						X	X
TB evaluation[h]/other infection assessment	X[q]					X	X
Vital signs[i]	X[p]					X	X
Weight				X		X	X
Urine pregnancy test	X[j]					X	X
Concomitant medication review	X[q]					X	X
AE review	X[q]					X	X
C SSRS[k]				X		X	
Study intervention injection site evaluation[n]	X[q]						
Clinical Laboratory Assessments							
Hematology and chemistry			X			X	
CRP				X		X	
Fecal calprotectin[u]				X		X	
Pharmacokinetics/Immunogenicity							
Serum guselkumab concentration[l]				X		X	X
Antibodies to guselkumab[l]				X		X	X
Pharmacodynamics and Biomarkers (where local regulations permit)							
Serum biomarkers[m]					X	X	
Biopsy (histology)[t]					X	X	

Table 3: Long-term Extension for Eligible Participants Who Have Completed the Maintenance Study

Study Procedures [a,b]	Every 4 weeks [c]	Every 8 weeks [e,v]	Every 16 weeks [e,s]	Every 24 weeks [d,e]	Every 48 weeks [e,w]	Final Efficacy Visit [f]	Final Safety Visit [g]

Abbreviations: AE adverse event; CRP C reactive protein; C SSRS Columbia Suicide Severity Rating Scale; IBDQ Inflammatory Bowel Disease Questionnaire; LTE long term extension; M maintenance; PRO patient reported outcome; PROMIS Patient Reported Outcomes Measurement Information System; q4w every 4 weeks; q8w every 8 weeks; SC subcutaneous; TB tuberculosis; WPAI GH Work Productivity and Activity Impairment Questionnaire General Health; UC ulcerative colitis.

a. Visit window is ±10 days for each visit.
b. All assessments are to be completed before study intervention administration unless otherwise specified. It is recommended that PRO assessments be completed first.
c. The first study intervention administration in the LTE will occur at Week M 44. After the Maintenance Study is unblinded to the investigative sites, participants receiving placebo (ie, initial clinical responders and placebo withdrawal) will be terminated from study participation, and participants receiving guselkumab will continue to receive guselkumab, but will have their study visits scheduled to coincide with their dose regimen (either q4w or q8w). Thus, study visits for participants on the q8w dosing regimen only need to be scheduled every 8 weeks thereafter. The last dose of study intervention will be administered at Week M 228 for participants who receive study intervention q8w in the LTE and Week M 232 for participants who receive study intervention q4w in the LTE.
d. Visits every 24 weeks include on site visits at LTE Weeks M 68, M 92, M 116, M 140, M 164, M 188, and M 212.
e. The evaluations specified for visits every 4 weeks should also be conducted at the on site visits every 8, 16, 24, and 48 weeks.
f. Participants who have completed LTE treatment through the last scheduled dose should complete the Final Efficacy Visit at Week M 236. Participants who discontinued study intervention or terminated study participation prior to the final efficacy visit should undergo procedures described for final efficacy visit at the time of discontinuation/termination.
g. Participants who have completed LTE treatment or discontinued study intervention prior to the last scheduled dose (but have not terminated study participation) should have a safety follow up visit approximately 12 weeks after their last dose of study intervention.
h. If TB is suspected at any time, a chest radiograph (or chest CT scan if obtained instead of a chest radiograph outside of the protocol) and QuantiFERON® TB (or T SPOT® for sites in Japan) test should be performed. In countries/territories where the QuantiFERON® TB test is not registered/approved, or the tuberculin skin test is mandated by local health authorities, TB skin testing should also be performed. Note: In Ukraine, while the QuantiFERON® TB test is not approved/registered, it is accepted, and a tuberculin skin test is not required.
i. Temperature, pulse/heart rate, respiratory rate, and blood pressure. At a study intervention administration visit, vital signs should be obtained before and approximately 30 minutes after SC injection, or if the participant reports any symptoms.
j. For an on site visit, a urine pregnancy test must be performed before each study intervention administration in women of childbearing potential. Before at home study intervention administration, a urine pregnancy test may be performed where required by investigator judgment or local practice or regulations. When performed, a negative urine pregnancy test result must be obtained before study intervention administration.
k. The C SSRS should be completed after all PROs and before any other tests, procedures, or other consultations to prevent influencing participant perceptions.
l. At a study intervention administration visit, blood samples should be collected before study intervention injection. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual dates and times of sample collections.
m. Serum biomarkers will be collected from all participants to evaluate the effects of study intervention on inflammatory proteins associated with UC, including cytokines associated with the IL 23 pathway where local regulations permit.
n. An injection site reaction is any adverse reaction at any SC study intervention injection site. Injection sites will be evaluated for reactions and any injection site reaction should be recorded as an adverse event.
o. At home self administration (or administration by a caregiver) can begin after the Week M 44 visit according to regional/local regulations and instruction at the discretion of the investigator and participant, and upon completion of training. At home administration can only be performed for the following visits (if applicable): Weeks M 48, M 56, M 64, M 72, M 80, M 88, M 96, M 104, M 112, M 120, M 128, M 136, M 144, M 152, M 160, M 168, M 176, M 184, M 192, M 200, M 208, M 216, M 224, and M 232. Participants will record all at home study intervention administrations on a diary card.
p. After Week M 44, vital signs will be collected only during on site visits.

Table 3: Long-term Extension for Eligible Participants Who Have Completed the Maintenance Study

Study Procedures [a,b]	Every 4 weeks [c]	Every 8 weeks [e,v]	Every 16 weeks [e,s]	Every 24 weeks [d,e]	Every 48 weeks [e,w]	Final Efficacy Visit [f]	Final Safety Visit [g]

q. For study participants who are trained to self inject or have a caregiver who is trained to administer the study intervention at home, study participants will be trained to perform self evaluation for injection site reactions and reporting of AEs and concomitant medications. After administering the study intervention at home, participants will also be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding.

r. Endoscopy will only be performed for participants at the Final Efficacy Visit if they discontinued before the Week M 236 endoscopy visit.

s. Visits every 16 weeks include on site visits at LTE Weeks M 60, M 76, M 92, M 108, M 124, M 140, M 156, M 172, M 188, M 204, and M 220.

t. Colonic biopsy samples for histologic assessment will be collected from all participants during endoscopy.

u. At visits also requiring endoscopy, stool samples should be collected prior to the initiation of endoscopy bowel preparations. Refer to the At Home Stool Collection Manual for instructions.

v. Visits every 8 weeks are on site visits at LTE Weeks M 52, M 60, M 68, M 76, M 84, M 92, M 100, M 108, M 116, M 124, M 132, M 140, M 148, M 156, M 164, M 172, M 180, M 188, M 196, M 204, M 212, M 220, and M 228.

w. Visits every 48 weeks are on site visits at LTE Weeks M 92, M 140, and M 188.

2. INTRODUCTION

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

Guselkumab has been approved for the treatment of adults with moderate to severe plaque psoriasis in the United States (US), European Union, Canada, Japan and a number of other countries/territories worldwide. In addition, guselkumab has been approved for the treatment of psoriatic arthritis (PsA), generalized pustular psoriasis, erythrodermic psoriasis, and palmoplantar pustulosis in Japan.

Guselkumab is currently being developed in other diseases including for the treatment of patients with PsA, hidradenitis suppurativa, familial adenomatous polyposis, and Crohn's disease. Phase 3 studies in PsA and a Phase 2/3 program in Crohn's disease are ongoing globally. The sponsor is also conducting a Phase 2a randomized, double-blind, active-controlled, parallel-group, multicenter, proof-of-concept (POC) clinical study to evaluate the efficacy and safety of combination therapy with guselkumab and golimumab in participants with moderately to severely active ulcerative colitis (UC).

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure (IB) for guselkumab.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "study intervention" is used throughout the protocol in place of "study drug."

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Ulcerative colitis is a chronic inflammatory bowel disorder of unknown etiology which involves the surface mucosa, the crypt epithelium, and submucosa of the colon (Ordas 2012; Stenson 2000). Ulcerative colitis is most commonly diagnosed in late adolescence and early adulthood, but a diagnosis may occur at any age (Loftus 2004). Clinically, patients with UC suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, fever, and may also display prominent extraintestinal manifestations, most commonly arthritis (Ordas 2012; Stenson 2000). Ulcerative colitis is characterized by a life-long course of remissions and exacerbations, with 15% of patients having an acute attack requiring hospitalization at some time during their illness (Willert 2008). In severe UC, the bowel wall may become extremely thin, the mucosa denuded, and the inflammation may extend to the serosa leading to dilatation, toxic megacolon, and subsequent perforation (Glickman 1998; Stenson 2000). Within 10 years of diagnosis, approximately 20% of adults with UC were reported to have undergone colectomy (Van Limbergen 2008). There is a high unmet

need for new treatment options in UC that are safe and effective, especially new therapies that can provide improved long-term efficacy (ie, sustained remission) over currently available therapies (Section 2.1.1).

The Phase 2b/3 clinical development program for guselkumab in UC will evaluate the safety and efficacy of guselkumab compared with placebo and will be conducted under a single protocol. Under this single protocol, the following studies will be analyzed as 3 separate studies: a Phase 2b induction dose-ranging study (Induction Study 1), a Phase 3 induction study (Induction Study 2), and a Phase 3 randomized withdrawal maintenance study (Maintenance Study). The overall Phase 2b/3 development program will enroll a target of approximately 1000 participants with a total duration of up to approximately 5 years for each participant.

An overview of the protocol design and supportive rationale is described in Section 4.

The clinical and scientific rationale in support of the overall development program is described in Section 2.1.2.

Relevant background information on the nonclinical and clinical development of guselkumab is summarized in Section 2.2.

2.1.1. Unmet Need in Ulcerative Colitis

Conventional therapies for the treatment of UC include mesalamine, glucocorticoids, and thiopurines. Approved biologic therapies for the treatment of UC include anti-tumor necrosis factor alpha (TNFα) agents such as SIMPONI® (golimumab), REMICADE® (infliximab), and HUMIRA® (adalimumab), and the α4β7 integrin antagonist ENTYVIO® (vedolizumab). These biologic agents are administered either intravenously (IV; infliximab and vedolizumab) or subcutaneously (SC; golimumab and adalimumab) (Côté-Daigneault 2015). More recently, the oral Janus kinase (JAK) inhibitor, XELJANZ® (tofacitinib), and STELARA® (ustekinumab) were approved for the treatment of moderately to severely active UC. These agents are currently available for the treatment of patients who have failed or were intolerant to corticosteroids or immunomodulators.

Despite the availability of these approved therapies, many patients either fail to respond (ie, primary nonresponse) or lose their initial response (ie, secondary nonresponse) to treatment, highlighting the significant unmet medical need for more effective therapies, especially over the longer term (Sandborn 2016).

2.1.2. Rationale for Targeting IL-23 in Ulcerative Colitis

The clinical rationale for guselkumab in the treatment of UC is strong because clinical POC has been established for anti-IL-23 mAbs in both Crohn's disease and UC (Feagan 2016, 2017, 2018; Sandborn 2012, 2018; Sands 2017a). The therapeutic role of anti-IL-23 in inflammatory bowel disease (IBD) was first established by clinical studies of IL-12/23p40 antagonists (briakinumab [Panaccione 2015] and ustekinumab [Sandborn 2012]) in Crohn's disease. Ustekinumab, the sponsor's IL-12/23p40 antagonist, is approved for the treatment of moderate to severe Crohn's

disease in many countries/territories globally (ustekinumab United States Prescribing Information [USPI]/Summary of Product Characteristics [SmPC]). The ustekinumab Phase 3 program in UC has completed its pivotal portion with positive results and has recently been approved for UC (Danese 2019; Sandborn 2019b; Sands 2018). Two anti-IL-23 mAbs, risankizumab (BI 655066 [Feagan 2017, 2018]) and brazikumab (MEDI2070, AMG-139 [Sands 2017a]) have reported Phase 2 results demonstrating the efficacy of IL-23 blockade in participants with moderate to severe Crohn's disease. Phase 2 data for the anti-IL-23 mAb mirikizumab demonstrated the efficacy of IL-23 blockade in participants with moderately to severely active UC (Geert 2019; Sandborn 2018), and mirikizumab (mirikizumab NCT03518086, NCT03524092) as well as risankizumab (risankizumab NCT03398148, NCT03398135) have ongoing Phase 3 programs in UC.

Given the similarities in the biology and treatment of Crohn's disease and UC, as well as the efficacy and safety of anti-IL-23 treatment demonstrated to date in both Crohn's disease and UC, there is strong rationale for the clinical development of guselkumab in UC. CCI [redacted] In addition, the dose regimens selected for this UC program are in the range that is being evaluated in the ongoing guselkumab Phase 2/3 Crohn's disease study (guselkumab NCT03466411).

2.2. Background

2.2.1. Nonclinical Studies

A full nonclinical development program was conducted with guselkumab in support of initial global submissions and approvals. This program included general toxicology and toxicokinetic studies in support of first-in-human dosing, studies in support of Phase 2 and Phase 3 clinical development, and developmental and reproductive toxicology studies. A comprehensive overview of nonclinical data is presented in Section 3 of the guselkumab IB.

This section provides a summary of the sponsor's assessment of how the overall nonclinical data support the safety of the selected dosing for guselkumab in this Phase 2b/3 program in UC. Details regarding the selected clinical dose regimen and dose rationale are described in Section 4.3 of this protocol.

To place the selected clinical dosing for guselkumab in UC patients into perspective relative to the existing preclinical data, the predicted cumulative 12-week human exposures during the induction phase (based on the highest induction dose tested in this protocol, ie, 400 mg IV given at Weeks 0, 4, 8) were compared to the exposure at the no-observed-adverse-effect level (NOAEL) in cynomolgus monkeys following weekly IV administration in the 5-week arm of the subchronic toxicology study. In addition, predicted cumulative 12-week human exposures during the induction phase were compared to the exposure at the NOAEL in cynomolgus monkeys following weekly SC administration in the 24-week arm of the subchronic toxicology study. Thereafter, the predicted human exposure at steady-state (based on the highest maintenance dose tested in this protocol, ie, 200 mg SC every 4 weeks [q4w]) was compared with the exposure at the NOAEL in

cynomolgus monkeys following weekly SC administration in the 24-week arm of the subchronic toxicology study. These data are presented in Table 4.

Table 4: Guselkumab Predicted Exposure Margins for the Induction and Maintenance Phases of Treatment

Guselkumab Predicted Exposure Margins at 400 mg IV Induction Dosing		
Parameters	**Mean C_{max} (µg/mL)**	**Mean AUC (µg.day/mL)**
Cynomolgus Monkey Exposure at the NOAEL (50 mg/kg/week) Following 4 Weekly IV Doses	1432[a]	4817[b]
Human Predicted IV Exposure	109[c]	497[d]
Predicted Exposure Margin[e]	*13.1*	*9.7*
Guselkumab Predicted Exposure Margins at 200 mg SC Maintenance Dosing		
Parameters	**Mean C_{max} (µg/mL)**	**Mean AUC (µg.day/mL)**
Cynomolgus Monkey Exposure at the NOAEL (50 mg/kg/week) Following 24 Weekly SC Doses	993[a]	5412[b]
Human Predicted SC Exposure	30[c]	134[d]
Predicted Exposure Margin[e]	33.1	40.4

Abbreviations: AUC area under the curve; C_{max} maximum serum concentration; IV intravenous; NOAEL no observed adverse effect level; SC subcutaneous

a. Highest observed concentration following the fourth 50 mg/kg dose (IV) or the twenty fourth 50 mg/kg dose (SC)
b. For IV, AUC from Day 21 through 28 (1 week after the last 50 mg/kg dose); or for SC, AUC from Day 161 through 168 (1 week after the last 50 mg/kg dose).
c. Highest predicted concentration after the third 400 mg IV guselkumab dose, or at steady state following SC administration.
d. Predicted human AUC after the third 400 mg IV guselkumab dose (from Week 8 through Week 12), or at steady state following 200 mg SC every 4 weeks administration. Each value was divided by 4 to obtain the AUC over one week, which in turn corresponds to the AUC interval for cynomolgus monkeys.
e. Exposure margins represent the ratio between guselkumab exposure metrics in the cynomolgus monkey compared with those predicted in humans.

From a nonclinical perspective, the risk to UC patients at the selected guselkumab dose regimen is considered low based on no adverse findings observed in cynomolgus monkeys. As shown in Table 4, the predicted exposure margins for the selected highest guselkumab IV dose (400 mg IV q4w given 3 times) and SC dose (200 mg SC q4w) relative to the exposures at the NOAEL in cynomolgus monkeys are approximately 10 to 13 and 33 to 40, respectively, which is considered adequate to support the short-term IV dosing (for 12-weeks induction) and long-term SC dosing (for chronic maintenance) in the guselkumab UC Phase 2b/3 program. Further supportive clinical data for the selected guselkumab doses in terms of safety are described in Section 4.3.1.

2.2.2. Clinical Studies

Guselkumab has demonstrated efficacy in psoriasis and has received marketing approval in several countries and regions globally for the treatment of adults with moderate to severe plaque psoriasis, including in the US, Canada, European Union, Latin America, and the Asia Pacific region. The approved guselkumab dose for psoriasis is 100 mg by SC injection at Weeks 0, 4, and every 8 weeks (q8w) thereafter. In addition, guselkumab has been approved for the treatment of PsA, generalized pustular psoriasis, erythrodermic psoriasis, and palmoplantar pustulosis in Japan.

Guselkumab is also being studied in hidradenitis suppurativa and familial adenomatous polyposis. A pediatric study in subjects with chronic plaque psoriasis aged ≥6 to <18 years old is also ongoing. Phase 3 development is ongoing globally in PsA and a seamless global Phase 2/3 clinical program is ongoing in Crohn's disease. The ongoing Phase 2/3 guselkumab Crohn's disease program evaluated induction dose regimens up to a maximum dose of 1200 mg IV q4w given 3 times, as well as a maintenance dose range from 100 mg SC q8w to 200 SC q4w. In addition, a guselkumab and golimumab combination Phase 2a POC study in UC which includes a guselkumab monotherapy arm (guselkumab 200 mg IV at Weeks 0, 4, and 8 followed by guselkumab 100 mg SC q8w) is currently ongoing. Details about these guselkumab clinical development programs across various indications are provided in Section 4 of the latest version of the guselkumab IB.

Through the IB cutoff date of 12 July 2018, 2,798 subjects have been exposed to guselkumab across all indications in completed and ongoing Phase 2 and 3 studies, including 185 healthy subjects, 2,357 subjects with psoriasis, 129 subjects with PsA, and 312 subjects in other indications.

The largest clinical experience to date with guselkumab has been in plaque psoriasis. The safety profile of guselkumab in subjects with moderate to severe plaque psoriasis is based on data from the Phase 2 study CNTO1959PSO2001 and Phase 3 studies CNTO1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003. Of the 2,177 guselkumab treated subjects, 1,748 subjects were exposed for at least 1 year, 1,516 were exposed for at least 2 years, and 692 subjects were exposed for 3 years. Long-term extensions of 2 of the studies (CNTO1959PSO3001 and CNTO1959PSO3002) are ongoing and will continue through up to 5 years of follow-up.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of guselkumab may be found in the IB.

2.3.1. Risks of Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Clinical worsening of UC	The benefit-risk of guselkumab in the treatment of moderately to severely active UC has not been established.	• During the study, participants will be permitted to continue treatment of UC with certain concomitant medications (Section 6.5). • Participants will discontinue study intervention if it is not in their best interest or if they need to initiate protocol-prohibited medications including certain biologics (Sections 6.5.2 and 7.1.1). • Participants in the Maintenance Study who meet criteria for loss of clinical response will be eligible for a single blinded dose adjustment as detailed in Section 6.6.1.

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential Risks Due to Study Intervention Guselkumab		
CCI		
CCI		

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
CCI		
CCI		• CCI

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
CCI [redacted]	[redacted]	[redacted]
Risks Due to Study Procedures		
Risks associated with the endoscopy procedure including bleeding and colonic perforation	These risks are well recognized, but are rare (Arora 2009; Rabeneck 2008).	Trained and experienced endoscopists will be performing the procedure during this study.

2.3.2. Benefits of Study Participation

There is no established benefit to participants of receiving study intervention; however, given the well-established scientific and clinical rationale for IL-23 blockade in the treatment of UC (Section 2.1.2), participants may experience an improvement in disease status during treatment with guselkumab. Participants in the study will also help in furthering development of this drug to treat UC. Thus, the knowledge gained from this study has the potential to benefit many more patients suffering with UC, and thus offers potential public health benefits.

2.3.3. Benefit-Risk Assessment for Study Participation

Guselkumab has undergone extensive nonclinical and clinical development as summarized in the latest version of the IB and described briefly in Section 2.2.2. The collective efficacy and safety results of the Phase 1, Phase 2, and Phase 3 clinical studies in healthy volunteers and patients with plaque psoriasis established a favorable benefit-risk profile for guselkumab in the treatment of plaque psoriasis and regulatory approval for the plaque psoriasis indication. This clinical

experience provided support for the ongoing development of guselkumab in other inflammatory diseases such as Crohn's disease, PsA, generalized pustular psoriasis, erythrodermic psoriasis, and palmoplantar pustulosis. In addition, guselkumab is being evaluated in combination with golimumab and as a monotherapy in an ongoing Phase 2a POC study in UC (guselkumab and golimumab NCT03662542).

Although at present there are no clinical results for guselkumab in the treatment of UC, animal and human data support the critical role of IL-23 in the pathogenesis of UC. Notably, data from a Phase 2 study of another anti-IL-23 mAb (mirikizumab; see Section 2.1.2 [Geert 2019; Sandborn 2018]) has demonstrated POC for this mechanism in UC.

It is acknowledged that the proposed dose range to be evaluated in induction (ie, up to 400 mg IV q4w given 3 times) and in maintenance (ie, up to 200 mg SC q4w) in this protocol is higher than the approved dosing of guselkumab in psoriasis. Based on the data from nonclinical toxicology studies (Section 2.2.1), the predicted exposure margins during the induction and maintenance treatment periods relative to the exposure at the NOAEL identified in cynomolgus monkey are adequate to support the proposed clinical doses. The ongoing Phase 2/3 guselkumab Crohn's disease program evaluated induction dose regimens up to 1200 mg IV. In addition, similar doses/exposures have been previously evaluated in the Phase 2 studies of 2 other anti-IL-23 mAbs in Crohn's disease and UC (Section 4.3), and no significant safety concerns have been reported after treatment through up to 1 year; however, these Phase 2 studies evaluated a limited number of patients. This protocol will first evaluate 2 induction doses in the Phase 2b portion of the protocol, to enable selection of a safe and effective induction dose that is appropriate to take into the Phase 3 portion of the protocol for confirmatory evaluation of safety and efficacy.

Potential risks of guselkumab, including those of serious infection and malignancy, are being addressed via judicious inclusion/exclusion criteria, frequent study visits to allow for close monitoring of patient safety, guidelines for participant management (including monitoring of clinical laboratory tests and treatment discontinuation criteria), detailed description of allowed and prohibited concomitant medications, and comprehensive medical monitoring of data by the sponsor during the conduct of the studies. In addition, a comprehensive safety monitoring plan with oversight from an external, independent Data Monitoring Committee (DMC) will be implemented to ensure the safety of guselkumab in participants with moderately to severely active UC (Section 9.6).

In summary, the collective preclinical and clinical evidence for the anti-IL-23 mechanism of action in UC, and the benefit-risk profile of guselkumab established to date in psoriasis and other immune-mediated diseases, provide a strong scientific and clinical rationale for pursuing development of guselkumab in patients with moderately to severely active UC and for the investigation of guselkumab in this Phase 2b/3 program. Taking into account the measures taken to minimize risk to participants in this study, the potential risks associated with guselkumab are justified by the anticipated benefits that may be provided to participants with UC.

3. OBJECTIVES AND ENDPOINTS

Definitions for Time Points and Endpoints

The analysis time points mentioned for each study or phase refer to Week 0 of that study or phase (induction or maintenance); for example, Week I-12 refers to Week 12 of induction (Study 1 or Study 2), or 12 weeks after Week 0 of these studies. Similarly, Week M-44 refers to 44 weeks after the first maintenance visit (Week M-0) of that study and *not* 44 weeks after the first induction visit.

A description of the Mayo score, the modified Mayo score, and the partial Mayo score is provided in Section 8.1.1. Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

Baseline definitions and efficacy endpoints definitions are as follows:

- **Induction baseline**: Week 0 of Induction Study 1 and Induction Study 2 (I-0 visit).
- **Maintenance baseline**: Week 0 of the Maintenance Study (M-0 visit).
- **Clinical remission:** A stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.
- **Clinical response**: A decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.

  Modified Mayo score: 3-component (stool frequency, rectal bleeding, and endoscopy subscores) Mayo score without the physician's global assessment.
- **Endoscopic healing:** An endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
- **Endoscopic normalization**: An endoscopy subscore of 0.
- **Histologic healing**: Neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system (Geboes 2000).
- **Histologic remission**: Absence of neutrophils from the mucosa (both lamina propria and epithelium), no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system (Geboes 2000).
- **Histologic-endoscopic mucosal healing**: Achieving a combination of histologic healing and endoscopic healing, as defined above.
- **Histologic-endoscopic mucosal healing (Alternative definition)**: Achieving a combination of histologic remission and endoscopic healing, as defined above.
- **Deep histologic-endoscopic mucosal healing:** Achieving a combination of endoscopic normalization and histologic remission, as defined above.

- **Symptomatic remission:** A stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline.
- **IBDQ remission:** total Inflammatory Bowel Disease Questionnaire (IBDQ) score ≥170 (Higgins 2005; Irvine 1994).
- **Fatigue response:** ≥7-point improvement from induction baseline in Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue short form 7a.

3.1. Induction Study 1 (Phase 2b Induction Dose-ranging Study)

3.1.1. Objectives

Primary Objectives

The primary objectives of this study are, in participants with moderately to severely active UC:

- To evaluate the efficacy of guselkumab as induction therapy.
- To evaluate the safety of guselkumab as induction therapy.
- To evaluate the dose-response of guselkumab to inform induction dose selection for the Phase 3 induction study.

Secondary Objectives

The secondary objectives of this study are, in participants with moderately to severely active UC:

- To evaluate the impact of guselkumab on health-related quality of life (HRQoL) and health economics outcome measures.
- To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of guselkumab therapy, including changes in C-reactive protein (CRP) and fecal calprotectin.

3.1.2. Endpoints

All endpoints will evaluate the efficacy of guselkumab versus placebo, in participants with moderately to severely active UC.

Primary Endpoint

The primary endpoint in this study is clinical response at Induction Week 12 (Week I-12).

Major Secondary Endpoints

- Clinical remission at Week I-12.
- Symptomatic remission at Week I-12.
- Endoscopic healing at Week I-12.
- Histologic-endoscopic mucosal healing at Week I-12.
- Endoscopic normalization at Week I-12.

A complete list of the efficacy endpoints is provided in Section 9.4.1.1.

3.1.3. Hypothesis

The primary hypothesis is that guselkumab is superior to placebo in inducing clinical response at Week I-12 in participants with moderately to severely active UC.

3.2. Induction Study 2 (Phase 3 Induction Study)

3.2.1. Objectives

Primary Objectives

The primary objectives of this study are, in participants with moderately to severely active UC:

- To evaluate the efficacy of guselkumab as induction therapy.
- To evaluate the safety of guselkumab as induction therapy.

Secondary Objectives

The secondary objectives of this study are, in participants with moderately to severely active UC:

- To evaluate the impact of guselkumab on HRQoL and health economics outcome measures.
- To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin.

3.2.2. Endpoints

All endpoints will evaluate the efficacy of guselkumab versus placebo, in participants with moderately to severely active UC.

Primary Endpoint

The primary endpoint in this study is clinical remission at Week I-12.

Major Secondary Endpoints

- Symptomatic remission at Week I-12.
- Endoscopic healing at Week I-12.
- Clinical response at Week I-12.
- Symptomatic remission at Week I-4.
- IBDQ remission at Week I-12.
- Histologic-endoscopic mucosal healing at Week I-12.
- Fatigue response at Week I-12.
- Symptomatic remission at Week I-2.
- Endoscopic normalization at Week I-12.

Note: The final ordering of the major secondary endpoints will be provided in the Statistical Analysis Plan (SAP) for this study.

A complete list of the efficacy endpoints is provided in Section 9.4.1.2.

3.2.3. Hypothesis

The primary hypothesis is that guselkumab is superior to placebo in inducing clinical remission at Week I-12 in participants with moderately to severely active UC.

Hypotheses for major secondary endpoints in participants with moderately to severely active UC are listed below:

- Guselkumab is superior to placebo in inducing symptomatic remission at Week I-12.
- Guselkumab is superior to placebo in inducing endoscopic healing at Week I-12.
- Guselkumab is superior to placebo in inducing clinical response at Week I-12.
- Guselkumab is superior to placebo in inducing symptomatic remission at Week I-4.
- Guselkumab is superior to placebo in inducing IBDQ remission at Week I-12.
- Guselkumab is superior to placebo in inducing histologic-endoscopic mucosal healing at Week I-12.
- Guselkumab is superior to placebo in inducing fatigue response at Week I-12.
- Guselkumab is superior to placebo in inducing symptomatic remission at Week I-2.
- Guselkumab is superior to placebo in inducing endoscopic normalization at Week I-12.

3.3. Maintenance Study (Phase 3 Maintenance Study)

3.3.1. Objectives

Primary Objectives

The primary objectives of this study are, in participants with moderately to severely active UC who were induced into clinical response with guselkumab:

- To evaluate the efficacy of maintenance regimens of guselkumab.
- To evaluate the safety of maintenance regimens of guselkumab.

Secondary Objectives

The secondary objectives of this study are, in participants with moderately to severely active UC who were induced into clinical response with guselkumab:

- To evaluate the impact of guselkumab on HRQoL and health economics outcome measures.
- To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin.

3.3.2. Endpoints

All endpoints will evaluate the efficacy of guselkumab versus placebo, in participants with moderately to severely active UC who were in clinical response after 12 weeks of guselkumab IV induction therapy.

Primary Endpoint

The primary endpoint in this study is clinical remission at Maintenance Week 44 (Week M-44).

Major Secondary Endpoints

- Symptomatic remission at Week M-44.
- Endoscopic healing at Week M-44.
- Corticosteroid-free (ie, not requiring any treatment with corticosteroids for at least 8 weeks prior) clinical remission at Week M-44.
- Clinical response at Week M-44.
- Histologic-endoscopic mucosal healing at Week M-44.
- IBDQ remission at Week M-44.
- Fatigue response at Week M-44.
- Clinical remission at Week M-44 among the participants who had achieved clinical remission at maintenance baseline (ie, maintenance of clinical remission at M-44).
- Endoscopic normalization at Week M-44.

Note: The final ordering of the major secondary endpoints will be provided in the SAP for this study.

A complete list of the efficacy endpoints is provided in Section 9.4.1.3.

3.3.3. Hypothesis

The primary hypothesis is that guselkumab maintenance therapy is superior to placebo in achieving clinical remission at Week M-44 in participants with moderately to severely active UC who were induced into clinical response with guselkumab.

Hypotheses for major secondary endpoints in participants with moderately to severely active UC who were induced into clinical response with guselkumab are listed below:

- Guselkumab maintenance therapy is superior to placebo in achieving symptomatic remission at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving endoscopic healing at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving corticosteroid-free clinical remission at Week M-44.

- Guselkumab maintenance therapy is superior to placebo in maintaining clinical response through Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving histologic-endoscopic mucosal healing at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving IBDQ remission at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving fatigue response at Week M-44.
- Guselkumab maintenance therapy is superior to placebo in achieving endoscopic normalization at Week M-44.

The hypothesis for the major secondary endpoint in participants with moderately to severely active UC who were induced into clinical remission with guselkumab is listed below:

- Guselkumab maintenance therapy is superior to placebo in maintaining clinical remission through Week M-44.

4. STUDY DESIGN

4.1. Overall Design

The Phase 2b/3 clinical development program for guselkumab in UC will be conducted under a single protocol (CNTO1959UCO3001) consisting of 3 separate studies:

- Induction Study 1 (Phase 2b Induction Dose-ranging Study)
- Induction Study 2 (Phase 3 Induction Study)
- Maintenance Study (Phase 3 Maintenance Study)

All 3 studies will be randomized, double-blind, placebo-controlled, parallel-group, multicenter studies to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active UC. The induction studies (Induction Study 1 and Induction Study 2) will target participants 18 years of age or older with moderately to severely active UC who have demonstrated an inadequate response or failure to tolerate conventional (ie, 6-mercaptopurine [6-MP], azathioprine [AZA], or corticosteroids) or advanced therapy (ADT; ie, TNFα antagonists, vedolizumab, or tofacitinib). Participants who had an inadequate response or failure to tolerate advanced therapy (ADT-Failure) will comprise a minimum of approximately 40% and a maximum of approximately 50% of the population for the following: 1) the first 150 participants randomized in Induction Study 1 for the interim analysis and induction dose decision; and 2) the total population of Induction Study 2. The Maintenance Study is a randomized withdrawal study targeting participants with moderately to severely active UC who have demonstrated a clinical response to guselkumab treatment in either Induction Study 1 or Induction Study 2.

The primary analysis population for all 3 studies will be randomized and treated participants with a modified Mayo score of 5 to 9 at induction baseline. However, the program also allows for the

enrollment of participants with a modified Mayo score of 4, which is capped at ≤5% of the total population.

The total sample size across Induction Study 1 and Induction Study 2 is a target of approximately 1000 participants. This will include approximately 950 participants with a modified Mayo score of 5 to 9. The minimum sample size for Induction Study 1 is 150 participants. The minimum sample size for Induction Study 2 is 560 randomized participants with a modified Mayo score of 5 to 9. Note that the sample size for Induction Study 1 was not affected by the update to the primary analysis population for all 3 studies that came with Protocol Amendment 2 as the amendment did not occur until after enrollment for the study had already been completed. Induction Study 1 and Induction Study 2 are designed to feed clinical responders into the Phase 3 Maintenance Study. To facilitate uninterrupted enrollment of the Maintenance Study, the samples sizes for Induction Study 1 and Induction Study 2 are not fixed and will ultimately be determined by the number of participants randomized at the time of the guselkumab induction dose decision (based on the Induction Study 1 interim analysis). It is predicted, based on enrollment projections, that the number of participants randomized in Induction Study 1 at the time of the induction dose decision will be approximately 390 participants. However, if the guselkumab induction dose decision is made prior to randomizing 390 participants into Induction Study 1, subsequent participants will be randomized into Induction Study 2 with a resultant increase in the Induction Study 2 sample size. This strategy of shifting sample size from Induction Study 1 to Induction Study 2 will increase the number of participants in clinical response to the Phase 3 guselkumab induction dose entering the Maintenance Study while keeping the overall sample size of the clinical program consistent.

Overall, the program will evaluate guselkumab treatment through at least 56 weeks of induction and maintenance therapy. Participants who complete the safety and efficacy evaluations (including the required endoscopy procedure) at Week M-44 of the Maintenance Study and who may benefit from continued study intervention, in the opinion of the investigator, will have the opportunity to participate in the long-term extension (LTE) of the Maintenance Study for up to approximately an additional 4 years of treatment to evaluate the efficacy and safety of long-term maintenance treatment.

Efficacy, safety, PK, immunogenicity, and biomarkers (where local regulations permit) will be assessed for all 3 studies according to the Schedule of Activities (SoA; Section 1.3). An optional pharmacogenomic blood sample will be collected from participants who consent to the collection of these samples (where local regulations permit). Key efficacy assessments for all 3 studies include Mayo score and partial Mayo score, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), inflammatory PD markers including CRP and fecal calprotectin, patient-reported outcome (PRO) measures to assess HRQoL outcomes and fatigue (ie, IBDQ, PROMIS-29, PROMIS Fatigue Short Form 7a, Patient's Global Impression of Severity [PGIS] of UC, 5-level EuroQol 5 dimensions [EQ-5D-5L] instrument), and extraintestinal manifestations. Health economic evaluations will be performed using the Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH).

Key safety assessments include adverse events (AEs), clinical laboratory tests (hematology and chemistry), vital signs and physical examination, a screening electrocardiogram (ECG), suicidality

assessment, monitoring for hypersensitivity reactions, AEs temporally associated with infusion, injection-site reactions, and early detection of active tuberculosis (TB).

An external, independent DMC, with defined roles and responsibilities as governed by a DMC charter, will assess the safety of participants across the 3 studies. Refer to Section 9.6 for more details on the DMC.

A diagram of the overall Phase 2b/3 study design is provided in Section 1.2, Schema. Study schemas for Induction Study 1, Induction Study 2, and the Maintenance Study are provided in Sections 4.1.1, 4.1.2, and 4.1.3, respectively.

4.1.1. Induction Study 1 (Phase 2b Induction Dose-ranging Study)

Induction Study 1 has a projected sample size of approximately 390 participants (minimum 150 participants) who will be randomized in a 1:1:1 ratio to guselkumab 200 mg IV, guselkumab 400 mg IV, or placebo IV administered at Weeks I-0, I-4, and I-8 (Figure 2). Participants will be allocated to an intervention group using permuted block randomization stratified by ADT-Failure status (ie, inadequate response or failure to tolerate TNFα antagonists, vedolizumab, or tofacitinib) (Yes/No), region (Eastern Europe, Asia, or rest of world), and concomitant use of corticosteroids at baseline (Yes/No). At Week I-12, all participants will be evaluated for clinical response. Further study intervention administration will be determined by the participant's clinical response status (using the Mayo endoscopy subscore assigned by the local endoscopist) at Week I-12, as follows:

- Guselkumab clinical responders and placebo clinical responders at Week I-12 will enter the Maintenance Study (Section 4.1.3).
- Participants initially randomized to placebo who are not in clinical response at Week I-12 will then crossover to guselkumab and receive 3 doses of guselkumab 200 mg IV at Weeks I-12, I-16, and I-20.
- Participants initially randomized to guselkumab who are not in clinical response at Week I-12 will then receive 3 doses of guselkumab 200 mg SC at Weeks I-12, I-16, and I-20.

To maintain the blind, both IV and SC administrations will be given to all participants who are not in clinical response at Week I-12. Further information on study intervention administration for Induction Study 1 is provided in Section 6.1.1.

At Week I-24, participants who were not in clinical response at Week I-12 will be re-evaluated for clinical response (clinical response status will be based on the Mayo endoscopy subscore assigned by the local endoscopist). In addition to guselkumab clinical responders and placebo clinical responders at Week I-12, the following participants from Induction Study 1 will enter the Maintenance Study:

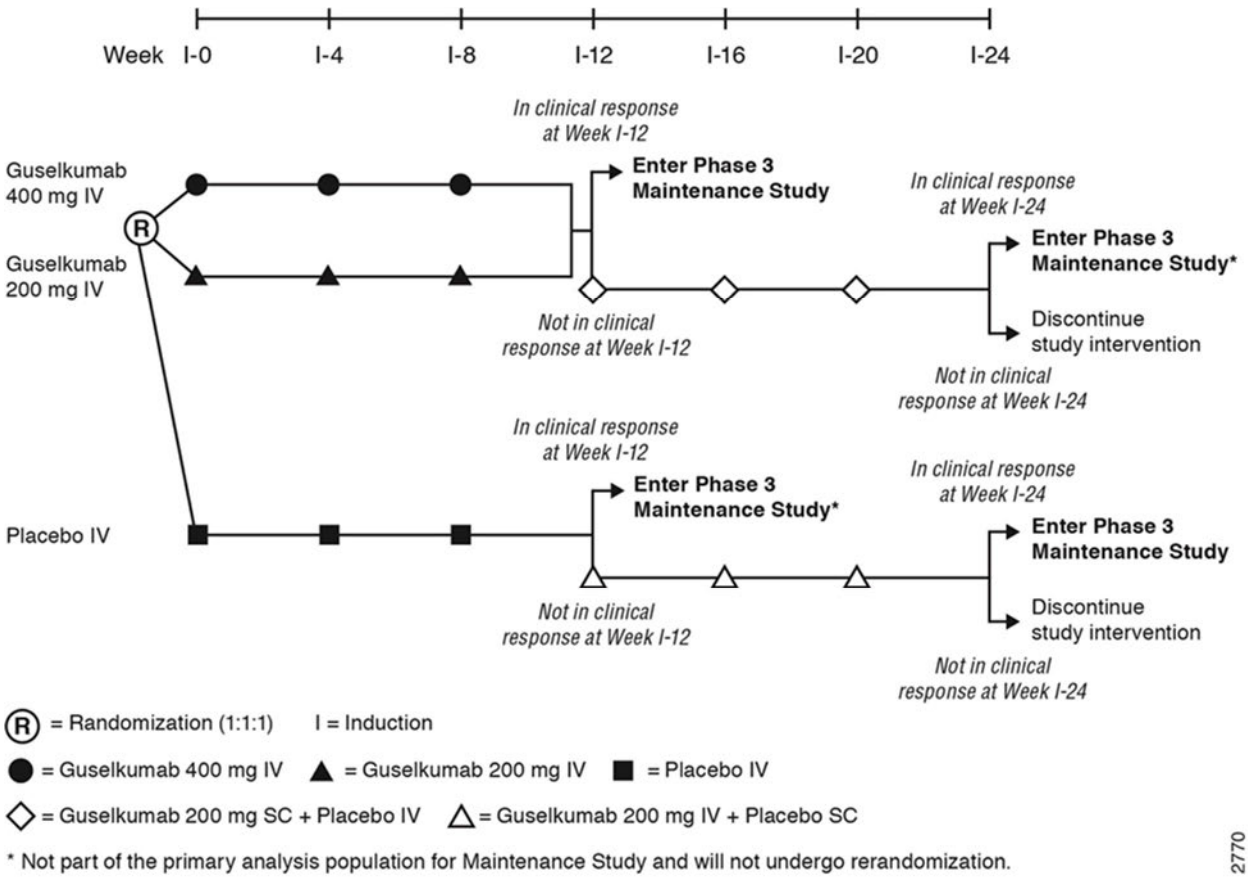
- Placebo crossover responders: Participants initially randomized to placebo who are not in clinical response at Week I-12 who then crossover to guselkumab induction 200 mg IV treatment and achieve clinical response at Week I-24.

- Guselkumab 24-Week responders: Participants initially randomized to guselkumab who are not in clinical response at Week I-12 who then receive 3 doses of guselkumab 200 mg SC and achieve clinical response at Week I-24.

Participants who are not in clinical response at Week I-24 will not receive further study intervention and should have a safety follow-up visit approximately 12 weeks after their last dose of study intervention.

All UC-specific medical therapies (ie, oral 5-aminosalicylic [5-ASA] compounds, oral corticosteroids, 6-MP, AZA, or MTX) must be maintained at a stable dose through to the end of Induction Study 1 and can only be discontinued or reduced in dose if investigator judgment requires it because of toxicity or medical necessity (Section 6.5). The initiation or increase in dose of UC-specific therapies (or any restricted/prohibited medication or therapy) during Induction Study 1 will prohibit a participant from entering the Maintenance Study (Section 6.5.2).

Figure 2: Study Schema for Induction Study 1 (Phase 2b Induction Dose-ranging Study)



Note: Treatment groups for the Phase 3 Maintenance Study are described in Section 4.1.3 and Figure 4 of the protocol.

Efficacy, PK parameters, biomarkers, and safety will be assessed according to the SoA (Section 1.3.1).

An interim analysis of the first 150 randomized participants who have completed the Week I-12 visit or have terminated study participation prior to Week I-12 will be performed (Section 9.5).

The purpose of this interim analysis is to select a single induction dose for confirmatory evaluation in the Phase 3 induction study (Induction Study 2). A Dose Selection Committee, composed of sponsor management representatives from Clinical, Safety, Biostatistics, and Clinical Pharmacology, who are not associated with study conduct, will be responsible for selecting the induction dose of guselkumab to be evaluated in Induction Study 2. While the data from the first 150 randomized participants is being evaluated, participants will continue to be enrolled in Induction Study 1, up to a maximum of 390 participants. Once the induction dose selection has occurred, participants will begin randomization into Induction Study 2.

Two database locks (DBLs) are planned for Induction Study 1. The first is for the interim analysis described above when the first 150 randomized participants have completed the Week I-12 visit or have terminated study participation prior to Week I-12. The second DBL will occur when all randomized participants in Induction Study 1 have either entered the Maintenance Study, or have completed their final safety visit (12 weeks after the last dose of study intervention) for those not participating in the Maintenance Study, or have terminated their study participation. Additional DBLs may be added if necessary and will be specified in the SAP.

4.1.2. Induction Study 2 (Phase 3 Induction Study)

In Induction Study 2, participants will be randomized in a 3:2 ratio to guselkumab or placebo administered at Weeks I-0, I-4, and I-8 (Figure 3). Induction Study 2 targets a sample size of at least 560 randomized participants with a modified Mayo score of 5 to 9. Selection of the guselkumab induction dose for Induction Study 2 will be based on an interim analysis of Induction Study 1. Participants will be allocated to an intervention group using permuted block randomization stratified by ADT-Failure status (ie, inadequate response or failure to tolerate TNFα antagonists, vedolizumab, or tofacitinib) (Yes/No), region (Eastern Europe, Asia, or rest of world), and concomitant use of corticosteroids at baseline (Yes/No). At Week I-12, all participants will be evaluated for clinical response. Similar to the approach outlined in Induction Study 1, further study intervention administration will be determined by the participant's clinical response status (using the Mayo endoscopy subscore assigned by the local endoscopist) at Week I-12, as follows:

- Guselkumab clinical responders and placebo clinical responders at Week I-12 will enter the Maintenance Study (Section 4.1.3).
- Participants initially randomized to placebo who are not in clinical response at Week I-12 will then crossover to guselkumab and receive 3 doses of guselkumab IV treatment (ie, induction dose selected based on Induction Study 1 interim analysis) at Weeks I-12, I-16, and I-20.
- Participants initially randomized to guselkumab who are not in clinical response at Week I-12 will then receive 3 doses of guselkumab 200 mg SC at Weeks I-12, I-16, and I-20.

To maintain the blind, both IV and SC administrations will be given to all participants who are not in clinical response at Week I-12. Further information on study intervention administration for Induction Study 2 is provided in Section 6.1.2.

At Week I-24, participants who were not in clinical response at Week I-12 will be re-evaluated for clinical response (clinical response status will be based on the Mayo endoscopy subscore assigned by the local endoscopist). In addition to guselkumab clinical responders and placebo clinical

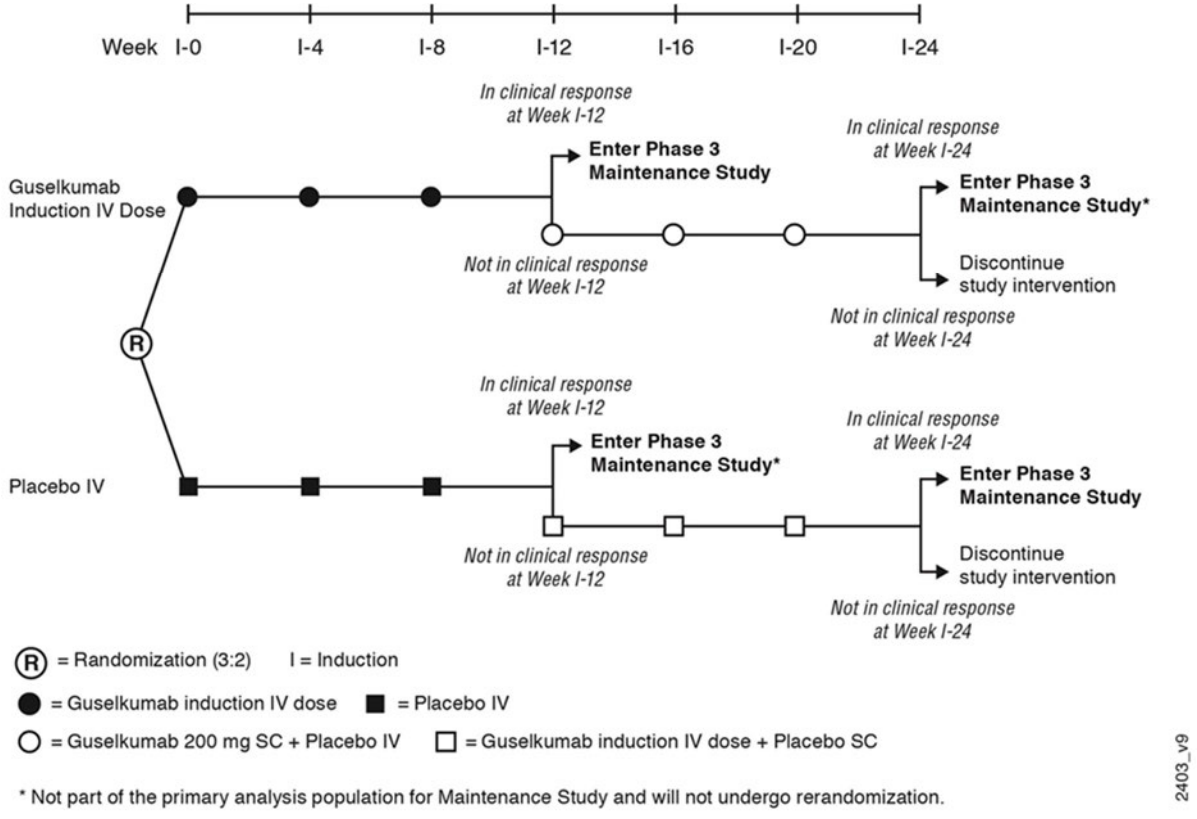
responders at Week I-12, the following participants from Induction Study 2 will enter the Maintenance Study:

- Placebo crossover responders: Participants initially randomized to placebo who are not in clinical response at Week I-12 who then crossover to guselkumab induction IV dose treatment and achieve clinical response at Week I-24.
- Guselkumab 24-Week responders: Participants initially randomized to guselkumab who are not in clinical response at Week I-12 who then receive 3 doses of guselkumab 200 mg SC and achieve clinical response at Week I-24.

Participants who are not in clinical response at Week I-24 will not receive further study intervention and should have a safety follow-up visit approximately 12 weeks after their last dose of study intervention.

All UC-specific medical therapies (ie, oral 5-ASA compounds, oral corticosteroids, 6-MP, AZA, or MTX) must be maintained at a stable dose through to the end of Induction Study 2 and can only be discontinued or reduced in dose if investigator judgment requires it because of toxicity or medical necessity (Section 6.5). The initiation or increase in dose of UC-specific therapies (or any restricted/prohibited medication or therapy) during Induction Study 2 will prohibit a participant from entering the Maintenance Study (Section 6.5.2).

Figure 3: Study Schema for Induction Study 2 (Phase 3 Induction Study)



Note: Treatment groups for the Phase 3 Maintenance Study are described in Section 4.1.3 and Figure 4 of the protocol.

Efficacy, PK parameters, biomarkers, and safety will be assessed according to the SoA (Section 1.3.1).

Two DBLs are planned for Induction Study 2. The first will occur when all randomized participants have completed the Week I-12 visit or have terminated study participation prior to Week I-12. The second DBL will occur when all randomized participants in Induction Study 2 have either entered the Maintenance Study, or have completed their final safety visit (12 weeks after the last dose of study intervention) for those not participating in the Maintenance Study, or have terminated their study participation.

4.1.3. Maintenance Study (Phase 3 Maintenance Study)

The study population for the Phase 3 Maintenance Study will be clinical responders from Induction Study 1 or Induction Study 2. The following populations will be rerandomized in a 1:1:1 ratio to guselkumab 200 mg SC q4w, guselkumab 100 mg SC q8w, or placebo SC:

- Guselkumab clinical responders at Week I-12.
- Placebo crossover responders at Week I-24.

Participants will be allocated to an intervention group using permuted block randomization stratified by clinical remission status at maintenance baseline (Yes/No), concomitant use of corticosteroids at maintenance baseline (Yes/No), and induction treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover [guselkumab 200 mg], and placebo crossover [guselkumab 400 mg, if chosen as the Phase 3 guselkumab induction dose]). The primary analysis population of the Maintenance Study will comprise randomized and treated participants who have a modified Mayo score of 5 to 9 at induction baseline. In addition to the aforementioned randomized population, guselkumab 24-Week responders and induction placebo responders at Week I-12 from Induction Study 1 or Induction Study 2 will enter the Maintenance Study but will not be rerandomized.

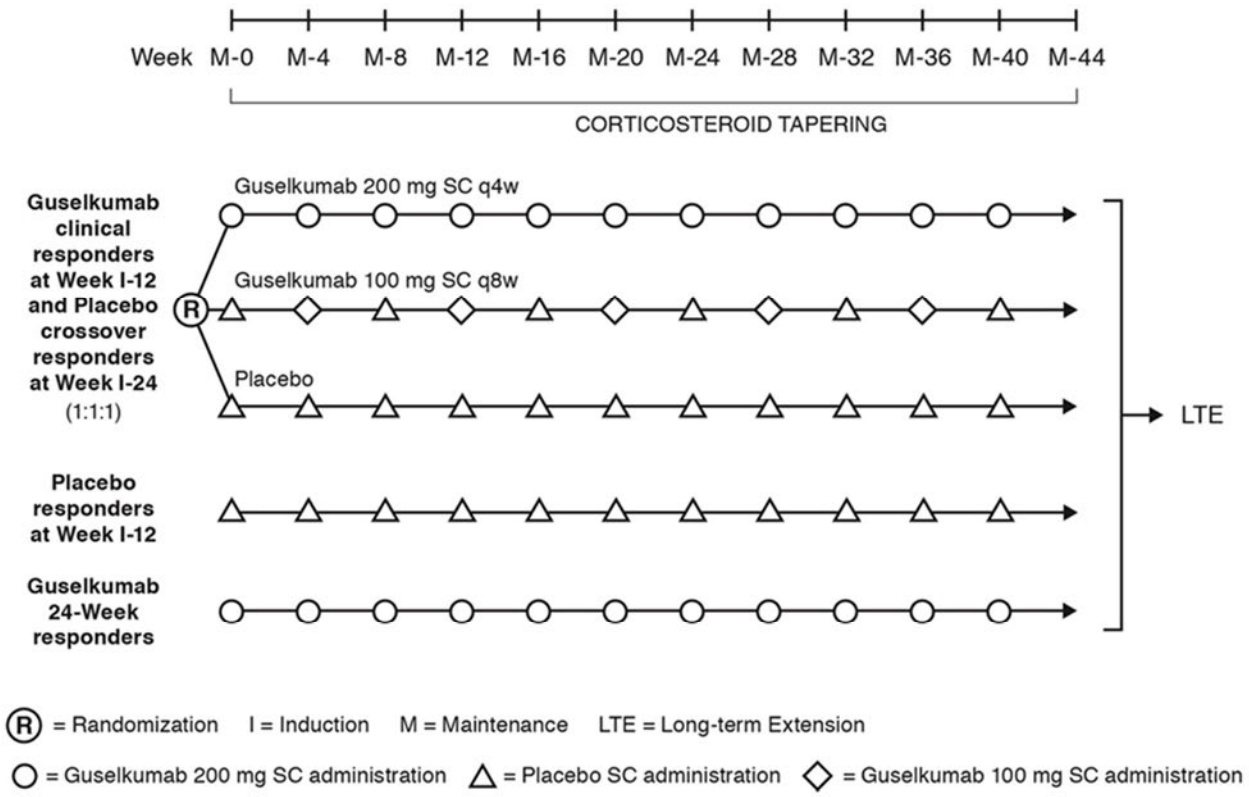
Treatment assignments for these groups are shown in the study schema (Figure 4). Placebo SC q8w will be given to the guselkumab 100 mg SC q8w group starting at Week M-0 to maintain the blind throughout the duration of the Maintenance Study. Further information on study intervention administration for the Maintenance Study is provided in Section 6.1.3.

Participants meeting criteria for loss of clinical response (ie, no longer satisfies the definition of clinical response as previously defined in Section 3) during the Maintenance Study will be eligible for a single blinded dose adjustment as described in Section 6.6.1. For additional details on the management of clinical flare and loss of clinical response see Section 4.1.3.1.

For participants who are receiving oral corticosteroids on entry in the Maintenance Study, the investigator must begin tapering the daily dose of corticosteroids at Week M-0 (Section 6.5.1). Other UC-specific medical therapies (ie, oral 5-ASA compounds, 6-MP, AZA, or MTX) must be maintained at stable doses through Week M-44 unless investigator judgment requires that the therapy be discontinued, or the dose reduced because of toxicity or medical necessity (Section 6.5).

Tapering of the daily dose of corticosteroids may be paused for participants meeting clinical flare criteria.

Figure 4: Study Schema for Maintenance Study (Phase 3 Maintenance Study)



Guselkumab 24-Week responders: Participants initially randomized to guselkumab who are not in clinical response at Week I-12 who then receive 3 doses of guselkumab 200 mg SC and achieve clinical response at Week I-24.

Placebo crossover responders: Participants initially randomized to placebo who are not in clinical response at Week I-12 who then crossover to guselkumab induction IV dose treatment and achieve clinical response at Week I-24.

Note: Participants in the Maintenance Study who meet criteria for loss of clinical response may be eligible for a single blinded dose adjustment (Section 6.6.1).

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Efficacy, PK parameters, biomarkers, and safety will be assessed according to the Maintenance Study SoA (Section 1.3.2).

Participants who complete the safety and efficacy evaluations (including the required endoscopy procedure) at Week M-44 of the Maintenance Study and who may benefit from continued study intervention, in the opinion of the investigator, will have the opportunity to participate in the LTE of the Maintenance Study (Section 4.1.3.2).

A DBL is planned for Week M-44 when all participants in the Maintenance Study have either completed the Week M-44 visit or have terminated study participation before Week M-44.

4.1.3.1. Management of Clinical Flare and Loss of Clinical Response

During the Maintenance Study, participants who meet the following criteria will be considered to be in clinical flare:

- an increase from maintenance baseline in the partial Mayo score (ie, the Mayo score without the endoscopy subscore) of at least 2 points and an absolute partial Mayo score ≥4;

  OR

- an absolute partial Mayo score ≥7 points (Section 8.1.1).

Participants in clinical flare between Week M-4 and Week M-32 (inclusive) will be evaluated for loss of clinical response based on the modified Mayo score that includes the endoscopy subscore assigned by the local endoscopist relative to their induction baseline Mayo score. Loss of clinical response means that a participant no longer satisfies the following definition of clinical response:

- a decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.

The management of clinical flare and loss of clinical response during the Maintenance Study is summarized in Figure 5 and described below.

Participants in clinical flare for the first time between Week M-4 and Week M-32 (inclusive) should undergo endoscopy, which need only be a sigmoidoscopy, and be evaluated for loss of clinical response (Table 2 footnote b). These participants should maintain stable doses of their UC medications after meeting clinical flare criteria and while waiting for their endoscopy subscore to establish loss of clinical response. Participants who meet the criteria for loss of clinical response will be eligible for a single blinded dose adjustment as detailed in Section 6.6.1. The dose adjustment can only start between Weeks M-8 and M-32.

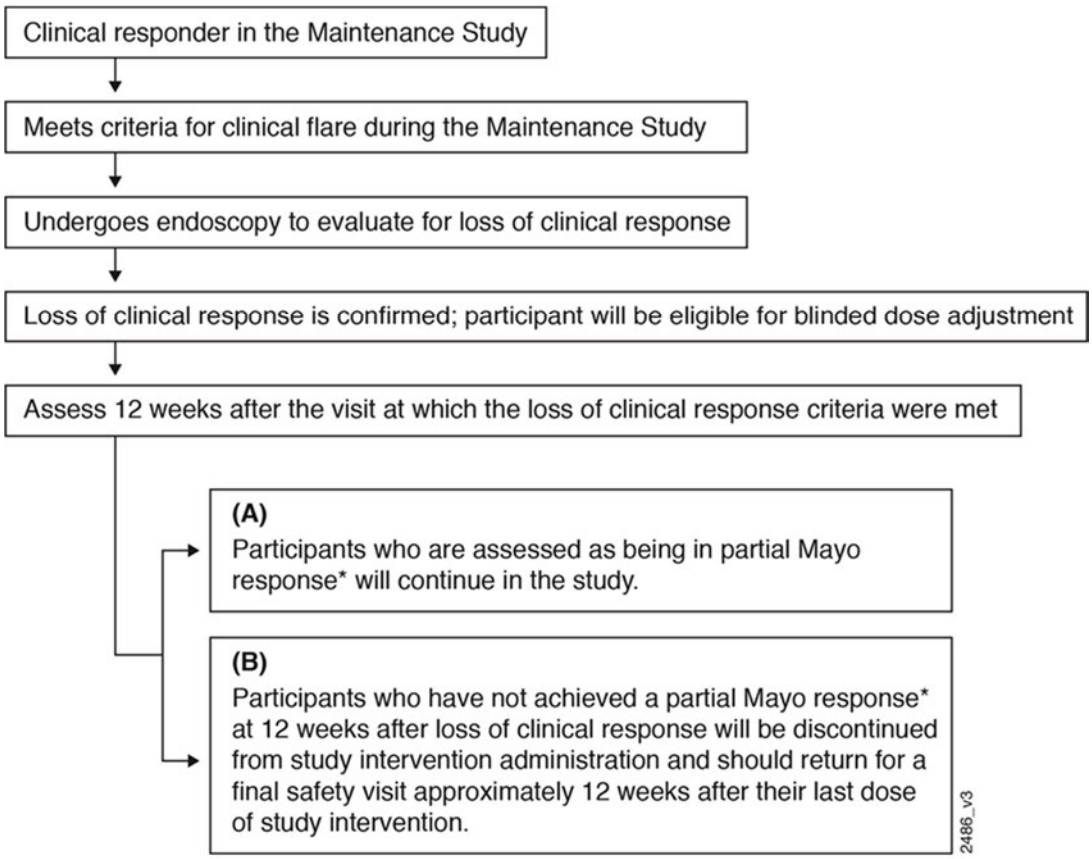
Participants are strongly encouraged to undergo endoscopy at the time of first clinical flare to establish if loss of clinical response criteria were met. A participant who declines to undergo an endoscopy on initial clinical flare of UC will be discontinued from study intervention administration and should return for a final safety visit approximately 12 weeks after their last dose of study intervention.

Participants who meet the criteria for loss of clinical response will be assessed 12 weeks after the visit at which the loss of clinical response criteria were met. During this 12-week interval, clinical flare criteria will not be applied. Participants who have not achieved a partial Mayo response (ie, a decrease from induction baseline of ≥2 in the partial Mayo score) at 12 weeks after meeting the criteria for loss of clinical response will be discontinued from study intervention administration and should return for a final safety visit approximately 12 weeks after their last dose of study intervention.

Participants who are assessed as being in partial Mayo response 12 weeks after loss of clinical response will continue in the study and continue to be assessed for clinical flare using the criteria based on the partial Mayo score.

A participant who meets the criteria of clinical flare on more than 1 occasion will not undergo a second evaluation for the loss of clinical response and may be discontinued from study intervention administration. If discontinued, the participant should return for a final safety visit approximately 12 weeks after their last dose of study intervention. Refer to considerations for discontinuation of study intervention for worsening of UC (Section 7.1.2).

Figure 5: Management of Clinical Flare and Loss of Clinical Response During the Maintenance Study



* A decrease from induction baseline of ≥2 in the partial Mayo score.

4.1.3.2. Long-term Extension of the Maintenance Study

The LTE of the maintenance study begins **after** the assessments listed for the M-44 visit of the Maintenance Study have been completed and will continue through approximately an additional 4 years of treatment or until the sponsor decides not to pursue an indication in UC, whichever occurs first.

Participants will continue to receive the same study intervention regimen during the LTE that they are receiving at the end of maintenance, with the first dose in the LTE being administered at Week M-44. During the LTE, all participants will be assessed for worsening of disease activity based on the clinical judgment of the investigator. Participants whose UC disease activity worsens during the LTE will be discontinued from study intervention and need to complete the final efficacy

and safety visits. Refer to considerations for discontinuation of study intervention for worsening of UC in Section 7.1.2.

During the LTE, all concomitant medications, including UC-specific medications (except for the prohibited medications listed in Section 6.5.2), may be administered at the discretion of the investigator.

All study evaluations to be performed during the LTE are listed in the SoA (Section 1.3.3).

The study blind will be maintained during the LTE until the last participant in the Maintenance Study has completed the M-44 visit evaluations and the Week M-44 analyses have been completed. Therefore, in order to maintain the blind participants will continue to receive study intervention at all visits until that time. After the Maintenance Study is unblinded to the investigative sites, participants receiving placebo will be terminated from study participation, and participants receiving guselkumab will continue to receive guselkumab, but will have their study visits scheduled to coincide with their dose regimen (either q4w or q8w).

During selected visits during the LTE, at the discretion of the investigator and participant, and after appropriate and documented training, participants will self-administer study intervention at home. Details are provided in Section 4.1.3.2.1.

The final DBL will occur when all participants have completed the final safety visit or terminated participation. Additional DBLs may occur during the LTE for publication or regulatory purposes.

4.1.3.2.1. Self-Administration of Study Intervention (or Administration by Caregiver) at Home

At Week M-44, all participants will receive training on how to self-administer study intervention at the investigative site. A caregiver may also be trained to administer study intervention.

At-home self-administration (or administration by a caregiver) will begin for selected visits according to regional/local regulations and instruction after the Week M-44 visit at the discretion of the investigator and participant, and upon completion of training. Participants who are eligible for self- (or caregiver) study intervention administration will be supplied with study intervention for at-home administration at Week M-44 and will have their first at-home administration at Week M-48. At-home administration will be performed for visits as outlined in the SoA (Section 1.3.3) (if applicable). Participants will record all at-home study intervention administrations on a diary card. Participants will be trained to perform self-evaluation for injection-site reactions and reporting of AEs and concomitant medications. Participants will also be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding. Participants will also continue to have on-site study visits and assessments q8w through the final efficacy visit, as outlined in Section 1.3.3.

Participants who are unable or unwilling to have injections administered away from the site will be required to return to the site for administration of study intervention. Participants will continue

to have study visits and assessments at the investigative site through the final efficacy visit, as outlined in Section 1.3.3.

All participants should return to the site for a safety follow-up visit approximately 12 weeks after their last dose of study intervention.

4.2. Scientific Rationale for Study Design

An operationally seamless Phase 2b/3 clinical development program was selected because it incorporates dose range finding and improves overall efficiency. Two induction dose regimens of guselkumab will be evaluated in Induction Study 1 with the intention of selecting 1 of these doses as the single induction dose regimen for Induction Study 2. Induction Study 1 and Induction Study 2 will both serve as feeder studies of guselkumab clinical responders for the Phase 3 randomized withdrawal maintenance study.

Since participants could have responded to 1 of 2 different guselkumab induction dose regimens being evaluated in Induction Study 1, the guselkumab induction dose regimen will serve as a stratification variable in the Maintenance Study. Therefore, the potential impact of the 2 IV induction dose levels on maintenance efficacy will be taken into account for the assessment of 2 guselkumab SC maintenance regimens versus placebo. The Maintenance Study will evaluate 2 maintenance dose regimens of guselkumab (ie, 100 mg SC q8w and 200 mg SC q4w) compared with placebo (ie, withdrawal of guselkumab) to establish the need and optimal dose regimen for maintenance treatment. More details regarding the dose selection are provided in Section 4.3.

The study population is consistent with regulatory guidance as well as recently completed and ongoing Phase 3 clinical development programs evaluating biologic agents for the treatment of moderately to severely active UC (European Medicines Agency 2018; Feagan 2013; Food and Drug Administration 2016; Mirikizumab NCT03518086, NCT03524092; Risankizumab NCT03398135, NCT03398148; Sandborn 2017). The primary analysis population for all 3 studies will be randomized and treated participants with a modified Mayo score of 5 to 9 at induction baseline. However, the protocol also allows for the enrollment of participants with a modified Mayo score of 4, which is capped at ≤5% of the total population. The modified Mayo score is the 3-component (stool frequency, rectal bleeding, and endoscopy subscores) Mayo score without the physician's global assessment. The study population reflects the high unmet medical need in UC as participants must have demonstrated an inadequate response or failure to tolerate conventional (ie, 6-MP, AZA, or corticosteroids) or advanced therapy (ie, TNFα antagonists, vedolizumab, or tofacitinib) to be eligible.

The timing of the short and long-term efficacy measures in this program is consistent with regulatory guidance (European Medicines Agency 2018; Food and Drug Administration 2016). The length of study periods is thought sufficient to evaluate induction and maintenance efficacy (in the context of a randomized withdrawal design). Participants on corticosteroids will undergo mandatory tapering according to pre-defined recommended tapering schedule as obtaining corticosteroid-free clinical remission is an important goal of therapy (Kornbluth 2010).

4.2.1. Blinding, Control, Study Phase/Periods, Intervention Groups

Placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Participants initially randomized to placebo during the induction studies who are not in clinical response at Week I-12 will crossover to guselkumab induction treatment. At Week I-12, guselkumab clinical nonresponders will receive guselkumab SC and placebo IV to maintain the blind and not to reveal previous treatment received.

Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. In addition, there are distinct stratification variables for the induction and maintenance studies to ensure balance across intervention groups which have been used in recent UC studies per the recommendation of health authorities (Danese 2019; Feagan 2013; Sandborn 2017).

4.2.2. Biomarker and DNA Collection

Biomarker samples (where local regulations permit) will be collected to evaluate the cellular and molecular mechanism of action of guselkumab, or help to explain interindividual variability in clinical outcomes, or to identify population subgroups that respond differently to an intervention. Serum biomarkers will be collected from whole blood in all participants to assess PD markers associated with the IL-23 pathway, and with response to guselkumab. Whole blood samples will be collected from all participants to assess the effect of study intervention on ribonucleic acid (RNA) expression profiles. Colonic biopsies will also be obtained from all participants to assess cellular and molecular changes within the colonic tissue, including association of clinical response with enrichment of a molecular predictive signature obtained at baseline. Fecal samples will be collected from all participants to measure inflammatory proteins and potential changes in microbiome composition. The goal of the biomarker analyses is to further define the mechanism of action of the selective blockade of IL-23 with guselkumab in UC and aid in evaluating the intervention-clinical response relationship.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

An optional pharmacogenomic substudy is planned. It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis (Cuffari 2010; Li 2016; Ye 2016). Pharmacogenomic research may help to explain interindividual variability in clinical outcomes, identify markers associated with disease susceptibility and prognosis, and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow for the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of guselkumab and to identify genetic factors associated with UC or the response to guselkumab

treatment. The focus of this analysis will be the evaluation of genetic single nucleic polymorphisms (SNP) associated with UC and response to treatment with guselkumab. No genetic research will be done on samples from participants unless specific consent is provided by signing the Optional Genetic Research informed consent form (ICF).

4.2.3. Health Economic Assessments

Medical resource utilization evaluations, all medical encounters including UC-related hospitalizations and UC-related surgeries, will be collected for evaluation of the health economics of guselkumab treatment. Additionally, the impact of guselkumab treatment on work productivity will be assessed using the WPAI-GH.

4.2.4. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected from each participant in this study is less than the American Red Cross standard limit for whole blood donation (approximately 475 mL q8w) and is, therefore, considered an acceptable amount of blood to be collected over this time. For more details regarding blood collection, see Blood Sample Collection in Section 8.

4.3. Justification for Dose

This section provides the rationale for the dose regimens to be evaluated in the guselkumab Phase 2b/3 UC clinical development program. Published data in UC from mAbs with the same mechanism of action (anti-IL-23, eg, mirikizumab [Geert 2019; Reich 2019; Sandborn 2018]) and a similar mechanism of action (anti-IL-12/23, eg, ustekinumab [Sands 2019]) were considered.

4.3.1. Induction Dose Regimens

Induction Study 1 (Phase 2b Induction Dose-Ranging Study)

For Induction Study 1, 2 guselkumab dose regimens will be investigated compared with placebo:

- Guselkumab 400 mg IV at Weeks I-0, I-4, and I-8
- Guselkumab 200 mg IV at Weeks I-0, I-4, and I-8

The selection of the guselkumab induction dose regimens for Induction Study 1 was based on the interim results from the guselkumab Phase 2/3 Crohn's disease program (guselkumab NCT03466411) and considered data from a mirikizumab Phase 2 UC study (Sandborn 2018).

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In the guselkumab Phase 2 Crohn's disease study, 3 guselkumab IV induction dose regimens were assessed (200 mg, 600 mg, and 1200 mg IV at Weeks 0, 4, and 8). A Dose Selection Committee reviewed the unblinded Week 12 interim analysis and recommended the guselkumab 200 mg IV induction dose for confirmatory evaluation in Phase 3. The only currently approved agent that targets IL-23, ustekinumab (also targeting IL-12), employed a similar dosing regimen in Crohn's disease and UC, suggesting that the 200 mg IV regimen may also be appropriate for study in UC. However, UC may need an induction dose higher than 200 mg IV, as patients with UC may have a higher inflammatory burden and a "leakier" gut (ie, leading to increased drug clearance) compared to Crohn's disease (Furfaro 2015; Levitt 2017). Therefore, it is also reasonable to evaluate a higher induction dose, eg 400 mg IV. Of note, the guselkumab 200 mg IV induction dose is also being tested in an ongoing Phase 2a combination therapy study with guselkumab and golimumab in participants with UC (guselkumab and golimumab NCT03662542).

The safety of 200 mg and 600 mg IV regimens in the Phase 2b Crohn's disease trial was acceptable. A single case of potential drug-induced liver injury possibly related to guselkumab was reported in a participant who received the guselkumab 1200 mg IV dose regimen. Compared to the guselkumab 1200 mg IV dose, the guselkumab 400 mg IV dose would provide an approximately 3-fold lower exposure. In addition, the predicted exposure margin for 400 mg IV relative to the NOAEL of 50 mg/kg/week in cynomolgus monkeys is approximately 10- to 13-fold (Table 4), which is considered adequate to support the limited duration of IV dosing (ie, 3 doses over 12 weeks). For context, mirikizumab and risankizumab (both anti-IL-23 mAbs) have been studied at up to 1000 mg IV given q4w for 12 weeks in participants with UC (Sandborn 2019a) and up to 600 mg IV given q4w for 6 months in participants with Crohn's disease (Feagan 2017), respectively, and both were reported to be well tolerated.

Based on these considerations, guselkumab induction doses of 200 mg and 400 mg IV were selected for evaluation in the Phase 2b induction dose-ranging study. Overall, the potential benefit to patients with UC appear to outweigh the known and potential risks of the 2 guselkumab induction doses (200 mg IV and 400 mg IV) to be evaluated in this Phase 2b induction dose-ranging study.

Induction Study 2 (Phase 3 Induction Study)

Based on data from the interim analysis of Induction Study 1, a single guselkumab induction dose will be selected for further evaluation in Induction Study 2 and compared to placebo. This choice will be based on the totality of data at the time of dose selection, including efficacy, safety, and dose/exposure-response.

4.3.2. Maintenance Dose Regimens

For the Maintenance Study, 2 guselkumab dose regimens will be investigated and compared with placebo:

- Guselkumab 100 mg SC q8w
- Guselkumab 200 mg SC q4w

The selected guselkumab SC maintenance dose regimens are lower than the selected induction IV dose regimens, taking into account dose level, dosing frequency, and the SC bioavailability of approximately 50% (as reported in a Phase 1 study in healthy subjects [refer to the guselkumab IB]). The posology of other biologics (including infliximab [USPI/SmPC], adalimumab [USPI/SmPC], golimumab [USPI/SmPC], vedolizumab [USPI/SmPC], and ustekinumab [USPI/SmPC]) in UC suggests that once the disease inflammatory burden is reduced, the drug exposures required to maintain efficacy may be lower than the exposures required for induction (Côté-Daigneault 2015). These 2 guselkumab maintenance dose regimens were selected based on the Phase 2 maintenance efficacy data from mirikizumab (Geert 2019) and Phase 3 pivotal study efficacy data from ustekinumab (Sands 2019) in the treatment of UC.

A guselkumab maintenance dose regimen of 100 mg SC q8w, anchored at the approved psoriasis dose, was selected for the Maintenance Study. This guselkumab maintenance dose (ie, 100 mg SC q8w) is expected to provide efficacy similar to, or greater than that observed with ustekinumab (anti-IL-12/23 mAb) 90 mg SC q8w, the approved maintenance dose regimen for the treatment of UC (USPI/SmPC). In the ustekinumab UC Phase 3 clinical program, among patients who had a response to induction therapy with ustekinumab and underwent a second randomization, the 90 mg SC q8w maintenance regimen resulted in 44% of patients achieving clinical remission at Week 44 (compared to 24% for those patients assigned to placebo) (Sands 2019). Additionally, the guselkumab 100 mg SC q8w maintenance regimen is being tested in an ongoing Phase 2a combination therapy study with guselkumab and golimumab in participants with UC (guselkumab and golimumab NCT03662542).

A higher guselkumab maintenance dose regimen of 200 mg SC q4w was also selected for the Maintenance Study to ascertain if higher efficacy is possible. The maintenance efficacy observed

for mirikizumab 200 mg SC q4w in the Phase 2 UC study supports this selection. In this Phase 2 UC study, a dose-response in maintenance efficacy was shown with the mirikizumab 200 mg SC q4w and 200 mg SC q12w dose regimens (Geert 2019). Among participants who achieved a clinical response to mirikizumab induction treatment at Week 12, the 200 mg SC q4w and 200 mg SC q12w regimens resulted in 47% and 37% of participants in remission at Week 52, respectively. In addition, among those in clinical remission at Week 12, 61% (200 mg q4w) and 39% (200 mg q12w) remained in clinical remission at Week 52. These data demonstrate that higher efficacy was observed based on key endpoints with the 200 mg SC q4w regimen relative to 200 mg SC q12w.

Of note, the maintenance dose regimens selected for this UC program are the same as those that are being evaluated in the ongoing guselkumab Phase 2/3 Crohn's disease study (guselkumab NCT03466411). Overall, the 2 guselkumab maintenance dose regimens (ie, 200 mg SC q4w and 100 mg SC q8w) would provide an approximately 4-fold dose range for the dose/exposure-response assessment of maintenance therapy in the treatment of UC.

With respect to safety of the maintenance dose regimens, and as shown in Table 4, the predicted exposure margins for the highest SC dose (200 mg q4w) relative to the NOAEL of 50 mg/kg/week in cynomolgus monkeys are approximately 33 to 40, which is considered adequate to support the long-term SC dosing (for chronic maintenance) in the guselkumab UC clinical development programs. Guselkumab is approved for the treatment of plaque psoriasis with a good long-term clinical safety profile (with data generated primarily at 100 mg SC q8w), and dose regimens as high as 200 mg SC q8w have been shown to have favorable safety in a 6 month Phase 2 trial in rheumatoid arthritis (Smolen 2017). In addition, mirikizumab (anti-IL-23 mAb) has been studied in participants with UC at up to 200 mg SC q4w for 40 weeks following the 12 week IV induction treatment, and was reported to be well tolerated (Geert 2019).

4.4. End of Study Definition

End of Study Definition

For each of the 3 studies conducted under this protocol, the study is considered completed when the last participant completes the last scheduled study assessment as shown in the SoA (Section 1.3), or if a decision has been made by the sponsor not to pursue an indication in UC. For each study, the final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed Induction Study 1 or Induction Study 2 if he or she completed all the assessments at either Week I-12 or Week I-24, and completed the final safety follow-up visit if applicable. A participant will be considered to have completed the Maintenance Study if he or she completed the Week M-44 assessments and the final safety follow-up visit if applicable. Participants who prematurely discontinue study intervention for any reason before completion of either of the 3 studies can be considered to have completed the study if they have completed the follow-up assessments as indicated on the SoA (Section 1.3).

5. STUDY POPULATION

Screening for eligible participants will be performed within 8 weeks before administration of the study intervention. Refer to Section 5.4, Screen Failures, for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in Induction Study 1 or Induction Study 2 are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in either induction study. Waivers are not allowed.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in Induction Study 1 or Induction Study 2:

1. Male or female, 18 years of age or older.

2. Documented diagnosis (histological and either endoscopic or radiographic) of UC at least 3 months prior to screening. A biopsy report supporting the diagnosis must be available in the source documents.

3. Moderately to severely active UC, defined as a baseline (Week I-0) modified Mayo score of 4 to 9, inclusive, using the Mayo endoscopy subscore obtained during the central review of the video endoscopy.

4. Mayo rectal bleeding subscore ≥1 at baseline.

5. Screening endoscopy with ≥2 on the endoscopy subscore of the Mayo score as obtained during the central review of the video endoscopy.

6. A participant who had extensive colitis for ≥8 years, or disease limited to the left side of the colon for ≥10 years, must either have had a full colonoscopy to assess for the presence of dysplasia within 1 year before the first dose of study intervention or a full colonoscopy to assess for the presence of malignancy at the screening visit.

7. A participant ≥45 years of age must either have had a full colonoscopy to assess for the presence of adenomatous polyps within 5 years before the first dose of study intervention or a full colonoscopy to assess for the presence of adenomatous polyps at the screening visit. The adenomatous polyps must be removed before the first dose of study intervention.

Concomitant or previous medical therapies received

8. A participant must:

    a. Have failed an advanced therapy, ie, have received treatment with 1 or more TNFα antagonists, vedolizumab, or tofacitinib at a dose approved for the treatment of UC, and have a documented history of failure to respond to or tolerate such treatment as defined in Appendix 2 (Section 10.2) and Appendix 3 (Section 10.3);

    OR

    b. Be naïve to advanced therapy (ie, TNFα antagonists, vedolizumab, and tofacitinib) or not have demonstrated a history of failure to respond to, or tolerate, advanced therapy **and** have a prior or current UC medication history that includes at least 1 of the following:

        1) Inadequate response to or failure to tolerate current treatment with oral corticosteroids or immunomodulators (6-MP or AZA) as defined in Appendix 4 (Section 10.4).

        OR

        2) History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA) as defined in Appendix 4 (Section 10.4).

        OR

        3) History of corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of UC) as defined in Appendix 4 (Section 10.4).

9. Before the first dose of study intervention, the following conditions must be met:

    a. If receiving conventional immunomodulators (ie, AZA, 6-MP, or MTX), must have been taking them for ≥12 weeks, and on a stable dose for at least 4 weeks.

    b. If AZA, 6-MP, or MTX has been recently discontinued, it must have been stopped for at least 4 weeks.

    c. If receiving oral 5-ASA compounds, the dose must have been stable for at least 2 weeks.

    d. If receiving oral corticosteroids other than budesonide or beclomethasone dipropionate, the dose must be ≤20 mg/day prednisone or its equivalent and must have been stable for at least 2 weeks.

    e. If receiving oral budesonide or beclomethasone dipropionate, the dose must have been stable for at least 2 weeks.

    f. If oral 5-ASA compounds or oral corticosteroids have been recently discontinued, they must have been stopped for at least 2 weeks.

10. The following medications/therapies must have been discontinued before the first dose of study intervention:

    a. Vedolizumab for at least 12 weeks.
    b. Tofacitinib and other inhibitors of JAK for at least 2 weeks or 5 half-lives, whichever is longer.
    c. TNFα-antagonist therapy (eg, infliximab, adalimumab, or golimumab [or approved biosimilars for these therapies]) for at least 8 weeks.
    d. Cyclosporine, mycophenolate mofetil, tacrolimus, or sirolimus for at least 4 weeks.
    e. 6-thioguanine must have been discontinued for at least 4 weeks.
    f. Rectal corticosteroids (ie, corticosteroids administered to the rectum or sigmoid colon via foam or enema or suppository) for at least 2 weeks.
    g. Rectal 5-ASA compounds (ie, 5-ASAs administered to the rectum or sigmoid colon via foam or enema or suppository) for at least 2 weeks.
    h. Parenteral corticosteroids for at least 2 weeks.
    i. Total parenteral nutrition or enteral nutrition for at least 2 weeks.
    j. Antibiotics for the primary treatment of UC (eg, ciprofloxacin, metronidazole, or rifaximin) for at least 2 weeks.

Screening laboratory tests

11. Screening laboratory test results within the following parameters, and if 1 or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted during the approximately 8-week screening period:

    a. Hemoglobin ≥8.0 g/dL (International System of Units [SI]: ≥80.0 g/L)
    b. White blood cell count (WBC) $\geq 3 \times 10^3$ cells/μL (SI: $\geq 3.0 \times 10^9$ cells/L)
    c. Neutrophils $\geq 1.5 \times 10^3$ cells/μL (SI: $\geq 1.5 \times 10^9$ cells/L)
    d. Platelets $\geq 100 \times 10^3$ cells/μL (SI: $\geq 100 \times 10^9$ cells/L)
    e. Serum creatinine ≤1.5 mg/dL (SI: ≤133 μmol/L)
    f. ALT and AST concentrations must be ≤2 times the upper limit of the normal range for the laboratory conducting the test.
    g. Direct (conjugated) bilirubin <1.0 mg/dL.

Tuberculosis

12. Is considered eligible according to the following TB screening criteria:

    a. Has no history of latent or active TB before screening. An exception is made for participants who have a history of latent TB AND satisfy one of the following criteria:

1) are currently receiving treatment for latent TB

OR

2) will initiate treatment for latent TB before the first dose of study intervention

OR

3) have documentation of having completed appropriate treatment for latent TB within 5 years before the first dose of study intervention. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculous treatment and provide appropriate documentation. Patients with a history and documentation of having completed appropriate treatment for latent TB more than 5 years before the first dose of study intervention are not eligible.

b. Has no signs or symptoms suggestive of active TB based on medical history and/or physical examination.

c. Has had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before the first dose of study intervention.

d. Criterion modified per Amendment 3.

d.1. Within 8 weeks prior to the first dose of study intervention, have a negative QuantiFERON-TB® (or T-SPOT® for sites in Japan) test result, or have a newly identified positive QuantiFERON-TB® test (or T-SPOT® for sites in Japan) in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first dose of study intervention (see Section 8.2.11). Indeterminate or borderline results should have the test repeated as described in Section 8.2.11.

Note: A negative tuberculin skin test result (see Appendix 5 [Section 10.5]) is additionally required if the QuantiFERON-TB® test is not approved/registered in the country/territory in which this protocol is being conducted. In Ukraine, while the QuantiFERON-TB® test is not approved/registered, it is acceptable, and an additional tuberculin skin test is not required. The QuantiFERON-TB® (or T-SPOT® for sites in Japan) test and the tuberculin skin test are not required at screening for participants with a history of latent TB, if active TB has been ruled out, and if appropriate treatment has been initiated/completed as described above in Inclusion Criterion #12a.

e. Criterion modified per Amendment 1.

e.1. Criterion modified per Amendment 3.

e.2. Has a chest radiograph (both posterior-anterior and lateral views, or per country/territory regulations where applicable), taken within 12 weeks before the first dose of study intervention and read by a qualified radiologist or qualified pulmonologist according to local clinical practice, with no evidence of current, active TB or old, inactive TB. A chest CT scan is also acceptable if obtained instead of a chest radiograph outside of the protocol.

Contraception

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

13. A woman of childbearing potential must have a negative urine pregnancy test at screening and at Week 0.

14. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 12 weeks after the last dose of study intervention.

15. Before randomization, a woman must be (as defined in Appendix 6 [Section 10.6], Contraceptive and Barrier Guidance and Collection of Pregnancy Information):

    a. Not of childbearing potential

    OR

    b. Of childbearing potential and:

        - If heterosexually active, practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 12 weeks after last dose (ie, the end of relevant systemic exposure). Examples of highly effective methods of contraception are located in Appendix 6 (Section 10.6), Contraceptive and Barrier Guidance and Collection of Pregnancy Information; however, the method selected must meet local/regional regulations/guidelines for highly effective contraception.

    Note: If a participant's childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin using a highly effective method of contraception, as described above.

16. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control, eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

17. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 12 weeks after receiving the last dose of study intervention.

General

18. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the participant and his or her legally acceptable representative.

19. Must sign a separate ICF if he or she agrees to provide optional DNA samples for research where local regulations permit. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the participant and his or her legally acceptable representative. Refusal to give consent for the optional DNA samples does not exclude a participant from participation in the study.

20. Must be willing and able to adhere to all specified requirements, including but not limited to completion of the required assessments, adherence to the visit schedule, and compliance with the lifestyle restrictions as specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in Induction Study 1 or Induction Study 2:

1. Severe extensive colitis as evidenced by:

    a. Current hospitalization for the treatment of UC.

    OR

    b. Investigator judgment that the participant is likely to require a colectomy within 12 weeks of baseline.

    OR

    c. Symptom complex at screening or baseline visits that includes at least 4 of the following:

        1) Diarrhea with ≥6 bowel movements/day with macroscopic blood in stool
        2) Focal severe or rebound abdominal tenderness
        3) Persistent fever (temperature ≥38°C)
        4) Tachycardia (>100 beats/minute)
        5) Anemia (hemoglobin <8.5 g/dL)

2. UC limited to the rectum only or to <20 cm of the colon.

3. Presence of a stoma.

4. Presence or history of a fistula.

5. Require, or required within the 2 months before screening, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage, or other conditions possibly confounding the evaluation of benefit from study intervention treatment.

6. Presence of symptomatic colonic or small bowel obstruction, confirmed by objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the colon or small bowel proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy).

7. History of extensive colonic resection (eg, less than 30 cm of colon remaining) that would prevent adequate evaluation of the effect of study intervention on clinical disease activity.

8. History of colonic mucosal dysplasia. Participants will not be excluded from the study because of a pathology finding of "indefinite for dysplasia with reactive atypia."

9. Presence on screening endoscopy of adenomatous colonic polyps, if not removed before study entry, or history of adenomatous colonic polyps that were not removed.

10. Diagnosis of indeterminate colitis, microscopic colitis, ischemic colitis, or Crohn's disease or clinical findings suggestive of Crohn's disease.

11. Criterion modified per Amendment 1.

    11.1 Stool culture or other examination positive for an enteric pathogen, including *Clostridium difficile* toxin, within 4 months before the first dose of study intervention, unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen. Note: If time allows, treatment and repeat testing can occur in the current screening period.

Concomitant or previous medical therapies received

12. Has received the following prescribed medications or therapies:

    a. A biologic therapy targeted at IL-12 and/or IL-23 (eg, ustekinumab, briakinumab, guselkumab, mirikizumab, tildrakizumab, brazikumab, or risankizumab).

    b. Natalizumab within 12 months of the first dose of study intervention.

    c. Agents that deplete B or T cells (eg, rituximab, alemtuzumab) within 12 months of the first dose of study intervention or continue to manifest depletion of B or T cells more than 12 months after completion of therapy with lymphocyte-depleting agents.

d. Any investigational drug/therapy within 4 weeks before the first dose of study intervention or within 5 half-lives of the investigational agent, whichever is longer.

e. Apheresis (eg, Adacolumn or Cellsorba apheresis) within 2 weeks before the first dose of study intervention.

f. Fecal microbiota transplantation within 12 weeks before the first dose of study intervention.

Infections or predisposition to infections

13. History of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Inclusion Criterion #12 for information regarding eligibility with a history of latent TB.

14. History of, or ongoing, chronic or recurrent infectious disease, including but not limited to, recurrent sinopulmonary infections, bronchiectasis, recurrent renal/urinary tract infection (eg, recurrent pyelonephritis, recurrent cystitis), an open, draining, or infected skin wound, or an ulcer.

15. Chest radiograph within 12 weeks before the first dose of study intervention that shows an abnormality suggestive of a malignancy or current active infection, including TB.

16. History of being human immunodeficiency virus (HIV) antibody-positive, or tests positive for HIV at screening.

17. Criterion modified per Amendment 2.

    17.1. Is seropositive for antibodies to hepatitis C virus (HCV), unless they satisfy 1 of the following conditions:

    a. Has a history of successful treatment, defined as being negative for HCV RNA at least 12 weeks after completing antiviral treatment, and has a negative HCV RNA test result at screening,

    OR

    b. While seropositive, has a negative HCV RNA test result at least 12 weeks prior to screening and a negative HCV RNA test at the screening.

18. Tests positive for hepatitis B virus (HBV) infection, see (Appendix 7 [Section 10.7]).

    Note: For participants who are not eligible for this study due to HIV, HCV, and HBV test results, consultation with a physician with expertise in the treatment of those infections is recommended.

19. Bacille Calmette-guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks of baseline.

20. Has or has had a nontuberculous mycobacterial infection or clinically significant opportunistic infection (eg, cytomegalovirus colitis, pneumocystosis, invasive aspergillosis).

21. Has had a clinically significant infection (eg, hepatitis, sepsis, pneumonia, pyelonephritis), has been hospitalized for an infection, or has been treated with parenteral antibiotics for an infection within 2 months before the first dose of study intervention. Treated and resolved infections not considered clinically significant at the discretion of the investigator need not be exclusionary (eg, acute upper respiratory tract infection, uncomplicated urinary tract infection).

22. Evidence of a herpes zoster infection within 8 weeks of baseline.

Malignancy or increased potential for malignancy

23. Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a nonmelanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months [defined as a minimum of 12 weeks] before the first dose of study intervention or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first dose of study intervention).

24. History of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly.

Coexisting medical conditions or past medical history

25. History of severe, progressive, or uncontrolled renal, genitourinary, hepatic, hematologic, endocrine, cardiac, vascular, pulmonary, rheumatologic, neurologic, psychiatric, or metabolic disturbances, or signs and symptoms thereof.

26. Transplanted organ (with the exception of a corneal transplant performed >12 weeks before screening).

27. Poor tolerability of venipuncture or lacks adequate venous access for required blood sample collections during the study period.

28. History of drug or alcohol abuse according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), within 1 year before screening.

29. Unstable suicidal ideation or suicidal behavior in the last 6 months that may be defined as a Columbia-Suicide Severity Rating Scale (C-SSRS) rating at screening of: Suicidal

Ideation with Intention to Act ("Ideation level 4"), Suicidal Ideation with Specific Plan and Intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt), and is considered to be at risk by the investigator based on an evaluation by a mental health professional. In addition, participants with C-SSRS ratings of Wish to be Dead ("Ideation level 1"), Non-Specific Active Suicidal Thoughts ("Ideation level 2"), Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act ("Ideation level 3"), or non-suicidal self-injurious behavior who are determined to be at risk by the investigator may not be randomized.

30. Known allergy, hypersensitivity, or intolerance to guselkumab or its excipients (refer to the guselkumab IB).

31. Is a woman who is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 12 weeks after the last dose of study intervention.

32. Is a man who plans to father a child while enrolled in this study or within 12 weeks after the last dose of study intervention.

General

33. Currently participating or intends to participate in any other study using an investigational agent or procedure during the conduct of this study.

34. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

35. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

Infections or predisposition to infections

36. Coronavirus disease 2019 (COVID-19) infection:

    During the 6 weeks prior to baseline, has had **any** of the following: (a) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (test positive) **OR** (b) suspected SARS-CoV-2 infection (clinical features of COVID-19 without documented test results) **OR** (c) close contact with a person with known or suspected SARS-CoV-2 infection.

    - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, [eg, fever, cough, dyspnea])

AND

ii) with absence of all conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

Note on COVID-19-related exclusion:

- The field of COVID-19-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/standards of care.

Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 8 (Section 10.8), Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Lifestyle restriction modified per Amendment 2.

    1.1. Refer to Section 6.5 for details regarding prohibited and restricted therapy during the study.

    It is recommended that participants are up to date on age-appropriate vaccinations prior to screening per routine local medical guidelines. For study participants who received locally-approved (including emergency use-authorized) COVID-19 vaccines recently prior to study entry, consider study eligibility and follow applicable local vaccine labelling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.5.3).

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Must agree not to receive a live virus or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention.

4. Lifestyle restriction modified per Amendment 2.

    4.1. Must agree not to receive a BCG vaccination during the study and for 12 weeks after receiving the last dose of study intervention.

5. Must not receive guselkumab outside of this protocol or participate in any other clinical study with an investigational agent while in this study and must terminate study participation if they do. A participant who intends to participate in any other clinical study with an investigational agent should complete the appropriate visit(s) as described in Section 1.3 before he or she terminates study participation.

6. Must be willing and able to complete daily diaries to document clinical symptoms, AEs, etc.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Completion of screening and randomization procedures within the specified up to 8-week window is required. If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph, endoscopy), the participant will be considered a screen failure because he/she will not meet eligibility criteria, and the expired assessments (along with the non-time-specific laboratory tests) will have to be repeated on rescreening.

Retesting

Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the screening phase, as long as this is done within the specified screening window of up to 8 weeks.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. Rescreened participants should be assigned a new participant number, undergo the informed consent process, and then start a new screening phase.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

Intravenous study intervention (including the flush) should be administered over a period of no less than 1 hour, and not more than 2 hours. The infusion (including the flush) should be completed within 6 hours of preparation.

For visits with both IV and SC dosing during Induction Study 1 or Induction Study 2, the IV study intervention should be administered first. The SC study intervention should be administered approximately 30 minutes after the IV study intervention infusion is complete.

During the Maintenance Study, each group will receive 2 SC injections at each visit. The guselkumab 200 mg SC q4w group will receive 2 injections of 100 mg guselkumab at each visit. The guselkumab 100 mg SC q8w group will receive 1 injection of 100 mg guselkumab and 1 injection of placebo to maintain the blind beginning at Week M-4 and 2 SC injections of placebo at alternate visits. The placebo group will receive 2 SC injections of placebo at each visit. Since multiple SC injections are administered at each visit, each injection of study intervention should be given at a different location of the body.

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF). Study-site personnel will instruct participants on how to store and record study intervention for at-home use as indicated for this protocol.

Guselkumab and placebo for guselkumab are Investigational Medicinal Products (IMPs) and will be manufactured and provided under the responsibility of the sponsor. Refer to the guselkumab IB for a list of excipients.

Detailed instructions on the administration of study intervention will be provided in the Site Investigational Product Procedures Manual (IPPM) and Investigational Product Preparation Instructions (IPPI). Of note, instructions on the administration of study intervention in Induction Study 2 will be finalized and provided to investigative sites when the induction dose decision is made and implemented.

6.1.1. Induction Study 1 (Phase 2b Induction Dose-ranging Study)

6.1.1.1. From Week I-0 Through Week I-12

In Induction Study 1, participants will be randomized to 1 of 3 study intervention groups as described below. Participants will remain on their assigned study intervention through Week I-12.

- **Guselkumab 400 mg IV:** Participants will receive guselkumab 400 mg IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).
- **Guselkumab 200 mg IV:** Participants will receive guselkumab 200 mg IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).
- **Placebo:** Participants will receive placebo IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).

6.1.1.2. From Week I-12 Through Week I-24

Guselkumab

For participants who received 3 IV guselkumab doses (400 mg or 200 mg), subsequent study intervention will be based on clinical response status at Week I-12 as follows:

- Guselkumab clinical responders at Week I-12: Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg SC q8w, or placebo.
- Guselkumab clinical nonresponders at Week I-12: Participants will receive guselkumab 200 mg SC at Weeks I-12, I-16, and I-20. Placebo IV will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-24 (ie, guselkumab 24-Week responders): Participants will enter the Maintenance Study and will receive guselkumab 200 mg SC q4w.
- Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

Placebo

For participants who received 3 IV placebo doses, subsequent study intervention will be based on clinical response status at Week I-12 as follows:

- Placebo clinical responders at Week I-12: Participants will enter the Maintenance Study and receive placebo SC q4w.
- Placebo clinical nonresponders at Week I-12: Participants will receive guselkumab 200 mg IV at Weeks I-12, I-16, and I-20. Placebo SC will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-24 (ie, placebo crossover responders): Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg q8w, or placebo.
- Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

6.1.2. Induction Study 2 (Phase 3 Induction Study)

In Induction Study 2, participants will be randomized to 1 of 2 study intervention groups as described below. Participants will remain on their assigned study intervention through Week I-12.

Guselkumab Induction Dose Regimen

Selection of the Phase 3 guselkumab induction dose for Induction Study 2 will be based on an interim analysis of Induction Study 1. The participants will receive study intervention at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).

At Week I-12, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-12: Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg q8w, or placebo.
- Guselkumab clinical nonresponders at Week I-12: Participants will receive guselkumab 200 mg SC at Weeks I-12, I-16, and I-20. Placebo IV will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-24 (ie, guselkumab 24-Week responders): Participants will enter the Maintenance Study and will receive guselkumab 200 mg SC q4w.
- Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

Placebo

Participants will receive placebo IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).

At Week I-12, subsequent study intervention will be based on clinical response status as follows:

- Placebo clinical responders at Week I-12: Participants will enter the Maintenance Study and receive placebo SC q4w.
- Placebo clinical nonresponders at Week I-12: Participants will receive the Phase 3 guselkumab induction IV dose at Weeks I-12, I-16, and I-20. Placebo SC will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:

- Guselkumab clinical responders at Week I-24 (ie, placebo crossover responders): Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg q8w, or placebo.
- Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

6.1.3. Maintenance Study (Phase 3 Maintenance Study)

In the Maintenance Study, the randomized population will include guselkumab clinical responders at Week I-12 and placebo crossover responders at Week I-24 (from Induction Study 1 or Induction Study 2). These participants will be rerandomized to 1 of 3 study intervention groups as described below.

- **Guselkumab 200 mg SC q4w**: Participants will receive guselkumab 200 mg SC q4w starting at Week M-0 through Week M-44.
- **Guselkumab 100 mg SC q8w**: Participants will receive guselkumab 100 mg SC q8w starting at Week M-4 through Week M-44. Placebo SC will also be administered at alternate visits to maintain the blind.
- **Placebo:** Participants will receive placebo SC q4w starting at Week M-0 through Week M-44.

Participants will remain on their assigned study intervention through Week M-44. Participants who subsequently meet criteria for loss of clinical response will be eligible for a single blinded dose adjustment as described in Section 6.6.1. The primary analysis population for the Maintenance Study will be randomized participants with a modified Mayo score of 5 to 9 at induction baseline.

In the Maintenance Study, the nonrandomized population will consist of guselkumab 24-Week responders and induction placebo responders at Week I-12. Guselkumab 24-Week responders will receive guselkumab 200 mg SC q4w starting at Week M-0 through Week M-44. Induction placebo responders at Week I-12 will receive placebo SC q4w starting at Week M-0 through Week M-44. These populations are not eligible for dose adjustment.

6.1.4. Long-term Extension of the Maintenance Study

During the LTE of the Maintenance Study, participants will continue to receive the same study intervention regimen that they were receiving at the end of the Maintenance Study, with the first dose in the LTE being administered at Week M-44. There is no dose adjustment during the LTE.

After Week M-44, participants who have been appropriately trained in the self-administration of study intervention may self-administer study intervention at home for selected visits. More details are provided in Section 4.1.3.2.1.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Guselkumab will be supplied as a 100 mg/mL sterile liquid in a single dose prefilled syringe (PFS) assembled in an UltraSafe Plus™ Passive Needle Guard (PFS-U). Placebo for guselkumab will be supplied as a 1 mL sterile liquid in a single dose PFS assembled in a PFS-U.

Guselkumab and placebo for guselkumab will be supplied to the study sites. All study interventions must be stored according to the labeled storage condition, 2°C to 8°C (36°F to 46°F) and protected from exposure to light. Do not freeze the study interventions. The products are designed for single-use only.

Guselkumab and placebo for guselkumab should be clear and colorless to light yellow solution that may contain small translucent particles. Do not use guselkumab or placebo for guselkumab if the liquid is cloudy or discolored or has large particles. Protection from light is not required during the preparation and administration of the study intervention material; avoid direct exposure to sunlight. Aseptic procedures must be used during the preparation and administration of the study intervention material.

Study personnel will instruct participants on how to transport, store, and administer study intervention for at-home use during the LTE as indicated for this protocol.

Refer to the site IPPM and IPPI for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor’s or designee’s study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used ampules, needles, syringes, and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on-site.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees not to dispense the study intervention from, or store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Laboratory Manual.

Participants who will be self-administering study intervention at home will receive detailed instructions for study intervention storage and disposal of used syringes and handling of unused study material. These participants will receive a sharps container to dispose of used syringes and will be instructed to return the sharps container and/or unused cartons with syringes. Participants who self-administer at home will record study intervention administrations with time and date information on a diary card.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Intervention Allocation

Central randomization will be implemented in all 3 studies based on a computer-generated randomization schedule prepared before the studies by or under the supervision of the sponsor. In Induction Study 1, participants will be randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio. In Induction Study 2, participants will be randomly assigned to guselkumab or placebo in a 3:2 ratio, respectively. In both Induction Study 1 and Induction Study 2, the randomization will be balanced by using randomly permuted blocks and will be stratified by ADT-Failure status (ie, participants who had an inadequate response or failure to tolerate TNFα antagonists, vedolizumab, or tofacitinib) (Yes/No), region (Eastern Europe, Asia, or rest of world), and concomitant use of corticosteroids at baseline (Yes/No). In the Maintenance Study, participants will be randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio. The randomization will be balanced by using randomly permuted blocks and will be stratified by clinical remission status at maintenance baseline (Yes/No), concomitant use of corticosteroids at maintenance baseline (Yes/No), and induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover [guselkumab 200 mg], and placebo crossover [guselkumab 400 mg, if chosen as the Phase 3 guselkumab induction dose]). For all 3 studies, the Interactive Web Response System (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study intervention kit(s) for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then be given the relevant participant details to uniquely identify the participant.

Blinding

To maintain the study blind, the study intervention container will have a label containing the study name, study intervention number, and reference number. The study intervention number will be entered in the eCRF when the study intervention is dispensed for on-site administration. Each active study intervention and its matching placebo will be identical in appearance.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the treatment assignment (ie, study intervention serum concentrations, antibodies to study intervention) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the study unblinding.

The CRP and fecal calprotectin test results performed by the central laboratory will be blinded to the investigative sites. If an investigative site requests these data, it will be provided to them after the Week M-44 analyses of the Maintenance Study have been completed.

Treatment assignment blinding for all 3 studies will be maintained for investigative sites, site monitors, and participants in this protocol until the Week M-44 analyses for the Maintenance Study have been completed.

In Induction Study 1 and Induction Study 2, the sponsor (with the exceptions noted below) will remain blinded to the induction treatment assignment until the Week M-44 DBL of the Maintenance Study. However, in Induction Study 1, a limited number of sponsor personnel (independent from study conduct) will become unblinded at an interim analysis for a dosing decision after the first 150 randomized participants have either completed the Week I-12 visit or have terminated study participation before Week I-12. At the time of this analysis, selected sponsor personnel will be unblinded for only the first 150 randomized participants' induction treatment assignment. The induction treatment assignment for the remaining participants will remain blinded at that time. The induction treatment assignment information will be unblinded for all participants and released to selected sponsor personnel for analysis when the following DBLs occur: 1) Induction Study 1: when all randomized participants in Induction Study 1 have either entered the Maintenance Study, or have completed their final safety visit (12 weeks after the last dose of study intervention) for those not participating in the Maintenance Study, or have terminated their study participation; 2) Induction Study 2: at the Week I-12 DBL when all randomized participants have either completed the Week I-12 visit or have terminated study participation before Week I-12. The maintenance treatment assignment information for all participants will remain blinded at all the analyses mentioned above. Identification of sponsor personnel who will have access to the unblinded participant-level data at the time of each analysis will be documented before unblinding.

In the Maintenance Study, when all randomized participants have either completed the Week M-44 visit or have terminated study participation before Week M-44, the treatment assignment information will be unblinded for all participants and released to the sponsor for analysis. The sponsor will remain blinded to the assigned maintenance treatment until after the Week M-44 DBL has occurred.

Under normal circumstances, the investigator blind should not be broken unless specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant. In such cases, the investigator may in an emergency determine the identity of the treatment via the IWRS. It is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. If the blind is broken,

the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Additionally, a given participant's treatment assignment may be unblinded to the sponsor, the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and site personnel to fulfill regulatory reporting requirements for suspected unexpected serious adverse reactions (SUSARs). If a participant is unblinded by the site, the information must be entered in the appropriate section of the eCRF and in the participant's source documents.

Participants who have had their treatment assignment unblinded by the investigator will not be eligible to receive further study intervention but should complete evaluations specified in the appropriate SoA for participants who discontinue study intervention (Section 1.3).

A separate code break procedure will be available for use by the J&J Global Medical Safety group to allow for unblinding of individual participants to comply with specific requests from regulatory or health authorities.

6.4. Study Intervention Compliance

When study intervention is administered as an IV infusion or SC injection by qualified staff, the details of each administration will be recorded in the eCRF. For IV infusions, this will include date and start and stop times of the IV infusion and volume infused; for SC injections, this will include date and time of SC injection.

Participants will receive instructions on compliance with study intervention when they begin self-administration of study intervention at home. When participants begin self-administration at home, the investigator or designated study personnel will maintain a log of all study intervention dispensed and returned.

When study intervention is self-administered by participants at home, participants will record all study interventions on a diary card.

Additional details may be provided in the site IPPM and IPPI that is provided separately. Compliance with the treatment schedule is strongly encouraged.

6.5. Concomitant Therapy

Prestudy therapies administered up to 30 days before the first dose of study intervention must be recorded on the eCRF. Any COVID-19 vaccines administered, regardless of timing, must be recorded on the eCRF. Concomitant therapies must be recorded throughout the study, from signing of the informed consent to the last study visit.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation and acupuncture) different from the study intervention must be recorded in the eCRF.

Recorded information will include a description of the type of therapy, treatment period, dosage, route of administration, and indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

Participants who are receiving oral 5-ASA compounds, oral corticosteroids, 6-MP, AZA, or MTX for the treatment of UC at baseline (ie, Week I-0) should maintain a stable dose for the specified period before baseline, as defined in the Inclusion Criteria (Section 5.1).

In general, participants who are receiving these medications for UC at baseline of either Induction Study 1 or Induction Study 2 (ie, Week I-0) should maintain a stable dose through Week M-44, except for oral corticosteroids. Therapies can only be discontinued or reduced in dose after Week I-0 if investigator judgment requires it because of toxicity or other medical necessity; even if the toxicity resolves, the therapy should not be restarted. Oral corticosteroids must be maintained at baseline doses during Induction Study 1 and Induction Study 2, and all participants must begin tapering oral corticosteroids at Week M-0 of the Maintenance Study, unless medically not feasible (for additional details, see Section 6.5.1).

Enrolled participants should not **initiate** any of the following concomitant UC-specific medical therapies at any time during any of the 3 studies:

- Oral or rectal 5-ASA compounds.
- Oral, parenteral, or rectal corticosteroids, including budesonide and beclomethasone dipropionate.
- 6-MP, AZA, or MTX.
- Antibiotics as a primary treatment for UC.
- Total parenteral nutrition or enteral nutrition as a treatment for UC.

If the above medical therapies are initiated or medication doses are changed based on medical necessity as assessed by the investigator, participants should continue to attend all study visits and have all assessments. While this does not represent a deviation from the study protocol, and the participants may remain on their assigned study intervention, participants who initiate or increase the dose above baseline of these UC medications during induction (ie, Induction Study 1 or Induction Study 2) will not be eligible to enter the Maintenance Study. Treatment failures due to UC medication changes will be defined in the SAP.

Laxatives should generally be avoided and should be used only in preparation for endoscopy or other procedures.

The sponsor must be notified in advance (or as soon as possible thereafter) of any changes in concomitant therapy as noted above.

6.5.1. Corticosteroids

As mentioned in Section 6.5, oral corticosteroids for UC **should not be initiated or have the dose increased above baseline** during all 3 studies. The one exception is that participants may

transiently (ie, for ≤4 weeks) use increased doses of corticosteroids **for reasons other than** worsening of UC (eg, stress doses of corticosteroids for surgery, asthma flare, adrenocortical insufficiency) during the Maintenance Study.

For participants who are receiving oral corticosteroids on entry into the Maintenance Study, the investigator must begin tapering the daily dose of corticosteroids beginning at Week M-0 (Table 5). Tapering of the daily dose of corticosteroids may be paused for participants meeting clinical flare criteria as described in Section 4.1.3.1. For participants whose corticosteroid taper is interrupted, investigators are encouraged to resume tapering within 4 weeks if clinically appropriate. Tapering may exceed this schedule only if warranted by medical necessity (eg, participant experiencing corticosteroid-related side effects).

Table 5: Recommended Tapering Schedule for Oral Corticosteroids

Recommended Tapering Schedule for Oral Corticosteroids (Other than Oral Budesonide and Oral Beclomethasone dipropionate)	
Dose >15 mg/day prednisone or equivalent:	Taper daily dose by 5 mg/week until receiving 10 mg/day, then continue tapering by 2.5 mg/week until 0 mg/day
Dose 11 to 15 mg/day prednisone or equivalent:	Taper daily dose to 10 mg/day for 1 week, then continue by 2.5 mg/week until 0 mg/day
Dose ≤10 mg/day prednisone or equivalent:	Taper daily dose by 2.5 mg/week until 0 mg/day
Recommended Tapering Schedule for Oral Budesonide and Oral Beclomethasone dipropionate	
Participants receiving oral budesonide or oral beclomethasone dipropionate should have their daily dose tapered according to local clinical practice until 0 mg/day.	

6.5.2. Prohibited Medications/Therapies

Participants who initiate the following treatments will be discontinued from further study intervention administration and should have a final safety follow-up visit approximately 12 weeks after their last dose of study intervention:

- Immunomodulatory agents other than 6-MP, AZA, or MTX (including, but not limited to, 6-thioguanine, cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus, tofacitinib, and other JAK inhibitors).
- Immunomodulatory biologic agents (including, but not limited to, TNFα antagonists, ustekinumab, vedolizumab, abatacept, anakinra).
- Experimental IBD medications (including, but not limited to, upadacitinib, filgotinib, ozanimod, etrolizumab, brazikumab, mirikizumab, risankizumab) or other investigational medications/therapies.
- Thalidomide or related agents.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.5.3. Vaccinations (Including COVID-19)

When considering use of locally-approved (including emergency use-authorized) COVID-19 vaccines in study participants, consider protocol lifestyle considerations (Section 5.3) and follow

applicable local vaccine labeling, guidelines, and standards of care for patients receiving immune-targeted therapy.

For study participants receiving a locally-approved (including emergency use-authorized) COVID-19 vaccine, in order to help identify acute reactions potentially related to the COVID-19 vaccine, it is recommended that, where possible, vaccine and study intervention be administered on different days, separated by as large an interval as is practical within the protocol.

6.6. Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study-site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

Details regarding the management of clinical flare and loss of clinical response in participants during the Maintenance Study are provided in Section 4.1.3.1.

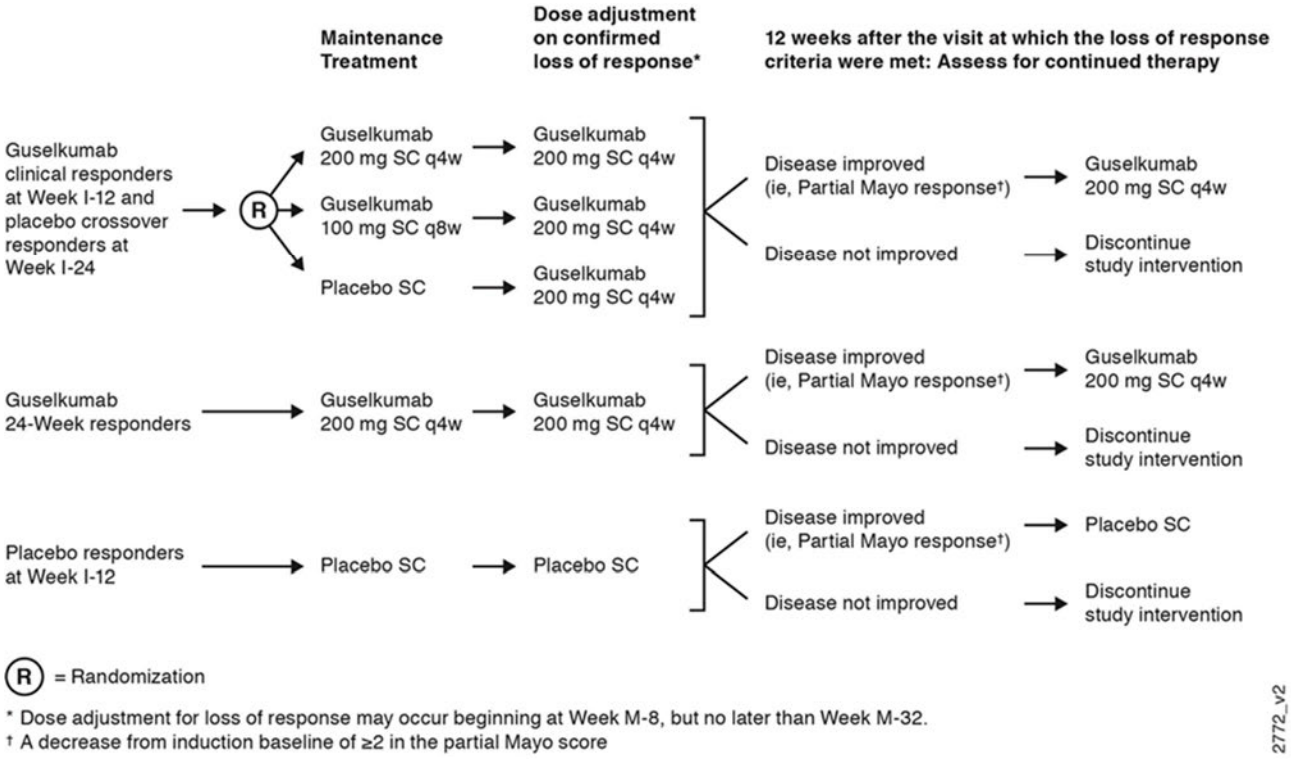
6.6.1. Phase 3 Maintenance Study

Participants who were rerandomized in the Maintenance Study (ie, guselkumab clinical responders at Week I-12 and placebo crossover responders at Week I-24) and meet criteria for loss of clinical response (ie, no longer satisfies the definition of clinical response as previously defined in Section 3) will be eligible to receive a single blinded dose adjustment as described below and in Figure 6:

- Guselkumab 200 mg SC q4w group: Participants will continue on guselkumab 200 mg SC q4w (ie, no adjustment).
- Guselkumab 100 mg SC q8w group: Participants will adjust to receive guselkumab 200 mg SC q4w.
- Placebo SC: Participants will adjust to receive guselkumab 200 mg SC q4w.

Guselkumab 24-Week responders will continue to receive guselkumab 200 mg SC q4w. Participants induced into clinical response at Week I-12 with placebo will continue to receive SC placebo and are not eligible for a dose adjustment.

Figure 6: Dose Adjustment Treatment Groups in the Maintenance Study for Participants in Clinical Response Following Induction



Participants are only eligible for a single blinded dose adjustment (ie, the first time loss of response criteria are met). The first visit at which a participant can be considered for a dose adjustment is Week M-8. In order to allow sufficient time to assess benefit after dose adjustment, the Week M-32 visit will be the final visit when loss of clinical response criteria (and subsequent dose adjustment) can occur.

Participants who have dose adjusted will be assessed 12 weeks after the visit where the loss of clinical response criteria was met to determine if benefit was achieved from the dose adjustment. Participants who have not shown improvement in their UC activity at that time (as assessed by the partial Mayo response) will be discontinued from study intervention and should return for a final safety visit approximately 12 weeks after their last dose of study intervention. Participants assessed by the investigator to be clinically improved (partial Mayo response) will continue to receive the same adjusted dose in a blinded manner.

6.7. Intervention After the End of the Study

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine standard of care. Local regulations on continued access will take precedence.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant discontinues study intervention or withdraws from the study before the end of the study, assessments should be obtained as specified in the SoA (Section 1.3).

7.1. Discontinuation of Study Intervention

A participant who discontinues study intervention will not be automatically withdrawn from the study (see Section 7.2).

7.1.1. Conditions That Require Study Intervention Discontinuation

A participant's study intervention must be discontinued under the following conditions:

1. The participant (or the participant's representative) withdraws consent to receive study intervention.
2. The investigator believes that for safety or tolerability reasons (eg, adverse event), it is in the best interest of the participant to discontinue study intervention.
3. The participant becomes pregnant or plans a pregnancy within the study period. Refer to Appendix 6 (Section 10.6), Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
4. The participant initiates treatment with prohibited therapies for UC (Section 6.5.2).
5. The participant has a colectomy.
6. The participant develops an opportunistic infection.
7. The participant is deemed ineligible according to the following TB screening criteria:

   A diagnosis of active TB is made.

   A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.

   A participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB® (or T-SPOT® for sites in Japan) test result (and/or a positive tuberculin skin test result in countries/territories in which the QuantiFERON-TB® test is not approved/registered or the tuberculin skin test is mandated by local health authorities), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next study intervention administration and continued to completion (see also Section 8.2.11 and Appendix 5 [Section 10.5]). Indeterminate QuantiFERON-TB® (or borderline T-SPOT® for sites in Japan) test results should be handled as described in Section 8.2.11. Participants with persistently indeterminate QuantiFERON-TB® (or borderline T-SPOT® for sites in Japan) test results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the medical monitor or designee and recorded in the participant's source documents and initialed by the investigator.

Note: In Ukraine, while the QuantiFERON-TB® test is not approved/registered, it is acceptable, and an additional tuberculin skin test is not required.

A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

8. The participant has a serious adverse reaction that is related to an injection or an infusion resulting in bronchospasm with wheezing and/or dyspnea that requires ventilatory support **OR** that results in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg.
9. The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study intervention. These may be accompanied by other events including pruritus, facial/hand/lip edema, dysphagia, urticaria, sore throat, and/or headache.
10. The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allowing participants who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study intervention.
11. The participant has severe liver test abnormalities that are not transient and are not explained by other etiologies, as described in Section 8.2.4 and Appendix 9 (Section 10.9; Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants With No Underlying Liver Disease). Such abnormalities would include the following:
    - ALT or AST >8 x the upper limit of normal (ULN)
    - ALT or AST >5 x ULN for more than 2 weeks
    - ALT or AST >3 x ULN **and** total bilirubin >2 x ULN **or** international normalized ratio (INR) >1.5
    - ALT or AST >3 x ULN and symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%])

7.1.2. Conditions to Consider Study Intervention Discontinuation

Discontinuation of a participant's study intervention must be strongly considered under the following conditions:

1. Persistent inadequate response or worsening of UC based on signs, symptoms, and/or laboratory values. If the participant experiences AEs consistent with clinically significant worsening of UC at any time during the study, these events should be evaluated by the investigator and the study medical monitor to decide on discontinuation of study intervention. Discontinuation of study intervention should be considered in participants with clinically significant worsening of UC where continuation of the study intervention is not in the best interest of the participant.
2. The participant develops a serious infection, including but not limited to sepsis or pneumonia.

   Note: Any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

3. The participant reports suicidal ideation with intention to act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), or any suicidal behavior (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline C-SSRS assessment. If a participant can be adequately treated with psychotherapy and/or pharmacotherapy based on an evaluation by a mental health professional, then the participant, at the discretion of the investigator, may be continued with treatment if agreed to by the medical monitor or designee. Discussion of such participants with the medical monitor or designee is required.
4. The participant develops a severe injection-site reaction or AE temporally associated with infusion.
5. Criterion deleted per Amendment 1.

If a participant discontinues study intervention for any reason before the end of the treatment period, assessments should be obtained as specified in the SoA (Section 1.3). Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up (see Section 7.3)
- Withdrawal of consent
- Death
- Sponsor decision (eg, participating in any other clinical study with an investigational agent)

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Participants who terminate study participation will not be required to return for any follow-up assessments; however, these participants should complete the safety and efficacy evaluations specified in the SoA (Section 1.3) at the time they terminate study participation. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.

- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 8 [Section 10.8], Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker (PD), pharmacogenomic, medical resource utilization, health economic, and safety measurements applicable to Induction Study 1, Induction Study 2, and the Maintenance Study.

Scheduled study visits should generally occur within the visit window per the protocol-specified visit schedule (as indicated in the SoA). All subsequent visits should be scheduled relative to the date of induction randomization (for the induction visits) and the Week M-0 visit date (for the maintenance visits). For study visits that cannot be held within the recommended visit window, the visit should be conducted as closely as possible to the study visit schedule by applying the allowable ± visit window.

All visit-specific PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions.

Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the source documentation.

For women of childbearing potential only, additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. When performed, a negative urine pregnancy test result must be obtained before study intervention administration.

Medical resource utilization and health economics data will be collected. Refer to Section 8.10, Medical Resource Utilization and Health Economics for details.

Screening Phase- Induction Study 1 or Induction Study 2

The screening phase is up to 8 weeks duration before randomization. After written informed consent has been obtained, all screening evaluations (eg, laboratory test results, clinical data, and concomitant medication data) that establish participant eligibility will be performed by the principal investigator or designee to confirm that the participant satisfies all inclusion criteria and does not violate any exclusion criteria. Participants who meet all of the inclusion and none of the exclusion criteria can be enrolled in the study. Every effort should be made to adhere to the SoA (Section 1.3) for each participant. The collection of AEs will start at the time informed consent is obtained.

Diaries will be provided to each participant to record concomitant medications, stool production, and episodes of rectal bleeding. A Mayo diary should be completed from recall at screening and will be used to calculate a partial Mayo score (Section 8.1.1) to assess the participant's eligibility for further screening and to train the participant on the use of the diary. If a participant is unable to recall sufficient diary information to confirm eligibility at the initial screening visit, the participant may take the screening diary home to collect additional required data during the

screening phase. Participants with a rectal bleeding subscore ≥1 can proceed with endoscopy. Participants will be instructed to complete the Mayo diary daily through Week I-4 and for the 7 days immediately before each visit thereafter and bring them to every visit for data collection and review by the investigator/study coordinator.

The screening endoscopy should be performed within 2 weeks (and at least 4 days) before the baseline (Week I-0) visit. Participants who are identified as being at increased risk for colon cancer (Section 5.1, Inclusion Criterion #6) or for adenomatous polyps (Section 5.1, Inclusion Criterion #7) will undergo a full colonoscopy instead of a sigmoidoscopy to allow screening for dysplasia or to assess for the presence of adenomatous polyps, respectively. Any screening colonoscopy for malignancy should include surveillance biopsies consistent with local practice. At least 48 hours should elapse between a colonoscopy with polypectomy and the Week I-0 visit. Local pathology results from the screening endoscopy should be available before the first dose of study intervention.

Women of childbearing potential must have a negative urine pregnancy test result at screening and before any induction study intervention administration. Participants who are women of childbearing potential must be reminded that they are required to use a highly effective method of contraception during the study (as described in Section 5.1, Inclusion Criterion 15) and must continue taking such precautions for 12 weeks after receiving the last dose of study intervention. The method(s) of contraception used by each participant must be documented.

Participants must undergo testing for TB (Section 8.2.11 and Appendix 5 [Section 10.5]) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. A participant's eligibility according to TB screening criteria is described in Section 5.1, Inclusion Criterion #12.

Blood Sample Collection

Blood samples should be collected at the visits indicated in the SoA (Section 1.3). The date and time of collection will be recorded. When blood samples are to be collected for safety, PK/immunogenicity, efficacy, and biomarkers evaluations at the same time point, the order of blood draws will be samples for CRP, hematology and chemistry, PK/immunogenicity, serum biomarkers, whole blood DNA (for those participating in the optional pharmacogenomic substudy at Week I-0), and whole blood RNA.

The maximum total blood volume to be collected from each participant in this protocol (Induction Study 1 or Induction Study 2, Maintenance Study) will be approximately 570 mL over approximately 256 to 268 weeks. This total may vary due to:

- whether or not the participant consents to take part in the optional pharmacogenomics substudy (6 mL).
- whether or not whole blood samples are collected from participants that provide biopsy samples for single cell analyses (maximum 32 mL).

- repeat or unscheduled samples taken for safety reasons or technical issues with the samples.
- regional or country- or territory-specific variation in blood collection systems.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the SoA (Section 1.3) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are provided in the Laboratory Manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IB)
- IPPM
- IPPI
- Laboratory Manual
- eCRF completion instructions
- Patient recruitment materials
- Sample ICFs
- IWRS Manual
- Biopsy Manual
- ePRO equipment
- Endoscopy kit
- Imaging Manual
- Laboratory kits
- Participant diary cards
- At-Home Stool Collection Manual

8.1. Efficacy Assessments

Efficacy evaluations for all 3 studies will include the following:

- Mayo score and Partial Mayo score.
- UCEIS.
- Inflammatory PD markers including CRP and fecal calprotectin.

- Patient-reported outcome measures to assess HRQoL outcomes and fatigue (ie, IBDQ, PROMIS-29, PROMIS Fatigue Short Form 7a, Patient's Global Impression of Change [PGIC] of Severity of UC [Induction Study 1 and Induction Study 2 only], PGIS of UC, and EQ-5D-5L).
- Extraintestinal manifestations.

8.1.1. Mayo Score

The **Mayo score** (see Appendix 10 [Section 10.10]) was developed from the criteria of Truelove and Witts (Truelove 1955) for mild, moderate, and severe UC and from the criteria of Baron et al (Baron 1964) for grading endoscopic appearance. The Mayo score is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, physician's global assessment, and endoscopy findings) and ranges from 0 to 12 points. The **partial Mayo score** is the Mayo score without the endoscopy subscore and ranges from 0 to 9 points. The **modified Mayo score** is the Mayo score without the physician's global assessment and ranges from 0 to 9 points. **Mayo scores** are calculated using the following:

1. The stool frequency and rectal bleeding data from the most recent consecutive 3-day period within the 1 week before the visit. The average of the 3-day period will be used to calculate the stool frequency and rectal bleeding scores for the visit. Days on which the following conditions are met should be excluded from the calculation:
    a. The day on which medications for constipation, diarrhea, or irregularity were taken. (For participants maintained on a stable dose of bulking or stool-softening agents throughout the study, the days on which these agents are taken should not be excluded from consideration in calculating the Mayo score.)
    b. The day(s) of a procedure or preparation for a procedure (eg, enemas, other laxatives, a clear liquid diet) that would affect bowel frequency and/or blood content of the stool.
    c. The 48 hours after the use of antimotility agents (ie, diphenoxylate hydrochloride with atropine sulfate, loperamide, or other opioids).

       Note: For participants maintained on a chronic stable dose of antimotility agents throughout the study, the days on which these agents are taken should not be excluded from consideration in calculating the Mayo score.
    d. The 48 hours immediately following a colonoscopy.
2. The physician's global assessment.
3. The results of a sigmoidoscopy or colonoscopy.

The endoscopic findings will be assessed by the investigator (ie, local endoscopist) during the endoscopy procedure and by the central reader reviewing a video of the endoscopy. Participant eligibility at baseline will be based on the final reported endoscopic subscore as determined by the following process:

- If the local endoscopist and the central reader agree on the endoscopic subscore, the agreed score will be the final reported endoscopic subscore.

- If there is a discrepancy between the local endoscopist and the central reader subscores, the video endoscopy will be submitted to a second central reader (designated for adjudication). The median score of the 3 completed reads (ie, local read, central read 1, and central read 2 designated for adjudication) will be the final reported endoscopic subscore.

Additional details will be provided in the imaging charter.

8.1.2. Ulcerative Colitis Endoscopic Index of Severity

The UCEIS is an index that provides an overall assessment of endoscopic severity of UC, based on mucosal vascular pattern, bleeding, and ulceration (Travis 2012). The score ranges from 3 to 11, with a higher score indicating more severe disease by endoscopy. The UCEIS score will be assessed only by the central video readers for all endoscopies.

8.1.3. C-Reactive Protein

C-reactive protein has been demonstrated to be useful as a marker of inflammation in participants with IBD. In participants with UC, elevated CRP has been associated with severe clinical activity, an elevated sedimentation rate, and active disease as detected by colonoscopy (Solem 2005; Vermeire 2004). Serum samples for the measurement of CRP will be collected from all participants at visits indicated in the SoA (Section 1.3). C-reactive protein will be assayed using a validated, high sensitivity CRP assay.

8.1.4. Fecal Calprotectin

Fecal calprotectin has been demonstrated to be a sensitive and specific marker in identifying colonic inflammation and response to treatment in participants with IBD, especially in UC (Abraham 2012). Stool samples for calprotectin concentrations will be collected from all participants at visits as indicated in the SoA (Section 1.3).

Assays for fecal calprotectin will be performed by the central laboratory using a validated method. Additional tests may also be performed on the stool samples for markers that are related to colonic inflammation, response to treatment, or changes in the microbiome.

8.1.5. Inflammatory Bowel Disease Questionnaire

The IBDQ (Irvine 1994) is a validated, 32-item, self-reported questionnaire for participants with IBD that will be used to evaluate the disease-specific HRQoL across 4 dimensional scores: bowel symptoms (loose stools, abdominal pain), systemic functions (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). Scores range from 32 to 224, with higher scores indicating better outcomes.

The individual IBDQ dimensions will be calculated when no more than 1 item is missing in the dimension. If an item is missing, it will be estimated using the average value across the non-missing items. If any of the 4 dimensions of the IBDQ cannot be calculated, then the total IBDQ score cannot be calculated and will be missing for that visit.

8.1.6. PROMIS-29

The PROMIS-29 is a validated general health profile instrument that is not disease-specific. It is a collection of short forms containing 4 items for each of 7 domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities). PROMIS-29 also includes an overall average pain intensity 0-10 numeric rating scale. Norm-based scores have been calculated for each domain on the PROMIS measures, with a score of 50 representing the mean or average of the reference population. On symptom-oriented domains of PROMIS-29 (anxiety, depression, fatigue, pain interference, and sleep disturbance), higher scores represent worse symptomatology. On the function-oriented domains (physical functioning and social role), higher scores represent better functioning.

8.1.7. PROMIS Fatigue 7-items Short Form

The PROMIS Fatigue Short Form 7a contains 7 items evaluating fatigue-related symptoms (ie, tiredness, exhaustion, mental tiredness, and lack of energy) and associated impacts on daily activities (ie, activity limitations related to work, self-care, and exercise). PROMIS Fatigue Short Form 7a has a recall period of past 7 days. Compared to the fatigue scale of PROMIS-29, PROMIS Fatigue Short Form 7a provides additional information to evaluate severity of fatigue.

8.1.8. Patient's Global Impression of Change of Severity of Ulcerative Colitis

Participants' perceived change (improvement or deterioration) in the severity of their UC will be assessed using the PGIC during Induction Study 1 and Induction Study 2. Participants will rate how their UC has changed since the beginning of the study using a 7-point scale ranging from "a lot better now" to "a lot worse now" with a neutral center point ("neither better nor worse").

8.1.9. Patient's Global Impression of Severity of Ulcerative Colitis

Participants will rate their UC disease activity at the baseline and planned visit using a 5-point scale ("None", "Mild", "Moderate", "Severe" and "Very Severe").

8.1.10. EQ-5D-5L

The EQ-5D-5L is a validated instrument consisting of the EuroQol 5 dimensions descriptive system (EQ-5D) and the EuroQol visual analog scale (EQ-VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by checking the most appropriate statement in each of the 5 dimensions. The EQ-VAS records the respondent's self-rated health on a 20-cm vertical, visual analog scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. The respondents mark an "X" on the scale to indicate their health TODAY and then write the number marked on the scale in the box.

8.1.11. Extraintestinal Manifestations

Extraintestinal manifestations such as arthritis/arthralgia, aphthous stomatitis, erythema nodosum, iritis/uveitis, primary sclerosing cholangitis, and pyoderma gangrenosum will be assessed according to the SoA.

8.2. Safety Assessments

Details regarding the independent DMC are provided in Section 9.6.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Appendix 11 (Section 10.11), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA (Section 1.3):

8.2.1. Physical Examinations

Physical examinations, including height and weight, will be performed as specified in the SoA. While assessment of the participants for safety and efficacy requires some physical examination by an investigator at all visits, a more complete, detailed physical exam should be performed as specified in the SoA. Participants will be instructed to remove shoes and outdoor apparel and gear prior to measurements for height and weight.

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques should be used only if an automated device is not available.

If feasible, blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

At a study intervention administration visit, vital signs should be obtained before, approximately every 30 minutes during, and twice (at approximately 30-minute intervals) after completion of the IV infusion(s), or before and approximately 30 minutes after the SC injection, or if the participant reports any symptoms.

8.2.3. Electrocardiogram

A 12-lead ECG will be performed at screening.

During the collection of the ECG, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 1.3. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the central laboratory unless otherwise specified or approved by the medical monitor or designee:

- **Hematology assessments** will include but are not limited to the following: hemoglobin, hematocrit, platelet count, total and differential WBC count.
- **Blood chemistry assessments** will include but are not limited to the following: chemistry panel (total and direct bilirubin, ALT, AST, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, blood urea nitrogen/urea, and creatinine).

  A medical monitor or designee and the clinical site will be notified if pre-specified abnormal laboratory values defined in the Laboratory Manual are identified in any participant during the conduct of the study.
- **Serology**: HIV antibody, HBV antibodies and surface antigen, and HCV antibody. For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines. Additional details are provided in Appendix 7 (Section 10.7; Hepatitis B Virus (HBV) Screening with HBV DNA Testing).
- **Liver function tests:** If laboratory testing for a subject who is enrolled in the study and receiving study intervention reveals an increase of serum aminotransferases (ALT or AST) to >3 x ULN and an increase of bilirubin to >2 x ULN, study agent should be suspended immediately. In addition, laboratory tests for ALT, AST, alkaline phosphatase, and total bilirubin should be confirmed by a retest within 24 hours if possible, but no later than 72 hours following notification of test results. Additional clinical and laboratory studies may be performed to evaluate the underlying etiology of abnormal findings. See Appendix 9 (Section 10.9; Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants With No Underlying Liver Disease) for additional information on monitoring and assessment of abnormal liver function tests.

Women participants of childbearing potential will undergo a urine pregnancy test at screening, before study intervention administration, at the early termination visit, and the safety follow-up visits as indicated in the SoA (Section 1.3).

8.2.5. Columbia-Suicide Severity Rating Scale

No signal of suicidal ideation and behavior has been observed in the clinical trials of guselkumab to date. However, in light of reports concerning suicidal ideation and behavior in patients with plaque psoriasis treated with an IL-17R antagonist (brodalumab) (Danesh 2016), the C-SSRS will be used as a screening tool to prospectively evaluate suicidal ideation and behavior among study participants.

The C-SSRS defines 5 subtypes of suicidal ideation and 4 possible suicidal behaviors, as well as non-suicidal self-injurious behavior and completed suicide. It will be used as a screening tool to prospectively evaluate suicidal ideation and behavior in this study, as part of a comprehensive evaluation of safety. The C-SSRS is an investigator-administered questionnaire (Mundt 2013; Posner 2011). Two versions of it will be used in this study: the 'Baseline/Screening' version of the C-SSRS will be conducted during the screening visit and the 'Since Last Visit' version of the C-SSRS will be completed at other visits as indicated in the SoA (Section 1.3).

The investigator or trained study site personnel will interview the participant and complete the C-SSRS. The C-SSRS will be provided in the local languages in accordance with local guidelines.

At screening, the C-SSRS will be the first assessment performed after signing informed consent, before any other study procedure. At all subsequent visits, the C-SSRS will be performed according to the assessment schedule and should be performed after other PROs but before any other study procedures. Participants will be interviewed by the investigator or trained study site personnel in a private, quiet place.

At the conclusion of each assessment, the trained personnel administering the C-SSRS will determine the level of suicidal ideation or behavior, if any. They will then determine the next course of action if any level of suicidal ideation or behavior is reported. The participant should not be released from the site until the C-SSRS has been reviewed by the investigator and the participant's risk has been assessed and follow-up determined, as appropriate.

At screening (within the last 6 months) and Week I-0, participants with a C-SSRS rating of Suicidal Ideation with Intention to Act ("Ideation level 4"), Suicidal Ideation with Specific Plan and Intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt), must be determined to not be at risk by the investigator based on an evaluation by a mental health professional (eg, psychiatrist, psychologist, or appropriately trained social worker or nurse) in order to be randomized.

Participants with C-SSRS ratings of Wish to be Dead ("Ideation level 1"), Non-Specific Active Suicidal Thoughts ("Ideation level 2"), Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act ("Ideation level 3") or non-suicidal self-injurious behavior must be

determined not to be at risk by the investigator in order to be randomized in the study. Any questions regarding eligibility of such participants should be discussed with the medical monitor or designee.

For each assessment after Week I-0, the following actions should be taken, if applicable:

- No suicidal ideation or behaviors (including self-injurious behavior without suicidal intent): No further action is needed.
- Suicidal ideation levels 1-3 or non-suicidal self-injurious behavior: Participant risk is assessed by the investigator.
- Suicidal ideation levels 4 or 5 or any suicidal behavior: Participant risk assessed and referral to a mental health professional.

Interruption or the discontinuation of study intervention should be considered for any participant who reports Suicidal Ideation with Intention to Act ("Ideation level 4"), Suicidal Ideation with Specific Plan and Intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a postbaseline C-SSRS assessment and who is deemed to be at risk by the investigator based upon evaluation by a mental health professional. If a participant can be adequately treated with psychotherapy and/or pharmacotherapy then the participant, at the discretion of the investigator, may be continued with treatment if agreed to by the medical monitor or designee. Discussion of such participants with the medical monitor or designee is required.

Any C-SSRS finding, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (see Appendix 11 [Section 10.11], Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

8.2.6. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

8.2.7. Injection-Site Reactions

An injection-site reaction is any adverse reaction at a SC study intervention injection-site. Injection sites will be evaluated for reactions and any injection-site reaction will be recorded as an AE.

8.2.8. Hypersensitivity Reactions

Before any administration of study intervention at the study site, appropriately trained personnel and medications (eg, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. All participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension).

8.2.9. Adverse Events Temporally Associated with Infusion

Any AE (except laboratory abnormalities) that occurs during or within 1 hour after the IV infusion of study intervention will be carefully evaluated. Minor infusion-related AEs may be managed by slowing the rate of the IV infusion and/or treating with antihistamines and/or acetaminophen (paracetamol) as clinically indicated. If an IV infusion of study intervention is interrupted because of an AE that, in the opinion of the investigator, is not severe or does not result in a SAE, the infusion may be restarted with caution.

8.2.10. Infections

Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits (see SoA, Section 1.3). Study intervention administration should not be given to a participant with a clinically significant, active infection. If a participant develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study intervention must be strongly considered (Section 7.1.2). Any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

8.2.11. Tuberculosis Evaluations

8.2.11.1. Initial Tuberculosis Evaluation

Participants must undergo testing for TB (refer to Appendix 5 [Section 10.5]) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. Investigators have the option to use both the QuantiFERON-TB® (or T-SPOT® for sites in Japan) test and the tuberculin skin test to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated to evaluate a participant who is high risk of having latent TB. If either the QuantiFERON-TB® (or T-SPOT® for sites in Japan) test or the tuberculin skin test is positive, the participant is considered to have latent TB infection for the purposes of eligibility for this study.

Participants with a negative QuantiFERON-TB® (or T-SPOT® for sites in Japan) test result (and a negative tuberculin skin test result in countries/territories in which the QuantiFERON-TB® test is not approved/registered or the tuberculin skin is mandated by local health authorities) are eligible to continue with pre-randomization procedures. Participants with a newly identified positive QuantiFERON-TB® (or T-SPOT® for sites in Japan or tuberculin skin) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country/territory guidelines for immunocompromised patients. If no local country/territory guidelines for immunocompromised patients exist, US guidelines should be followed, or the participant will be excluded from the study.

A participant whose first QuantiFERON-TB® test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB® test result is also indeterminate, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest

radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. For sites in Japan, a participant whose first T-SPOT® test result is borderline should have the test repeated. In the event that the second T-SPOT® (for sites in Japan) test result is also borderline, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the medical monitor or designee and recorded in the participant's source documents and initialed by the investigator.

8.2.11.2. Ongoing Tuberculosis Evaluation

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at scheduled visits (refer to the SoA in Section 1.3) or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:

  Persistent fever?

  Unintentional weight loss?

  Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB (or T-SPOT® for sites in Japan) test, a repeat tuberculin skin test in countries/territories in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment is warranted. Study intervention administration should be interrupted during the investigation. A positive QuantiFERON®-TB (or T-SPOT® for sites in Japan) test or tuberculin skin test result should be considered detection of latent TB. Participants with a newly identified positive QuantiFERON-TB® (or T-SPOT® for sites in Japan

or tuberculin skin) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country/territory guidelines for immunocompromised patients. If no local country/territory guidelines for immunocompromised patients exist, US guidelines should be followed, or the participant will be excluded from the study. If the QuantiFERON-TB® test result is indeterminate, the test should be repeated. For sites in Japan, a participant whose first T-SPOT® test result is borderline should have the test repeated. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol. Participants who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study intervention and be encouraged to return for all subsequent scheduled study visits according to the SoA (Section 1.3).

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 11 (Section 10.11), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately but no later than 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

A possible Hy's law case is defined by the occurrence of ALT/AST ≥3 x ULN together with total bilirubin ≥2 x ULN or INR >1.5 (if measured). Any possible Hy's law case is considered an important medical event and must be reported to the sponsor in an expedited manner using the SAE form, even before all other possible causes of liver injury have been excluded.

A confirmed Hy's law case must be reported as a SAE.

8.3.2. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 11 (Section 10.11), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events:

- Adverse events related to symptoms of UC
- Adverse events related to worsening or progression of UC

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries/territories in which the studies are conducted.

8.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention (see Section 7.1.1).

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required (see Appendix 6 [Section 10.6], Contraceptive and Barrier Guidance and Collection of Pregnancy Information and Appendix 11 [Section 10.11, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting).

8.3.5. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first study intervention administration(s) in subjects participating in this clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the event, according to the procedures in Appendix 11 (Section 10.11), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting, for SAEs. Investigators are also advised that active TB is considered a reportable disease in most countries/territories. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than the highest dose at a single dosing visit specified in this protocol will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Serum samples will be used to evaluate the PK of guselkumab at the timepoints presented in the SoA (Section 1.3). Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.5.1. Evaluations

At visits where only serum concentration of guselkumab will be evaluated (ie, no antibodies to guselkumab will be evaluated), 1 venous blood sample of sufficient volume should be collected. Each serum sample will be divided into 2 aliquots: 1 for serum concentration of guselkumab, and a back-up.

At visits where serum concentration of guselkumab and antibodies to guselkumab will be evaluated, 1 venous blood sample of sufficient volume should be collected. Each serum sample will be divided into 3 aliquots: 1 for serum concentration of guselkumab, 1 for antibodies to guselkumab, and a back-up. The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

Additional information about the collection, handling, and shipment of biologic samples can be found in the Laboratory Manual.

8.5.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of guselkumab using validated, specific, and sensitive immunoassay methods by or under the supervision of the sponsor. The sponsor, or its designee, under conditions in which the participants' identities remains blinded, will assay these samples.

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

Serum samples will be used to evaluate guselkumab PK parameters including (but not limited to) clearance, volume of distribution, etc, based on blood drawn from all participants according to the SoA (Section 1.3). A population PK analysis approach may be used to derive PK parameters when appropriate.

Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between serum concentrations of guselkumab and efficacy measures or relevant biomarker(s) may be examined when appropriate.

8.6. Pharmacodynamics

Pharmacodynamic markers will be evaluated using blood and fecal samples collected at visits as indicated in the SoA (Section 1.3). Post-baseline PD test results will not be released to the investigators by the central laboratory.

8.7. Genetics

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary where local regulations permit. Participation in pharmacogenomic research is optional.

Genetic (DNA) variation may be an important contributory factor to interindividual variability in drug response and associated clinical outcomes. Genetic factors may also serve as markers for disease susceptibility and prognosis and may identify population subgroups that respond differently to an intervention.

DNA samples will be analyzed for identification of genetic factors that may be associated with clinical response. This research may consist of the analysis of 1 or more candidate genes or assessment of SNPs in relation to guselkumab intervention and/or UC. Whole blood samples of approximately 6 mL will be collected for genetic analyses as specified in the SoA (Section 1.3).

8.8. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab treatment and/or UC. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, whole blood, stool, and colonic biopsy samples collected as specified in the SoA (Section 1.3), where local regulations permit.

Data collected from these samples will be used for exploratory research that will include the following objectives:

1. To understand the molecular effects of guselkumab.
2. To understand UC pathogenesis.
3. To understand why individual participants may respond differently to guselkumab.
4. To understand the impact of treatment with guselkumab on colonic inflammation.
5. To develop diagnostic tests to identify UC populations that may be responsive or non-responsive to treatment with guselkumab.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.8.1. Serum-based Biomarkers

Blood samples for serum-based biomarker analyses will be collected from all participants. Assays to be performed may include proteins associated with proinflammatory and anti-inflammatory effects, the recruitment and proliferation of cells associated with inflammation and repair, and markers associated with tissue injury or repair. These analyses will include but not be limited to IL-17A and IL-22. Proprietary algorithms and standard statistical techniques, such as analysis of variance (ANOVA) and analysis of covariance (ANCOVA), will be used to identify individual proteins exhibiting statistically significantly different changes in their levels between samples and/or between groups of samples. This will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to UC or the mechanism of action of guselkumab.

8.8.2. Whole Blood-based Biomarkers

Whole blood samples will be collected from all participants to assess the effect of study intervention on RNA expression profiles. Transcriptome studies will be conducted using microarray, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each blood sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to UC or the action of guselkumab. Whole blood samples will also be collected for peripheral blood mononuclear cell isolation from a subset of participants that provide biopsy samples for single cell analyses at selected sites.

The same samples may also be used to confirm findings by application of alternative technologies.

8.8.3. Biopsy-based Biomarkers

Colonic biopsy samples will be collected during endoscopy to study the effect of study intervention on gene and protein expression, and for the histologic assessment of disease and healing. Colonic biopsy analyses may also examine gene and protein expression associated with the pathogenesis of UC. RNA transcriptomic profiles derived from colonic biopsies will also be used to evaluate a molecular predictive signature previously developed in the context of anti-TNFα intervention in UC (Telesco 2018). Preparation for single cell isolation from colonic biopsy samples will occur at pre-defined study sites. Adjacent biopsy samples will be collected to support exploratory single cell analyses at pre-defined study sites capable of performing the tissue preparation procedures required for single cell isolation.

8.8.4. RNA Expression Research of a Subset of RNA Species

RNA expression studies on whole blood and colonic biopsy tissue will be conducted using gene expression array or sequencing technology, quantitative reverse transcriptase polymerase chain reaction, and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in a transcriptome profile for blood or intestinal biopsy tissue samples collected for RNA transcriptome research. The RNAs assayed may be those involved with the pathogenesis of UC; or in the participant's response to guselkumab. In addition, continuing research may identify other proteins or regulatory RNAs that

may be involved in the response to guselkumab or the pathogenesis of UC. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation the changes in RNA expression profiles that may correlate with biological response relating to UC or the mechanism of action of guselkumab.

8.8.5. Fecal Biomarkers

Fecal samples will be collected from all participants as specified in the SoA (Section 1.3). Microbiome and associated analyses will be conducted to evaluate the association between inflammatory proteins, microbial activities and guselkumab, and/or UC. The relationships between microbiome, metabolites, and biomarkers in other tissue samples will also be assessed.

8.8.6. Molecular Predictive Signature

The molecular predictive signature is a predictive gene expression signature, initially discovered from colon biopsies collected at baseline from a subset of participants in the ACT 1 infliximab UC study (Rutgeerts 2005), refined in the PURSUIT golimumab UC study (Sandborn 2014), and prospectively evaluated for prediction of mucosal healing in an open-label study of 103 UC participants treated with golimumab (PROgECT) (Telesco 2018). Using machine learning approaches, it was found that this length-13 gene signature predicted anti-TNFα nonresponse by mucosal healing with good accuracy, identifying 63% of mucosal healing nonresponders with a negative predictive value of 0.87. The signature had similar negative predictive value in a Phase 2a study of a JAK inhibitor in UC suggesting that it may be mechanism agnostic (Sands 2017b). Efficacy of guselkumab treatment will be evaluated by molecular predictive signature status at baseline.

8.9. Immunogenicity Assessments

Antibodies to guselkumab will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Serum samples will be screened for antibodies binding to guselkumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to guselkumab and/or further characterize the immunogenicity of guselkumab.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to guselkumab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to guselkumab will also be evaluated for guselkumab serum concentration to enable interpretation of the antibody data.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization, all medical encounters including UC-related emergency department visits, hospitalizations, and surgeries, will be collected in this study.

The WPAI-GH will also be utilized to evaluate work productivity. The WPAI-GH is a validated instrument created as a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to general health. The WPAI-GH consists of 6 questions to determine employment status, hours missed from work due to health problems, hours missed from work for other reasons, hours actually worked, the degree to which general health affected work productivity while at work, and the degree to which general health affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Higher scores indicate greater impairment.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

9.1. Statistical Hypotheses

Primary hypotheses are described below.

Secondary hypotheses are described in Section 3.

Induction Study 1

The primary hypothesis is that guselkumab is superior to placebo in inducing clinical response at Week I-12.

Induction Study 2

The primary hypothesis is that guselkumab is superior to placebo in inducing clinical remission at Week I-12.

Maintenance Study

The primary hypothesis is that guselkumab is superior to placebo in achieving clinical remission at Week M-44.

9.2. Sample Size Determination

The primary analysis population for all 3 studies will be randomized and treated participants with a modified Mayo score of 5 to 9 at induction baseline. For the purpose of the sample size calculation, it is assumed that all randomized participants are treated. Unless otherwise specified, the sample size described below consists of randomized participants with a modified Mayo score of 5 to 9 at induction baseline.

9.2.1. Induction Study 1 (Phase 2b Induction Dose-ranging Study)

Sample sizes were determined by the power to detect a significant difference in clinical response at Week I-12 (primary endpoint) between each guselkumab group and the placebo group using a 2-sided chi-square test with 0.05 significance level.

The assumptions for the sample size calculations were based on data from the Phase 3 ustekinumab (an anti-IL-12/23 mAb) UC program (CNTO1275UCO3001), a clinical program conducted by the sponsor in a very similar target population (participants with moderately to severely active UC who had failed or were intolerant to biologic or conventional therapies). Data from a Phase 2 UC study of another anti-IL-23 mAb (mirikizumab) were also taken into consideration (Sandborn 2018).

Clinical response at Week I-12

In CNTO1275UCO3001, the proportions of participants in clinical response at Week 8 based on the modified Mayo score were 31.0% and 57.8% for placebo and ustekinumab 6 mg/kg, respectively, for a treatment difference of 26.8%, with about 320 participants in each treatment group. The clinical response rate (20.6% at Week 12) for placebo from a recent study of mirikizumab in a similar population was also considered. The clinical response rates for different dose levels of mirikizumab did not demonstrate a clear dose-response trend and varied between 41.3% and 59.7%, with about 60 participants in each treatment group (Reich 2019; Sandborn 2018).

Based on the data above, the clinical response rates are assumed to be 30% for placebo and 60% for each of the guselkumab doses in this study.

In this study, a step-up multiple testing procedure (Hochberg 1988) will be employed to control the Type-I error rate for the primary endpoint. As discussed in Section 4.1, since Induction Study 1 also serves as a feeder study for the Phase 3 Maintenance Study and thus will keep enrolling until an induction dose decision is made for Induction Study 2, the sample size for Induction Study 1 is not fixed. The planned sample size (150 participants total or 50 per treatment group) for the interim analysis is considered sufficient as it provides at least 80% power to detect a treatment difference between either guselkumab group and placebo based on the current assumptions on clinical response rate and is consistent with past Phase 2 dose-ranging studies in UC. It is estimated that when the induction dose decision is made, there will be approximately 390 participants (130 per treatment group) randomized in Induction Study 1. Therefore, 130 participants in each of the 2 guselkumab groups and 130 participants in placebo will provide an overall power of >90% for the primary endpoint of clinical response at Week I-12 for each guselkumab group compared to placebo, based on the assumptions above.

The study is not being powered to detect treatment differences between guselkumab and placebo in the major secondary endpoints.

9.2.2. Induction Study 2 (Phase 3 Induction Study)

Sample sizes were determined by the power to detect a significant difference in clinical remission at Week I-12 (primary endpoint) between the guselkumab group and the placebo group using a 2-sided chi-square test with a 0.05 significance level. The study is sized such that the guselkumab therapy achieves ≥90% power for the primary endpoint compared with placebo.

The assumptions for the sample size calculations were also based on data from CNTO1275UCO3001. Data from mirikizumab were also taken into consideration (Sandborn 2018).

Clinical remission at Week I-12

In CNTO1275UCO3001, the proportions of participants in clinical remission at Week 8 based on a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on endoscopy, where the stool frequency subscore did not increase from induction baseline, were 6.9% and 19.3% for placebo and ustekinumab 6 mg/kg, respectively, for a treatment difference of 12.4%, with about 320 participants in each group. The clinical remission rate (4.8% at Week 12) for placebo from the Phase 2 study of another IL-23 mAb (ie, mirikizumab) in similar population was also considered (Sandborn 2018). The clinical remission rates for different dose levels of mirikizumab did not demonstrate a clear dose-response trend and varied between 11.5% and 22.6%, with about 60 participants in each treatment group (Reich 2019).

Based on the data above, the clinical remission rates at Week I-12 are assumed to be 8-10% for placebo and 20-24% for the selected guselkumab dose.

Assuming 8% clinical remission in the placebo group and 20% in the guselkumab group, 175 participants per group (350 participants in total) will provide statistical power of 90% for comparison of guselkumab versus placebo at a significance level of 0.05 (2-sided). However, to provide a sufficient number of participants for the primary analysis population in the Maintenance Study, the sample size for Induction Study 2 was increased to at least 560 participants in the primary analysis population and the randomization allocation was slightly skewed to guselkumab (3:2) to generate a sufficient number of guselkumab clinical responders. Table 6 shows the power for detecting a treatment difference between the guselkumab group and the placebo group based on different proportions of participants in clinical remission at Week I-12 with a fixed sample size of 560 participants.

Table 6: Power to Detect a Treatment Effect for Guselkumab Based on the Proportion of Participants Achieving Clinical Remission at Week I-12 for Induction Study 2		
Primary Endpoint of Clinical Remission at Week I-12		
Placebo (n = 224)	Guselkumab IV (n = 336)	Power
8%	18%	93%
8%	20%	98%
8%	22%	>99%
10%	20%	90%
10%	22%	97%
10%	24%	99%

A sample size of 560 participants in the primary analysis population also provides sufficient power for the majority of the major secondary endpoints. The given sample size will provide approximately 90% power for the following major secondary endpoints: symptomatic remission at Week I-12 (40% vs 25% for guselkumab vs placebo); endoscopic healing at Week I-12 (27% vs 14% for guselkumab vs placebo); clinical response at Week I-12 (60% vs 30% for guselkumab vs placebo); symptomatic remission at Week I-4 (33% vs 20% for guselkumab vs placebo); IBDQ remission at Week I-12 (47% vs 32% for guselkumab vs placebo); histologic-endoscopic mucosal healing at Week I-12 (17% vs 8% for guselkumab vs placebo); and fatigue response at Week I-12 (44% vs 25% for guselkumab vs placebo). The assumptions noted above are based on the CNTO1275UCO3001 data.

The total sample size across Induction Study 1 and Induction Study 2, for randomized participants with a modified Mayo score of 5 to 9, is a target of approximately 950 participants. However, the program also enrolled participants with a modified Mayo score of 4; therefore, the total sample size for the program is estimated to be 1000 participants.

9.2.3. Maintenance Study (Phase 3 Maintenance Study)

Most of the efficacy analyses in the Maintenance Study will be based on the primary analysis population, ie, guselkumab clinical responders at Week I-12 and placebo crossover responders at Week I-24 with a modified Mayo score of 5 to 9 at induction baseline who received at least 1 dose of study intervention in the Maintenance Study. Unless otherwise stated, the sample size/power calculations in this section refer to this population.

A multiplicity-controlled testing procedure, starting with the high guselkumab dose group (200 mg SC q4w), will be used to control the overall Type-I error rate at the 0.05 level (2-sided) over the primary and major secondary endpoints. As such, sample size/power calculations were based on the chi-square test to detect a significant difference between participants receiving SC guselkumab 200 mg q4w and those receiving placebo.

The assumptions for the sample size calculations were also based on data from CNTO1275UCO3001.

Clinical Remission at Week M-44

In CNTO1275UCO3001, the proportions of participants in clinical remission at Week 44 were 26.3% and 44.9% for placebo and ustekinumab 90 mg SC q8w, respectively, for a treatment difference of 18.6%.

Based on the data above, the clinical remission rates are assumed to be 25% for placebo and 45% for each of the guselkumab doses. Based on these assumptions, 118 participants in each group (354 participants in total) will provide statistical power of 90% at a significance level of 0.05 (2-sided).

Table 7 shows the power for detecting a treatment difference between the guselkumab 200 mg SC q4w and the placebo group based on different proportions of participants in clinical remission at Week M-44 with a sample size of 354.

Table 7: Power for Detecting a Treatment Effect Based on Different Proportions of Participants in Clinical Remission at Week M-44 With a Fixed Sample Size of 354 Participants (118 in Each Treatment Group)

Proportion of Participants in Clinical Remission at Week M-44 (%)		
Placebo	Guselkumab	Power[a] (%)
25	50	98
	47	95
	45	90
	42	79
	40	69

a: Based on testing the guselkumab 200 mg SC q4w group versus placebo at α 0.05 (2 sided).

The number of participants in the primary analysis population of the Maintenance Study will depend on the number of participants with a modified Mayo score of 5 to 9 at induction baseline from the following 2 groups of the induction studies:

- Group A: participants in clinical response to IV guselkumab at Week I-12 of either Induction Study 1 or Induction Study 2
- Group B: participants who were not in clinical response to IV placebo induction at Week I-12 of either Induction Study 1 or Induction Study 2 but were in clinical response at Week I-24 after receiving IV guselkumab at Weeks I-12, I-16, and I-20.

Based on the assumptions in Induction Study 1, the average clinical response rate to guselkumab IV induction is 60%, thus the 2 induction studies will result in approximately 484 participants in the primary analysis population of the Maintenance Study. However, the average clinical response rate to guselkumab IV induction could range from 50% to 65%. With 596 participants with a modified Mayo score of 5 to 9 expected to receive guselkumab and 354 participants with a modified Mayo score of 5 to 9 expected to receive placebo at Week I-0, the number of participants in the primary analysis population of the Maintenance Study could range from 404 to 525 (Table 8). The expected enrollment in the primary analysis population of the Maintenance Study is 484 participants, which is over the required sample size of 354. The targeted number was

increased because the maintenance study is intended to power at >90% for the majority of the major secondary endpoints based on the primary analysis population.

Table 8: Projected Number of Participants in the Primary Analysis Population of the Maintenance Study and Associated Power for the Primary Endpoint

Clinical Response Rate to IV Guselkumab Induction	Participants in Group A with a modified Mayo score of 5 to 9 Entering Maintenance	Participants in Group B with a modified Mayo score of 5 to 9 Entering Maintenance[a]	Number of Participants in the Primary Analysis Population of the Maintenance Study	Power (%)
50%	298	106	404	93
55%	328	117	445	95
60%	357	127	484	97
65%	387	138	525	98

Group A Participants in clinical response to IV guselkumab induction at Week I 12; Group B Participants not in clinical response to IV placebo induction at Week I 12 but in clinical response at Week I 24 after receiving induction IV guselkumab at Weeks I 12, I 16, and I 20.

a: The proportion of participants not in clinical response to IV placebo induction at Week I 12 and did not discontinue study intervention is assumed to be 60%.

The power for detecting a treatment difference between the guselkumab 200 mg SC q4w and the placebo group for the primary endpoint and each of the major secondary endpoints with 484 participants in the primary analysis population is shown (Table 9). The assumptions about the proportion of participants achieving the primary endpoint and each major secondary endpoint have been based on data from the CNTO1275UCO3001 maintenance study.

Table 9: Power for Detecting a Treatment Effect for the Primary Endpoint and Each of the Major Secondary Endpoints With 484 Participants in the Primary Analysis Population (161 in Each Treatment Group)

	Proportion of participants achieving the endpoint		
	Placebo	Guselkumab	Power[a] (%)
Primary endpoint			
Clinical remission at Week M-44	25	45	97
Major secondary endpoints			
Symptomatic remission at Week M-44	45	68	99
Endoscopic healing at Week M-44	30	50	96
Clinical response at Week M-44	51	77	99
Histologic-endoscopic mucosal healing at Week M-44	26	46	97
IBDQ remission at Week M-44	40	60	95
Fatigue response at Week M-44	26	55	>99
Corticosteroid-free (ie, not requiring any treatment with corticosteroids for at least 8 weeks prior) clinical remission at Week M-44	25	42	90
Clinical remission at Week M-44 *among the participants who had achieved clinical remission at maintenance baseline*[b]	36	61	74
Endoscopic normalization at Week M-44.	18	29	65

a: Based on testing the SC guselkumab 200 mg q4w group versus placebo at α=0.05 (2-sided).
b: It is estimated that about 33% of participants in the primary analysis population (53 participants per treatment group) will be in clinical remission at Week M-0.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Full Analysis Set (I) Randomized Full Analysis Set (M)	All randomized participants with a modified Mayo score of 5 to 9 at induction baseline who receive at least 1 dose of study intervention
Safety Analysis Set (I) Randomized Safety Analysis Set (M)	All randomized participants with a modified Mayo score of 5 to 9 at induction baseline who receive at least 1 dose of study intervention
PK Analysis Set (I) Randomized PK Analysis Set (M)	All randomized participants with a modified Mayo score of 5 to 9 at induction baseline who receive at least 1 complete dose of guselkumab and have at least 1 valid blood sample drawn for PK analysis after their first dose of guselkumab

Abbreviations: I induction study; M maintenance study

9.4. Statistical Analyses

9.4.1. Endpoints

This section describes primary, major secondary, and other endpoints. A complete list of the other endpoints will be provided in the SAP. The analysis details will be specified in the SAP.

9.4.1.1. Induction Study 1 (Phase 2b Induction Dose-ranging Study)

The primary, major secondary, and other endpoints evaluate the short-term efficacy of IV guselkumab versus placebo, in participants with moderately to severely active UC.

Primary Endpoint

The primary endpoint in this study is clinical response at Week I-12 (Induction Week 12).

Major Secondary Endpoints

- Clinical remission at Week I-12.
- Symptomatic remission at Week I-12.
- Endoscopic healing at Week I-12.
- Histologic-endoscopic mucosal healing at Week I-12.
- Endoscopic normalization at Week I-12.

Other Endpoints

Clinical Endpoints

- Clinical remission at Week I-12, based on a stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on endoscopy.
- Histologic healing at Week I-12.
- Histologic remission at Week I-12.
- Histologic-endoscopic mucosal healing (Alternative definition) at Week I-12.
- Deep histologic-endoscopic mucosal healing at Week I-12.
- Symptomatic remission at Week I-2, Week I-4, and Week I-8.
- Change from baseline in the modified Mayo score at Week I-12.
- Change from baseline in the partial Mayo score at each visit through Week I-12.
- Change from baseline in the stool frequency and rectal bleeding subscores at Weeks I-2, I-4, I-8, and I-12.
- Rectal bleeding subscore of 0 at each visit through Week I-12.
- Stool frequency subscore of 0 or 1 at each visit through Week I-12.
- Change from baseline in the full Mayo score at Week I-12.

- Clinical response, clinical remission, endoscopic healing, endoscopic normalization, histologic-endoscopic mucosal healing, histologic-endoscopic mucosal healing (Alternative definition), and deep histologic-endoscopic mucosal healing at Week I-12 based on the local endoscopy subscores.
- Clinical response, clinical remission, symptomatic remission, endoscopic healing, endoscopic normalization, histologic healing, histologic remission, histologic-endoscopic mucosal healing, histologic-endoscopic mucosal healing (Alternative definition), and deep histologic-endoscopic mucosal healing at Week I-12 by ADT-Failure status and biologic-failure status (eg, biologic-naïve, biologic-failure, biologic non-failure, and biologic-experienced without documented failure [ie, discontinued biologic therapy for other reasons], to be defined in the SAP).
- Clinical response, clinical remission, symptomatic remission, endoscopic healing, endoscopic normalization, histologic healing, histologic remission, histologic-endoscopic mucosal healing, histologic-endoscopic mucosal healing (Alternative definition), and deep histologic-endoscopic mucosal healing at Week I-12 by the colonic molecular prediction signature status at baseline.
- Change from baseline in the UCEIS score at Week I-12.
- UCEIS score ≤4 at Week I-12.
- Endpoints based on other definitions of clinical response and clinical remission at Week I-12 (to be specified in the SAP).
- Other histologic endpoints based on other definitions using the Robarts Histopathology Index (Mosli 2017) and the Nancy Histological Index (Marchal-Bressenot 2017) at Week I-12 (to be specified in the SAP).
- Extraintestinal manifestations at Week I-12.

CRP and Fecal Calprotectin

- Change from baseline in CRP at Weeks I-4, I-8, and I-12.
- Change from baseline in CRP at Weeks I-4, I-8, and I-12 among participants with abnormal CRP at baseline.
- Change from baseline in fecal calprotectin at Weeks I-4 and I 12.
- Change from baseline in fecal calprotectin at Weeks I-4 and I-12 among participants with abnormal fecal calprotectin at baseline.
- Normalization of CRP at Weeks I-4, I-8, and I-12 among participants with abnormal CRP at baseline.
- Normalization of fecal calprotectin at Weeks I-4 and I-12 among participants with abnormal fecal calprotectin at baseline.

Patient-Reported Outcomes

- Change from baseline in the total score of the IBDQ at Week I-12.
- A ≥16 or >20-point improvement from baseline in the IBDQ total score at Week I-12.

- IBDQ remission, defined as total IBDQ score ≥170 at Week I-12.
- Change from baseline in each of the 4 dimensions of the IBDQ at Week I-12.
- Change from baseline in the domains T-scores of PROMIS-29 and the pain intensity at Week I-12.
- Clinically meaningful improvement (to be defined in the SAP) in the domains T-scores of PROMIS-29 and the pain intensity at Week I-12.
- Fatigue response of PROMIS Fatigue Short Form 7a at Week I-12 (to be defined in the SAP).
- Change from baseline in the health state VAS score and EQ-5D dimensions at Week I-12.
- Improvement in PGIC of Severity of UC from baseline at Week I-12.
- Change in PGIS of UC from baseline at Week I-12.

Health Economics

- UC-related emergency department visits, hospitalizations, and surgeries through Week I-12.
- Change from baseline in WPAI-GH at Week I-12.

9.4.1.2. Induction Study 2 (Phase 3 Induction Study)

The primary, major secondary, and other endpoints evaluate the short-term efficacy of IV guselkumab versus placebo, in participants with moderately to severely active UC.

Primary Endpoint

The primary endpoint in this study is clinical remission at Week I-12.

Major Secondary Endpoints

- Symptomatic remission at Week I-12.
- Endoscopic healing at Week I-12.
- Clinical response at Week I-12.
- Symptomatic remission at Week I-4.
- IBDQ remission at Week I-12.
- Histologic-endoscopic mucosal healing at Week I-12.
- Fatigue response at Week I-12.
- Symptomatic remission at Week I-2.
- Endoscopic normalization at Week I-12.

Note: The final ordering of the major secondary endpoints will be provided in the SAP for this study.

Other Endpoints

Other endpoints for this study are similar to those noted for Induction Study 1 (Section 9.4.1.1) and are described below.

Clinical Endpoints

- Clinical remission at Week I-12, based on a stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on endoscopy.
- Endpoints based on other definitions of clinical response and clinical remission at Week I-12 (to be specified in the SAP).
- Histologic healing at Week I-12.
- Histologic remission at Week I-12.
- Histologic-endoscopic mucosal healing (Alternative definition) at Week I-12.
- Deep histologic-endoscopic mucosal healing at Week I-12.
- Other histologic endpoints based on other definitions using the Robarts Histopathology Index (Mosli 2017) and the Nancy Histological Index (Marchal-Bressenot 2017) at Week I-12 (to be specified in the SAP).
- Symptomatic remission at Week I-8.
- Change from baseline in the modified Mayo score at Week I-12.
- Change from baseline in the partial Mayo score at each visit through Week I-12.
- Change from baseline in the stool frequency and rectal bleeding subscores at Weeks I-2, I-4, I-8, and I-12.
- Rectal bleeding subscore of 0 at each visit through Week I-12.
- Stool frequency subscore of 0 or 1 at each visit through Week I-12.
- Time to partial Mayo response through Week I-12.
- Time to symptomatic remission through Week I-12.
- Change from baseline in the full Mayo score at Week I-12.
- Clinical response, clinical remission, endoscopic healing, endoscopic normalization, histologic-endoscopic mucosal healing, histologic-endoscopic mucosal healing (Alternative definition), and deep histologic-endoscopic mucosal healing at Week I-12 based on the local endoscopy subscores.
- Clinical response, clinical remission, symptomatic remission, endoscopic healing, endoscopic normalization, histologic healing, histologic remission, histologic-endoscopic mucosal healing, histologic-endoscopic mucosal healing (Alternative definition), and deep histologic-endoscopic mucosal healing at Week I-12 by ADT-Failure status and biologic-failure status (eg, biologic-naïve, biologic-failure, biologic non-failure, and biologic-experienced without documented failure [ie, discontinued biologic therapy for other reasons], to be defined in the SAP).

- Clinical response, clinical remission, symptomatic remission, endoscopic healing, endoscopic normalization, histologic healing, histologic remission, histologic-endoscopic mucosal healing, histologic-endoscopic mucosal healing (Alternative definition), and deep histologic-endoscopic mucosal healing at Week I-12 by the colonic molecular prediction signature status at baseline.
- Change from baseline in the UCEIS score at Week I-12.
- UCEIS score ≤4 at Week I-12.
- Extraintestinal manifestations at Week I-12.

CRP and Fecal Calprotectin

- Change from baseline in CRP at Weeks I-4, I-8, and I-12.
- Change from baseline in CRP at Weeks I-4, I-8, and I-12 among participants with abnormal CRP at baseline.
- Change from baseline in fecal calprotectin at Weeks I-4 and I-12.
- Change from baseline in fecal calprotectin at Weeks I-4 and I-12 among participants with abnormal fecal calprotectin at baseline.
- Normalization of CRP at Weeks I-4, I-8, and I-12 among participants with abnormal CRP at baseline.
- Normalization of fecal calprotectin at Weeks I-4 and I-12 among participants with abnormal fecal calprotectin at baseline.

Patient-Reported Outcomes

- Change from baseline in the total score of the IBDQ at Week I-12.
- A ≥16 or >20-point improvement from baseline in the IBDQ total score at Week I-12.
- Change from baseline in each of the 4 dimensions of the IBDQ at Week I-12.
- Change from baseline in the domains T-scores of PROMIS-29 and the pain intensity at Week I-12.
- Clinically meaningful improvement (to be defined in the SAP) in the domains T-scores of PROMIS-29 and the pain intensity at Week I-12.
- Change from baseline in the health state VAS score and EQ-5D dimensions at Week I-12.
- Improvement in PGIC of Severity of UC from baseline at Week I-12.
- Change in PGIS of UC from baseline at Week I-12.
- Abdominal pain (assessed by IBDQ question 13) and bowel urgency (assessed by IBDQ questions 16 and 24) at Week I-12 (to be defined in the SAP).

Health Economics

- UC-related emergency department visits, hospitalizations, and surgeries through Week I-12.
- Change from baseline in WPAI-GH at Week I-12.

9.4.1.3. Maintenance Study (Phase 3 Maintenance Study)

The primary, major secondary, and other endpoints evaluate the efficacy of guselkumab versus placebo, in participants with moderately to severely active UC who were in clinical response after 12 weeks of IV guselkumab induction therapy.

Primary Endpoint

The primary endpoint in this study is clinical remission at Week M-44 (Maintenance Week 44).

Major Secondary Endpoints

- Symptomatic remission at Week M-44.
- Endoscopic healing at Week M-44.
- Corticosteroid-free (ie, not requiring any treatment with corticosteroids for at least 8 weeks prior) clinical remission at Week M-44.
- Clinical response at Week M-44.
- Histologic-endoscopic mucosal healing at Week M-44.
- IBDQ remission at Week M-44.
- Fatigue response at Week M-44.
- Clinical remission at Week M-44 among the participants who had achieved clinical remission at maintenance baseline (ie, maintenance of clinical remission at M-44).
- Endoscopic normalization at Week M-44.

Note: The final ordering of the major secondary endpoints will be provided in the SAP for this study.

Other Endpoints

Clinical Endpoints

- Clinical remission at Week M-44, based on a stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on endoscopy.
- Endpoints based on other definitions of clinical response and clinical remission at Week M-44 (to be specified in the SAP).
- Change from maintenance baseline in the modified Mayo score at Week M-44.
- Change from maintenance baseline in the partial Mayo score at each visit through Week M-44.
- Change from maintenance baseline in the stool frequency and rectal bleeding subscores at each visit through Week M-44.
- Rectal bleeding subscore of 0 at each visit through Week M-44.
- Stool frequency subscore of 0 or 1 at each visit through Week M-44.

- Change from maintenance baseline in the full Mayo score at Week M-44.
- Symptomatic remission at each visit through Week M-44.
- Durable symptomatic remission through Week M-44 (symptomatic remission for ≥80% of all visits between Week M-0 and Week M-44 [ie, at least 10 of 12 visits], which must include Week M-44).
- Symptomatic remission at each visit through Week M-44 among the participants who had achieved symptomatic remission at maintenance baseline.
- Endoscopic healing at Week M-44 among the participants who had achieved endoscopic healing at maintenance baseline.
- Clinical remission at Week M-44 and not receiving corticosteroids for at least 12 weeks prior to Week M-44.
- Clinical remission at Week M-44 and not receiving corticosteroids for at least 4 weeks prior to Week M-44.
- Clinical response and not receiving corticosteroids at Week M-44.
- Change from maintenance baseline in the average daily prednisone-equivalent corticosteroid dose (excluding budesonide and beclomethasone dipropionate) at each visit through Week M-44 among the participants who were receiving concomitant corticosteroids at maintenance baseline.
- Elimination of concomitant corticosteroids at Week M-44 among the participants who were receiving concomitant corticosteroids at maintenance baseline.
- Elimination of corticosteroids for at least 12 weeks prior to Week M-44 among participants who were receiving corticosteroids at maintenance baseline.
- Elimination of corticosteroids for at least 4 weeks prior to Week M-44 among participants who were receiving corticosteroids at maintenance baseline.
- Clinical response, clinical remission, endoscopic healing, endoscopic normalization, histologic-endoscopic mucosal healing, histologic-endoscopic mucosal healing (Alternative definition), and deep histologic-endoscopic mucosal healing at Week M-44 based on the local endoscopy subscores.
- Primary and major secondary endpoints, histologic healing, histologic remission, histologic-endoscopic mucosal healing (alternative definition), and deep histologic endoscopic mucosal healing at Week M-44 by ADT-Failure status and biologic-failure status (eg, biologic-naïve, biologic-failure, biologic non-failure, and biologic-experienced without documented failure [ie, discontinued biologic therapy for other reasons], to be defined in the SAP), and by the colonic molecular prediction signature status at baseline.
- Association of histologic-endoscopic mucosal healing, histologic improvement alone, or endoscopic improvement alone at Week M-0 with other efficacy parameters at Week M-44.
- Change from maintenance baseline in UCEIS score at Week M-44.
- UCEIS score ≤4 at Week M-44.
- Histologic healing at Week M-44.

- Histologic remission at Week M-44.
- Histologic-endoscopic mucosal healing (Alternative definition) at Week M-44.
- Deep histologic-endoscopic mucosal healing at Week M-44.
- Other histologic endpoints based on other definitions using the Robarts Histopathology Index (Mosli 2017) and the Nancy Histological Index (Marchal-Bressenot 2017) at Week M-44 (to be specified in the SAP).
- Extraintestinal manifestations over time through Week M-44.

CRP and Fecal Calprotectin

- Change from maintenance baseline in CRP over time through Week M-44.
- Change from maintenance baseline in CRP over time through Week M-44 among participants with abnormal CRP at induction baseline.
- Change from maintenance baseline in fecal calprotectin over time through Week M-44.
- Change from maintenance baseline in fecal calprotectin over time through Week M-44 among participants with abnormal fecal calprotectin at induction baseline.
- Normalization of CRP over time through Week M-44 among participants with abnormal CRP at induction baseline.
- Normalization of fecal calprotectin over time through Week M-44 among participants with abnormal fecal calprotectin at induction baseline.

Patient-Reported Outcomes

- Change from maintenance baseline in the total IBDQ score and in each of the 4 IBDQ dimensions through Week M-44.
- A ≥16 or >20-point improvement from induction baseline in the IBDQ total score at Week M-44.
- Maintenance of ≥16 or >20-point improvement in IBDQ through Week M-44 among participants with a ≥16 or >20-point improvement in IBDQ at the maintenance baseline compared with the induction baseline.
- IBDQ remission through Week M-44.
- Change from maintenance baseline in the domains T-scores of the PROMIS-29 and the pain intensity through Week M-44.
- Clinically meaningful improvement (to be defined in the SAP) in the domains T-scores of PROMIS-29 and the pain intensity through Week M-44.
- Fatigue response of PROMIS Fatigue Short Form 7a through Week M-44.
- Changes from maintenance baseline in the health state VAS score and EQ-5D dimensions through Week M-44.
- Change in PGIS from maintenance baseline at Week M-44.

- Abdominal pain (assessed by IBDQ question 13) and bowel urgency (assessed by IBDQ questions 16 and 24) at Week M-44 (to be defined in the SAP).

Health Economics

- UC-related emergency department visits, hospitalizations, and surgeries through Week M-44.
- Change from maintenance baseline in WPAI-GH through Week M-44.

9.4.2. Efficacy Analyses

Unless otherwise specified, the endoscopy subscore as obtained during the central review of the video endoscopy will be used for all efficacy analyses involving endoscopy in this section.

9.4.2.1. Induction Study 1 (Phase 2b Induction Dose-ranging Study)

9.4.2.1.1. Population for Efficacy Analysis

Unless otherwise noted, efficacy analyses will be based on the **Full Analysis Set**, which is defined as all randomized participants with a modified Mayo score of 5 to 9 who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention group to which they were randomized regardless of the intervention they actually received.

9.4.2.1.2. Primary Endpoint Analysis

The primary endpoint is clinical response at Week I-12 defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1 decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. The analyses will be based on the Full Analysis Set.

Participants who have a colectomy or ostomy, have protocol-prohibited medication changes (to be defined in the SAP), or who discontinued study intervention due to unsatisfactory therapeutic effect or an AE of worsening UC before the Week I-12 visit will be considered as treatment failures and considered not to be in clinical response, regardless of the actual modified Mayo score. For participants who discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infection), data at all visits after discontinuation will not be used in analysis. For participants who discontinued study intervention due to COVID-19 infection or for reasons other than lack of efficacy or an AE of worsening of UC or any other COVID-19 related reasons, their observed clinical response status (if available) at Week I-12 will be used. Participants who are missing any or all of the 3 Mayo subscores that compose the modified Mayo score or who do not return for evaluation at Week I-12 will be considered not to be in clinical response.

A precise description of the treatment effect to be estimated from the study will be described in the estimand framework. The primary estimand will use a hybrid strategy for the intercurrent events. Details on the primary estimand and other estimand definitions will be described in the SAP.

For testing of the primary endpoint, the efficacy of each guselkumab group versus placebo will be compared. For all statistical comparisons of the primary endpoint, a Cochran-Mantel-Haenszel

(CMH) test (2-sided) stratified by ADT-Failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No) will be used. A step-up multiple testing procedure (Hochberg 1988) will be used to control the Type-I error at a 2-sided 0.05 significance level over the comparisons for the primary endpoint. For this procedure, if p-values for both guselkumab treatment groups are ≤0.05, then it will be concluded that both guselkumab treatment groups are effective compared with placebo. Otherwise, the smaller of the 2 p-values will be compared with α 0.025; if that p-value is ≤0.025, then it will be concluded that the guselkumab treatment group associated with the smaller p-value is effective compared with placebo. The study will be considered positive if at least 1 guselkumab group is significantly different from the placebo group for the primary endpoint.

To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint will be conducted using different missing data approaches; these analyses will be described in the SAP.

Subgroup analyses of the primary endpoint will be performed based on demographic and baseline disease characteristics, baseline use and history of use of UC medications (including ADT-Failure status), and molecular predictive signature status at baseline.

9.4.2.1.3. Major Secondary Endpoint Analyses

The major secondary endpoints are:

- Clinical remission at Week I-12.
- Symptomatic remission at Week I-12.
- Endoscopic healing at Week I-12.
- Histologic-endoscopic mucosal healing at Week I-12.
- Endoscopic normalization at Week I-12.

The same treatment failure rules that were specified for the primary endpoint analysis will also be used for the major secondary endpoints (Section 9.4.2.1.2). Participants who are missing any or all of the 3 Mayo subscores that compose the modified Mayo score or who do not return for evaluation at Week I-12 will be considered not to have achieved clinical remission. Participants who are missing both stool frequency and rectal bleeding subscores at Week I-12 will be considered not to have achieved symptomatic remission at Week I-12. Participants who have missing endoscopy subscore at Week I-12 will be considered not to have achieved endoscopic healing, endoscopic normalization, or histologic-endoscopic mucosal healing at Week I-12.

For testing of the major secondary endpoints, the efficacy of each guselkumab group versus placebo will be compared. For all statistical comparisons of the major secondary endpoints, a CMH test (2-sided) stratified by ADT-Failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No) will be used.

The study is not being powered to detect treatment differences between guselkumab and placebo for these major secondary endpoints. These endpoints will not be multiplicity-controlled for analysis purposes, and all p-values will be considered nominal.

9.4.2.1.4. Other Endpoint Analyses

Comparisons between each of the guselkumab groups and the placebo group at Week I-12 will be made for each of the endpoints.

Analyses suitable for categorical data (eg, chi-square test or CMH test, as appropriate) will be used to compare the proportion of participants achieving selected endpoints (eg, clinical response). In case of rare events, the Fisher's exact test will be used for treatment comparisons.

Continuous response parameters will be compared using an ANOVA or covariance (ANCOVA), unless otherwise specified. If the normality assumption is in question, an ANOVA or ANCOVA on the van der Waerden normal scores will be used.

All statistical testing will be performed at the 2-sided 0.05 significance level. No adjustments for multiple comparisons will be made for these other efficacy endpoints and nominal p-values will be presented.

9.4.2.2. Induction Study 2 (Phase 3 Induction Study)

9.4.2.2.1. Population for Efficacy Analysis

Unless otherwise noted, efficacy analyses will be based on the **Full Analysis Set**, which is defined as all randomized participants with a modified Mayo score of 5 to 9 who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention group to which they were randomized regardless of the intervention they actually received.

9.4.2.2.2. Primary Endpoint Analysis

The primary endpoint is clinical remission at Week I-12, defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline. The analyses will be based on the Full Analysis Set.

Participants who have a colectomy or ostomy, have protocol-prohibited medication changes (to be defined in the SAP), or who discontinued study intervention due to reasons other than COVID-19 related reasons or a regional crisis, including unsatisfactory therapeutic effect or an AE of worsening UC, before the Week I-12 visit will be considered as treatment failures and considered not to be in clinical remission, regardless of the actual modified Mayo score. For participants who discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis, their observed clinical remission status at Week I-12 will be used if available. After accounting for the treatment failure rules, participants who are missing any or all of the 3 Mayo subscores that compose the modified Mayo score or who do not return for evaluation at Week I-12 will be considered not to be in clinical remission.

A precise description of the treatment effect to be estimated from the study will be described in the estimand framework. The primary estimand will use a hybrid strategy for the intercurrent events. Details on the primary estimand and other estimand definitions will be described in the SAP.

For testing of the primary endpoint, the efficacy of the guselkumab group versus placebo will be compared. A CMH test (2-sided) stratified by ADT-Failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No) will be used. The comparison between guselkumab and placebo will be controlled at the 2-sided 0.05 significance level. The study will be considered positive if the guselkumab group is significantly different from the placebo group for the primary endpoint.

To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint will be conducted using different missing data approaches; these analyses will be described in the SAP.

Subgroup analyses of the primary endpoint will be performed based on demographic and baseline disease characteristics, baseline use and history of use of UC medications (including ADT-Failure status), and molecular predictive signature status at baseline.

9.4.2.2.3. Major Secondary Endpoint Analyses

The major secondary endpoints are:

- Symptomatic remission at Week I-12.
- Endoscopic healing at Week I-12.
- Clinical response at Week I-12.
- Symptomatic remission at Week I-4.
- IBDQ remission at Week I-12.
- Histologic-endoscopic mucosal healing at Week I-12.
- Fatigue response at Week I-12.
- Symptomatic remission at Week I-2.
- Endoscopic normalization at Week I-12.

Similar treatment failure and missing data rules that were specified for these endpoints in Section 9.4.2.2.2 will be used for these major secondary endpoints, with the exception that for the major secondary endpoints of symptomatic remission at Week I-4 and Week I-2 the treatment failure events will be limited to only those that occurred prior to the Week I-4 or Week I-2 visit, respectively (Section 9.4.2.1.3).

For testing of the major secondary endpoints, the efficacy of the guselkumab group versus placebo will be compared. For all statistical comparisons of the major secondary endpoints, a CMH test

(2-sided) stratified by ADT-Failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No) will be used.

A fixed sequence testing procedure will be used to control for multiplicity over the primary and major secondary endpoints. That is, the major secondary endpoints will be tested at the 2-sided 0.05 significance level after the test on the primary endpoint. However, if an endpoint is not significant, all subsequent tests in the hierarchy will be considered not to be significant, and the p-values associated with those tests will be considered to be nominal. The testing order of these major secondary endpoints will be specified in the SAP. Note that the ranking order for the major secondary endpoints is different for the US-specific and global testing procedures due to regional preferences. The major secondary endpoint of IBDQ remission at Week I-12 will not be included in the US-specific testing procedure.

9.4.2.2.4. Other Endpoint Analyses

Comparisons between the guselkumab group and the placebo group at Week I-12 will be made for each of the endpoints (Section 9.4.1).

Analyses suitable for categorical data (eg, chi-square test or CMH test, as appropriate) will be used to compare the proportion of participants achieving selected endpoints (eg, clinical response). In case of rare events, the Fisher's exact test will be used for treatment comparisons.

Continuous response parameters will be compared using an ANOVA or covariance (ANCOVA), unless otherwise specified. If the normality assumption is in question, an ANOVA or ANCOVA on the van der Waerden normal scores will be used.

All statistical testing will be performed at the 2-sided 0.05 significance level. No adjustments for multiple comparisons will be made for these other efficacy endpoints and nominal p-values will be presented.

9.4.2.3. Maintenance Study (Phase 3 Maintenance Study)

9.4.2.3.1. Population for Efficacy Analysis

Unless otherwise noted, efficacy analyses will be based on the **Randomized Full Analysis Set,** which is defined as all randomized participants in the Maintenance Study with a modified Mayo score of 5 to 9 at induction baseline who receive at least 1 dose of study intervention. The randomized participants will include guselkumab clinical responders at Week I-12 and placebo crossover responders at Week I-24 as determined by the IWRS. Note the IWRS will use the Mayo endoscopy subscore assigned by the local endoscopist to determine the clinical response status. All other clinical responders, including clinical responders to placebo at Week I-12 and guselkumab 24-Week responders, are not part of the randomized population. Participants will be analyzed according to the intervention group to which they were randomized regardless of the intervention they actually received.

9.4.2.3.2. Primary Endpoint Analysis

The primary endpoint is clinical remission at Week M-44, defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline. The analyses will be based on the Randomized Full Analysis Set.

Participants who have a colectomy or ostomy, have protocol-prohibited medication changes (to be defined in the SAP), have a dose adjustment, or who have discontinued study intervention due to any reasons other than COVID-19 related reasons or a regional crisis, including unsatisfactory therapeutic effect or an AE of worsening UC before the Week M-44 visit will be considered not to be in clinical remission at Week M-44. For participants who discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis, their observed clinical remission status at Week M-44 will be used if available. After accounting for the treatment failure rules, participants who are missing any or all of the 3 Mayo subscores that compose the modified Mayo score or who do not return for evaluation at Week M-44 will be considered not to be in clinical remission.

A precise description of the treatment effect to be estimated from the study will be described in the estimand framework. The primary estimand will use a hybrid strategy for the intercurrent events. Details on the primary estimand and other estimand definitions will be described in the SAP.

For testing of the primary endpoint, the efficacy of each guselkumab group versus placebo will be compared. For all statistical comparisons of the primary endpoint, a CMH test (2-sided) stratified by clinical remission status at maintenance baseline (Yes/No) and induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover [guselkumab 200 mg], and placebo crossover [guselkumab 400 mg, if chosen as the Phase 3 guselkumab induction dose]) will be used. A multiplicity-controlled testing procedure to control the Type-I error at a 2-sided 0.05 significance level over the primary and major secondary endpoints is briefly described below and will be described in further detail in the SAP. As part of this testing procedure, a fixed sequence testing procedure will be used where the guselkumab 200 mg SC q4w group for the primary endpoint will be tested first. The study will be considered positive if the guselkumab 200 mg SC q4w group is significantly different from the placebo group for the primary endpoint.

To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint will be conducted using different missing data approaches; these analyses will be described in the SAP.

Subgroup analyses of the primary endpoint will be performed based on demographic and baseline disease characteristics and baseline use and history of use of UC medications (including ADT-Failure status).

9.4.2.3.3. Major Secondary Endpoint Analyses

The major secondary endpoints are:

- Symptomatic remission at Week M-44.
- Endoscopic healing at Week M-44.
- Corticosteroid-free (ie, not requiring any treatment with corticosteroids for at least 8 weeks prior) clinical remission at Week M-44.
- Clinical response at Week M-44.
- Histologic-endoscopic mucosal healing at Week M-44.
- IBDQ remission at Week M-44.
- Fatigue response at Week M-44.
- Clinical remission at Week M-44 among the participants who had achieved clinical remission at maintenance baseline.
- Endoscopic normalization at Week M-44.

The same treatment failure rules that were specified for the primary endpoint analysis will also be used for the major secondary endpoints (Section 9.4.2.3.2). Participants who are missing any or all of the 3 Mayo subscores that compose the modified Mayo score at Week M-44 will be considered not to have achieved corticosteroid-free clinical remission, maintenance of clinical response, or maintenance of clinical remission. Participants who have a missing endoscopy subscore at Week M-44 will be considered not to have achieved endoscopic healing, endoscopic normalization, or histologic-endoscopic mucosal healing at Week M-44. Participants who are missing any or all of the components in the Geboes grading system pertaining to histologic healing endpoint will be considered not to have achieved histologic-endoscopic mucosal healing. Participants who are missing either stool frequency or rectal bleeding subscores at Week M-44 will be considered not to have achieved symptomatic remission at Week M-44. Participants who have a missing IBDQ total score at Week M-44 will be considered not to have achieved IBDQ remission at Week M-44. Participants who have any missing PROMIS-Fatigue short form 7a item at Week M-44 will be considered not to have achieved fatigue response at Week M-44.

For testing of the major secondary endpoints, the efficacy of each guselkumab group versus placebo will be compared. For all statistical comparisons of the major secondary endpoints (except for clinical remission at Week M-44 among the participants who had achieved clinical remission at maintenance baseline), a CMH test (2-sided) stratified by clinical remission status at maintenance baseline (Yes/No) and induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover [guselkumab 200 mg], and placebo crossover [guselkumab 400 mg, if chosen as the Phase 3 guselkumab induction dose]) will be used. For clinical remission at Week M-44 among the participants who had achieved clinical remission at maintenance baseline, a CMH test (2-sided) stratified by induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover [guselkumab 200 mg], and placebo crossover [guselkumab 400 mg, if chosen as the Phase 3 guselkumab induction dose]) will be used.

Type I error control for Rest of World (ie, countries/territories outside the United States): A multiple testing procedure will be employed to control the overall Type 1 error rate over the primary and all major secondary efficacy analyses at the 2-sided 0.05 significance level within a

guselkumab dose group. For this procedure, a fixed sequence testing procedure will be used for the primary endpoint, with the higher dose group being tested first. Following this, the major secondary endpoints will be tested in a hierarchical manner for each dose group that is significant for the primary endpoint and the testing order will be specified in the SAP. A major secondary endpoint for a guselkumab dose group will be considered significant only if both the previous endpoints in the hierarchy and current endpoint test positive at the 2-sided 0.05 level of significance. If an endpoint is not significant, all subsequent tests in the hierarchy will be considered not to be significant. Nominal p-values will be reported for all analyses that are not multiplicity controlled.

Type I error control in the United States: A different multiplicity-controlled testing procedure to strongly control the Type I error rate at the 2-sided 0.05 significance level will be used for submission for the US and will be specified in the SAP. Note that the rank order of the major secondary endpoints is different for the US-specific and global testing procedures due to regional preferences. In addition, the major secondary endpoint of IBDQ remission at Week M-44 will not be included in the US-specific testing procedure since the FDA does not accept the IBDQ endpoint to support future labeling claims.

9.4.2.3.4. Other Endpoint Analyses

Comparisons between each of the 2 guselkumab groups and the placebo group will be made for each of the endpoints.

Analyses suitable for categorical data (eg, chi-square test or CMH test, as appropriate) will be used to compare the proportion of participants achieving selected endpoints (eg, clinical response). In case of rare events, the Fisher's exact test will be used for treatment comparisons.

Continuous response parameters measured at more than one postbaseline visit will be compared using Mixed-Effect Model Repeated Measure (MMRM) model (unless otherwise specified). If the normality assumption is in question, an appropriate transformation may be implemented before fitting MMRM model. Continuous response parameters measured at only 1 postbaseline visit will be compared using an ANOVA or covariance (ANCOVA), unless otherwise specified. If the normality assumption is in question, an ANOVA or ANCOVA on the van der Waerden normal scores will be used.

All statistical testing will be performed at the 2-sided 0.05 significance level. No adjustments for multiple comparisons will be made for these other efficacy endpoints and nominal p-values will be presented.

9.4.3. Safety Analyses

Safety analyses will be based on the Safety Analysis Set (for the induction studies) or Randomized Safety Analysis Set (for the Maintenance Study), which is composed of all randomized participants with a modified Mayo score of 5 to 9 at induction baseline who receive at least 1 dose of study intervention. Safety summaries will also be provided for participants who are not randomized in the maintenance study who receive at least 1 dose of study intervention in maintenance, and for

all participants who receive at least 1 dose of study intervention in the maintenance study (including both randomized and nonrandomized participants).

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Any AE occurring at or after the initial administration of study intervention in each study is considered to be treatment-emergent for that study. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

The following analyses of AEs will be used to assess the safety of participants:

- Frequency and type of AEs.
- Frequency and type of SAEs.
- Frequency and type of reasonably related AEs as assessed by the investigator.
- Frequency and type of AEs leading to discontinuation of study intervention.
- Frequency and type of infections.
- Frequency and type of AEs temporally associated with infusion.
- Frequency and type of injection-site reactions.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or a serious AE.

Clinical Laboratory Tests

The following summaries of clinical laboratory tests will be used to assess participant safety:

- Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry).
- Summary of maximum National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grade for postbaseline laboratory values (hematology and chemistry).
- Summary of elevated liver tests (to be defined in the SAP) will be provided.

Listings of participants with any abnormal postbaseline laboratory values of NCI-CTCAE grade ≥2 will also be provided.

Suicidal Ideation and Behavior

Suicidal ideation and behavior based on the C-SSRS and AEs will be summarized descriptively.

9.4.4. Other Analyses

Pharmacokinetic Analyses

Unless otherwise noted, PK analyses will be based on the PK Analysis Set (for an induction study) or Randomized PK Analysis Set (the maintenance study), which is defined as all randomized participants with a modified Mayo score of 5 to 9 at induction baseline who receive at least 1 dose of study intervention and have at least 1 valid blood sample drawn for PK analysis after their first dose of study intervention. Serum guselkumab concentrations over time will be summarized. Descriptive statistics, including arithmetic mean, SD, CV%, median, interquartile range, minimum, and maximum will be calculated at each nominal sampling timepoint. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database or data presentations. Concentrations below the lowest quantifiable concentration will be treated as zero in the calculation of the summary statistics.

Participants will be excluded from the PK analyses if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing time of study intervention administration, etc.). Detailed rules for the analysis will be specified in the SAP.

Population PK modeling may be conducted when appropriate. If population PK analysis is conducted, the results of the modeling analysis will be presented in a separate report.

Immunogenicity Analyses

The incidence of antibodies to guselkumab will be summarized for all randomized participants with a modified Mayo score of 5 to 9 at induction baseline who receive at least 1 dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab (ie, participants with at least 1 sample obtained after their first dose of guselkumab).

A listing of participants who are positive for antibodies to guselkumab will be provided. The maximum titers of antibodies to guselkumab will be summarized for participants who are positive for antibodies to guselkumab.

The incidence of neutralizing antibodies to guselkumab will be summarized for participants who are positive for antibodies to guselkumab and have samples evaluable for neutralizing antibodies to guselkumab.

Biomarkers Analyses

Changes in serum protein analytes, whole blood RNA, and colonic biopsy RNA obtained over time (where local regulations permit) will be summarized by treatment group. Associations between baseline levels and changes from baseline in select biomarkers and response to treatment will be explored.

The biomarker analyses will characterize the effects of guselkumab to identify PD markers and biomarkers relevant to treatment, and to determine if these markers can predict response to guselkumab. Results of serum, whole blood analyses, stool, and colonic biopsy analyses will be reported in separate technical reports.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum concentrations of guselkumab and the efficacy measures and/or relevant PD endpoints may be explored graphically when appropriate. If any visual trend is observed, additional analysis may be conducted if deemed necessary.

Pharmacogenomic Analyses

Genetic (DNA) analyses will be conducted only in participants who sign the consent form to participate in the pharmacogenomic substudy. These analyses are considered exploratory and will be summarized in a separate technical report.

Medical Resource Utilization and Health Economics Analyses

Medical resource utilization and health economics will be descriptively summarized by intervention group.

9.5. Interim Analysis

In Induction Study 1 (Phase 2b induction dose-ranging study), an interim analysis of the first 150 randomized participants who have completed the Week I-12 visit or have terminated study participation prior to Week I-12 will be performed with the intention of determining a single induction dose for Induction Study 2 (Phase 3 induction study).

Further details will be provided in the Interim Analysis Plan.

No interim analysis is planned for Induction Study 2 or the Maintenance Study.

9.6. Data Monitoring Committee

An external, independent DMC will be established and will meet periodically to review interim unblinded safety data to ensure the continuing safety of the participants enrolled in the study. The DMC will consist of 2 physicians and a statistician. The DMC responsibilities, authorities, and procedures will be documented in the DMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADT	advanced therapy (ie, TNFα antagonists, vedolizumab, or tofacitinib)
ADT-Failure	inadequate response or failure to tolerate advanced therapy
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AZA	azathioprine
BCG	Bacille Calmette-guérin
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DBL	database lock
DCS	data collection system
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	EuroQol 5 dimensions descriptive system
EQ-5D-5L	5-level EuroQol five dimensions instrument (consisting of the EuroQol five dimensions descriptive system [EQ-5D] and the EuroQol Visual Analog Scale [EQ-VAS])
EQ-VAS	EuroQol visual analog scale
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IL	interleukin
IPPI	Investigational Product Preparation Instructions
IPPM	Investigational Product Procedures Manual
IRB	Institutional Review Board
IV	intravenous/ly
IWRS	Interactive Web Response System
JAK	Janus kinase
LTE	long-term extension
mAb	monoclonal antibody
MMRM	Mixed-Effect Model Repeated Measure
MTX	methotrexate
NOAEL	no-observed-adverse-effect-level
PD	pharmacodynamics
PFS	prefilled syringe
PFS-U	prefilled syringe UltraSafe
PGIC	Patient's Global Impression of Change (of Severity of Ulcerative Colitis)

PGIS	Patient's Global Impression of Severity
PK	pharmacokinetics
POC	proof-of-concept
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PsA	psoriatic arthritis
q4w	every 4 weeks
q8w	every 8 weeks
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous/ly
SI	International System of Units
SmPC	Summary of Product Characteristics
SNP	single nucleic polymorphisms
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	White blood cell
WPAI-GH	Work Productivity and Activity Impairment Questionnaire-General Health

Definitions of Terms

Data collection system (DCS)	Includes data collected via electronic case report forms (eCRFs) and ancillary systems such as the Interactive Web Response System (IWRS), patient-reported outcome (PRO) tablets, laboratory database and imaging database.

10.2. Appendix 2: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNF Antagonist Therapies (eg, Infliximab, Adalimumab, Golimumab), Vedolizumab, or Approved Biosimilars

The criteria for inadequate initial response, response followed by loss of response, or intolerance to infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars are described in items I, II, and III, below.

I. Inadequate initial response to at least 8 weeks of therapy with infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars (primary nonresponse)

Eligible participants must satisfy criteria A, B, and C.

A. Have received induction doses of:

- Infliximab; 3 intravenous (IV) doses ≥5 mg/kg at Weeks 0, 2, and 6

  OR

- Adalimumab; subcutaneous (SC) doses of 160 mg at Week 0 and ≥80 mg at Week 2 followed by a dose ≥40 mg every 2 weeks

  OR

- Golimumab; SC doses of 200 mg at Week 0 and 100 mg at Week 2, followed by 50 or 100 mg every 4 weeks

  OR

- Vedolizumab; IV doses of 300 mg at Weeks 0, 2, and 6 or other approved dose regimen/formulation

AND

B. Did not initially respond to these induction doses of infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars, as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of ulcerative colitis (UC), as assessed by a treating physician:

- Lack of improvement or worsening in stool frequency
- Lack of improvement or worsening in rectal bleeding
- Lack of improvement or worsening in daily abdominal pain
- Lack of improvement or worsening in urgency
- Lack of improvement or worsening in the endoscopic appearance of the colonic mucosa

These signs and symptoms of UC must have occurred ≥2 weeks after receiving the last induction dose of infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having had an inadequate initial response to infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

AND

C. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the dates and doses of the failed induction therapy with infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.
- Documents that the participant had persistence of disease activity following induction therapy with infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

II. Initial response followed by loss of response to current or prior therapy with infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars (secondary nonresponse)

Eligible participants must satisfy criteria A, B, C, and D.

A. Initially responded to induction therapy

AND

B. Have received at least 2 maintenance doses of:

- Infliximab (at a dose ≥5 mg/kg)

  or
- Adalimumab (at a dose ≥40 mg)

  or
- Golimumab (at a dose of 50 of 100 mg)

  or
- Vedolizumab (at a dose ≥300 mg or other approved dose regimen/formulation)

AND

C. Have or had at least 1 of the following signs or symptoms related to recurrence of UC disease activity, as assessed by a treating physician:

- Worsening in stool frequency
- Worsening in rectal bleeding
- Worsening in daily abdominal pain
- Worsening in urgency

- Worsening in the endoscopic appearance of the colonic mucosa

These signs and symptoms of UC must have occurred ≥2 weeks after receiving the last maintenance dose of infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having lost response to infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

AND

D. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the dates and doses of the failed maintenance therapy with infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.
- Documents that the participant had recurrence of UC disease activity despite maintenance therapy with infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

III. Current or prior intolerance to therapy with infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

Eligible participants must satisfy criteria A and B.

A. Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (eg, delayed hypersensitivity or serum-sickness-like reaction); or 3) significant injection site reaction. Definitions of these 3 criteria are provided below.

Adverse reactions must have followed ≥1 dose of infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars and, in the treating physician's opinion, precluded continued use of the therapy.

1) A significant acute infusion/administration reaction is defined as an adverse reaction that was:

- Manifested through ≥1 of the following symptoms.
  a. Fever (ie, temperature greater than 100°F [38°C])
  b. Chills or rigors
  c. Pruritis
  d. Rash
  e. Flushing
  f. Urticaria or angioedema
  g. Respiratory distress (eg, dyspnea, chest pain or tightness, shortness of breath, wheezing, stridor)
  h. Clinical hypotension (eg, pallor, diaphoresis, faintness, syncope), blood pressure <90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure >20 mm Hg.

and

- Occurred ≤24 hours after infusion/administration of infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

and

- Was considered related to the infusion/administration of infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

2) A significant delayed infusion/administration reaction is defined as an adverse reaction that:

- Was manifested through 1 or more of the following symptoms:

  a. Myalgias
  b. Arthralgias
  c. Fever (ie, temperature greater than 100°F [38°C])
  d. Malaise
  e. Rash

and

- Occurred >24 hours and <15 days after infusion/administration of infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

and

- Was considered related to the infusion/administration of infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

3) A significant injection site reaction is defined as an adverse reaction that:

- Was manifested through 1 or more of the following symptoms:

  a. Significant bruising
  b. Erythema
  c. Hemorrhage
  d. Irritation
  e. Pain
  f. Pruritus
  g. "Injection site reaction"

and

- Occurred within 24 hours of an SC injection of adalimumab, golimumab, vedolizumab, or approved biosimilars.

and

- Was considered related to the injection.

B. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the date of discontinuation of infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

- Documents that the participant had intolerance to infliximab, adalimumab, golimumab, vedolizumab, or approved biosimilars.

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

10.3. Appendix 3: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to Tofacitinib

The criteria for inadequate initial response, response followed by loss of response, or intolerance to tofacitinib are described in items I, II, and III, below.

I. Inadequate initial response to at least 8 weeks of induction therapy with tofacitinib (primary nonresponse)

Eligible participants must satisfy criteria A, B, and C.

A. Have received induction therapy with tofacitinib 10 mg by mouth (PO) twice daily (or other approved dose regimen) for at least 8 weeks

AND

B. Did not initially respond to induction therapy with tofacitinib, as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of ulcerative colitis (UC), as assessed by a treating physician:

- Lack of improvement or worsening in stool frequency
- Lack of improvement or worsening in rectal bleeding
- Lack of improvement or worsening in daily abdominal pain
- Lack of improvement or worsening in urgency
- Lack of improvement or worsening in the endoscopic appearance of the colonic mucosa

These signs and symptoms of UC are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having had an inadequate initial response to tofacitinib.

AND

C. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the dates and doses of the failed tofacitinib induction therapy
- Documents that the participant had persistence of disease activity following tofacitinib induction therapy

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

II. Initial response followed by loss of response to current or prior therapy with tofacitinib (secondary nonresponse)

Eligible participants must satisfy criteria A, B, C, and D.

A. Initially responded to induction therapy

AND

B. Have received at least 8 weeks of tofacitinib at a dose ≥5 mg PO twice daily or other approved dose regimen

AND

C. Have or had at least 1 of the following signs or symptoms related to recurrence of UC disease activity, as assessed by a treating physician:

- Worsening in stool frequency
- Worsening in rectal bleeding
- Worsening in daily abdominal pain
- Worsening in urgency
- Worsening in the endoscopic appearance of the colonic mucosa

These signs and symptoms of UC are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having lost response to tofacitinib therapy.

AND

D. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the dates and doses of the failed tofacitinib maintenance therapy
- Documents that the participant had recurrence of UC disease activity despite tofacitinib maintenance therapy

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

III. Current or prior intolerance to therapy with tofacitinib

Eligible participants must satisfy criteria A and B.

A. Have developed a clinically significant adverse event (eg, serious infection, gastrointestinal perforation, lymphopenia, neutropenia, anemia, or persistently elevated liver enzymes) unresponsive to dose reduction that, in the judgment of the investigator, precluded continued use of tofacitinib to treat UC

AND

B. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the date of discontinuation of tofacitinib.
- Documents that the participant had intolerance to tofacitinib

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

10.4. Appendix 4: Definition of Inadequate Response to or Intolerance of Corticosteroids or AZA/6-MP and Corticosteroid Dependence

CORTICOSTEROIDS

Participants have failed to respond to corticosteroids if they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving at least 0.75 mg/kg/day or ≥40 mg/day of prednisone (or corticosteroid equivalent, given orally or intravenously) for 2 weeks; or ≥9 mg/day of budesonide or ≥5 mg/day of beclomethasone dipropionate given orally for at least 4 weeks.

Participants are intolerant of corticosteroids if:

- They have developed clinically significant adverse events (eg, osteonecrosis or osteoporosis, psychosis, uncontrolled diabetes) unresponsive to dose reduction that, in the judgment of the investigator, precluded the use of corticosteroids to treat ulcerative colitis (UC).

  OR

- They have a medical condition that precludes the use of corticosteroids as a treatment for UC.

Participants are corticosteroid dependent if they have failed to successfully taper their corticosteroid (ie, had a flare of disease) within 3 months of starting therapy, or if a relapse occurs within 3 months after stopping corticosteroids or if they are unable to discontinue these agents without flare within 3 months after starting them.

6-MERCAPTOPURINE (6-MP) OR AZATHIOPRINE (AZA)

Participants have failed to respond to 6-MP or AZA if they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving:

- At least 3 months of therapy with 1 mg/kg/day of 6-MP or 2 mg/kg/day of AZA.

  OR

- A lower dosage of 6-MP or AZA when country, territory, or local guidelines specify a different treatment regimen. (In such an event, the country, territory, or local guidelines needs to be included in the source document).

  OR

- The dosage of 6-MP or AZA confirmed to be therapeutic for the participant with whole blood thioguanine nucleotide levels >200 pmole/8 x 10^8 RBCs.

  OR

- The highest tolerated dosage due to leukopenia, elevated liver enzymes, or nausea.

Participants are intolerant of 6-MP or AZA if:

- They have developed clinically significant adverse events (eg, pancreatitis, arthritis accompanied by high fever and/or rash, leukopenia, or persistently elevated liver enzymes) unresponsive to dose reduction that, in the judgment of the investigator, precluded the use of 6-MP or AZA to treat UC.

  OR

- They have a medical condition that precludes the use of 6-MP or AZA.

10.5. Appendix 5: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Participants should never be allowed to read their own tuberculin skin test results. If a participant fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a participant who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries/territories, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the participants may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries/territories outside the US and Canada, country- or territory-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country/territory guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country/territory guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country/territory guidelines for immunocompromised patients exist, US guidelines must be followed.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). *Tuberculosis, a comprehensive international approach*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

10.6. Appendix 6: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy and Appendix 11 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**

  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

  Has congenital abnormalities resulting in sterility.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal female experiences menarche) or the risk of pregnancy changes (eg, a female participant who is not heterosexually active becomes active), a female participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by male or female participants must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner (vasectomized or due to medical cause) *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor or designee by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.7. Appendix 7: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA test is **negative**, the participant ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this protocol.

These eligibility criteria based on HBV test results are also represented in Table 1 below. For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines.

Table 1: Eligibility based on hepatitis B virus test results

HEPATITIS B TEST RESULT			STATUS
Hepatitis B surface antigen (HBsAg)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	
negative	negative	negative	**Eligible**
negative	(+)	negative	
negative	(+)	(+)	
(+)	negative *or* (+)	negative *or* (+)	**Not eligible**
negative	negative	(+)	**(Require testing for presence of HBV DNA*)**

* If HBV DNA is detectable, the participant is not eligible for this protocol. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, the participant is not eligible for the protocol.

For participants who **are not eligible for this protocol due to HBV test results**, consultation with a physician with expertise in the treatment of HBV infection is recommended

10.8. Appendix 8: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country- or territory-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source

documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.4, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.4.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent

must be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

A participant may be rescreened 1 time. Participants who are rescreened are required to sign a new ICF.

Completion of screening and randomization procedures within the specified screening window of approximately 8 weeks is required. If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph, endoscopy), the participant will be considered a screen failure because he/she will not meet eligibility criteria, and the expired assessments (along with the non-time-specific laboratory tests) will have to be repeated on rescreening.

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate

technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects, taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory DNA, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. They will not be used for medical care of the participant or to make a diagnosis about the participant's health. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. The start of the storage period is defined as last participant last visit. Samples will only be used to understand guselkumab, to understand ulcerative colitis, to understand differential intervention responders, and to develop tests/assays related to guselkumab and ulcerative colitis. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

Detail regarding the DMC are presented in Section 9.6

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of guselkumab and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed 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.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor may review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION AND DATA COLLECTION

Data from each study participant will be captured in an eCRF or ancillary data collection systems (DCS) such as the IWRS, PRO tablets, laboratory database, and imaging database. Electronic CRFs prepared by the sponsor are provided to the site for each participant. If the site is required to enter data directly into an ancillary DCS, the applicable system will be prepared by the ancillary data provider and provided to the site for each participant.

The study data will be transcribed by study site personnel from the source documents onto the eCRF or the ancillary DCS, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor. Worksheets may be used as source documentation to capture data and facilitate completion of the eCRF or entry of data into the applicable ancillary data system. Any such worksheets will become part of the participant's source documents. Data must be entered into the CRF or ancillary DCS in English. The CRF and data entry in the applicable DCS must be completed as soon as possible after a participant visit and the data should be available for review at the next scheduled monitoring visit. The investigator must verify that all data entries in the eCRF are accurate and correct.

Study-specific data from each source will be transmitted in a secure manner to the sponsor.

Necessary eCRF or ancillary data modifications can only be made/authorized by the investigator or appropriate site personnel using eCRF system functionality and/or ancillary data revision procedures. All data changes will be recorded in an audit trail.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF or ancillary DCS are needed after the initial entry into the CRF or ancillary DCS, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or

- Complete history of medical notes at the site or
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source (eSource) system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

MONITORING

The sponsor will use a combination of monitoring techniques (central, remote, and on-site monitoring) to monitor this study.

The sponsor designee will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site, as allowed by local regulation. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the applicable DCS component (as defined in the monitoring guidelines) with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the applicable DCS component are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor or designee as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first subject screened is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

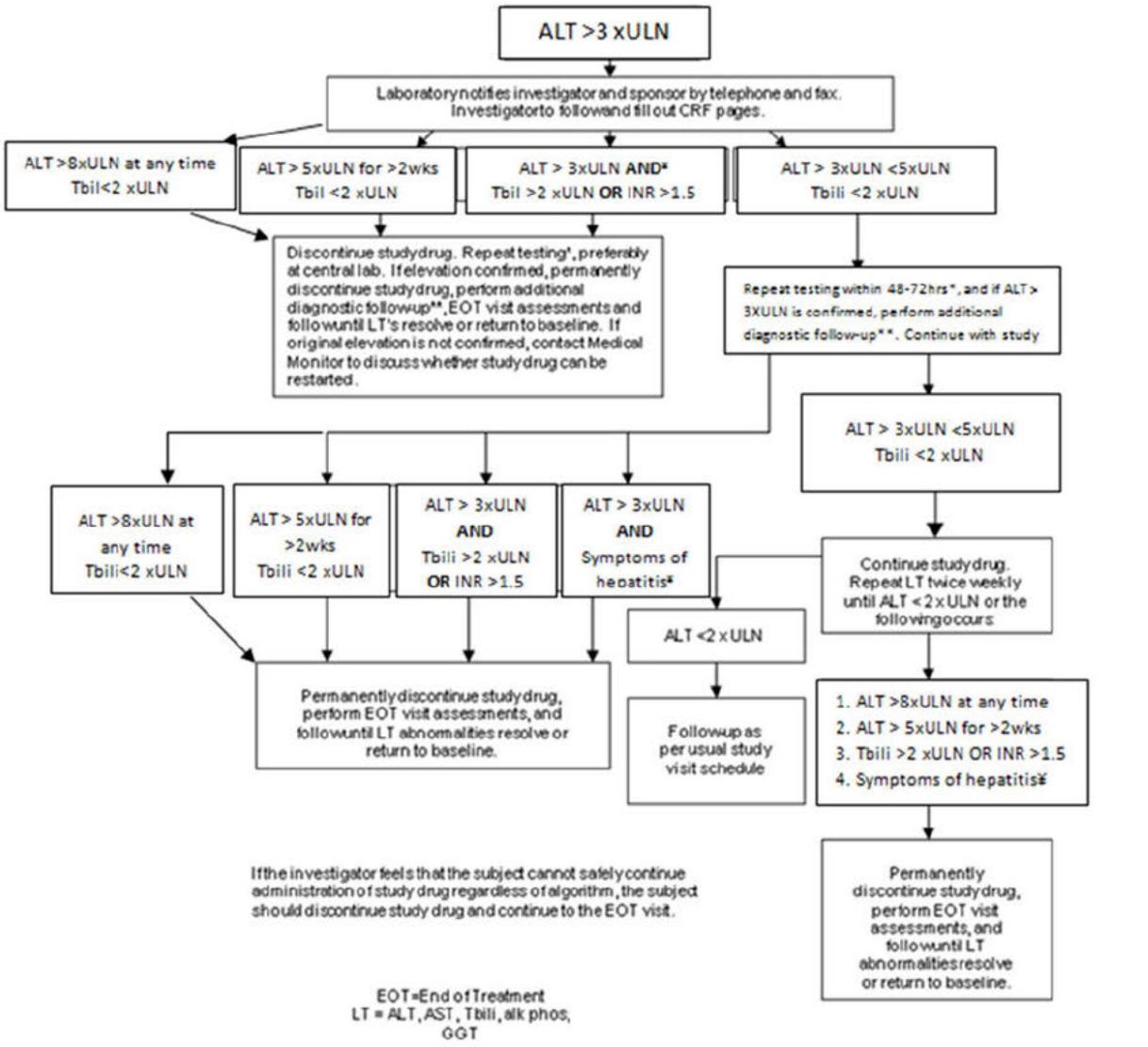
Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.9. Appendix 9: Guideline Algorithm for Monitoring, Assessment & Evaluation of Abnormal Liver Tests in Participants with No Underlying Liver Disease

The ALT criteria in this algorithm are also applicable to AST.

NOTE: "Liver tests" or "LT's" is the proper name for what are often called "liver function tests" or "LFT's"



*Repeat testing within 48-72 hours in patients with initial ALT elevations, particularly if these are not events reported previously with the drug. If ALT transient elevations have been already established as part of the safety profile, the required frequency of retesting can be decreased

¥ OR ALT >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

**SEE NEXT PAGE FOR TESTS AND EVALUATIONS TO BE OBTAINED

THE COMPLETE WORK-UP BELOW (ITEMS 1-5) SHOULD BE PERFORMED IN EVERY SITUATION WHERE "" APPEARS ABOVE. ITEMS 6-7 ARE OPTIONAL, TO BE CONSIDERED ON CASE-BY-CASE BASIS. ALL STUDIES SHOULD BE REPORTED WITH APPROPRIATE SOURCE DOCUMENTATION.**
THE STUDY MEDICAL MONITOR SHOULD BE NOTIFIED WHEN THE ABNORMALITIES ARE DETECTED AND PROVIDED WITH AN UPDATE OF THE RESULTS OF THE DIAGNOSTIC WORK-UP

The following definition of patterns of Drug Induced Liver Injury (DILI) is used when directing the work-up for potential DILI based on elevations of common laboratory tests (LT):

Histopathology	LT	Ratio (ALT/ULN)/(Alk Phos/ULN)
Hepatocellular	ALT ≥ 3 × ULN	≥ 5
Cholestatic	ALT ≥ 3 × ULN	≤ 2
Mixed	ALT ≥ 3 × ULN and AP ≥ 2 × ULN	> 2 to < 5

1. Obtain detailed history of present illness (abnormal LT's) including (if not already obtained at baseline) height, weight, body mass index (BMI). Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure (CHF), occupational exposure to hepatotoxins, diabetes mellitus (DM), gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other medications including acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), over the counter (OTC) herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical exam, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy). Allow free text in case report form for other relevant history and physical information.

2. Mandatory liver ultrasound with consideration of further imaging (eg, computerized tomography [CT], magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation).

3. If total bilirubin (Tbili) is >2xULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with

white blood count (WBC) and eosinophil count platelet count, international normalized ratio (INR), and total protein and albumin (compute globulin fraction) should also be documented. If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.

4. If initial LTs and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin M (anti-HAV IgM), anti-HAV total, hepatitis B surface antigen (HBsAg), anti-HBs, anti-HB core total, anti-HB core IgM, anti-hepatitis C virus (anti-HCV), anti-hepatitis E virus IgM (anti-HEV IgM) (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) screen.

   If patient is immunosuppressed, test for HCV RNA and HEV RNA.

   If HBsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in patients who are immunosuppressed.

   If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.

5. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: Total protein and albumin (estimate globulin fraction and obtain quantitative immunoglobulins if elevated), antinuclear antibody (ANA), anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-liver-kidney microsomal antibodies (anti-LKM antibodies), anti-smooth muscle antibodies (ASMA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then gamma-glutamyl transferase (GGT), anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody (pANCA) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/Total iron binding capacity (TIBC) and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If patient is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.

6. A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

   A liver biopsy may be considered:

if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.

if peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak Alk P has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.

in cases of DILI where continued use or re-exposure to the implicated agent is expected.

if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

7. If pertinent, copies of hospital discharge summary, radiology, pathology and autopsy reports should be obtained.

Abbreviations

AlkP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibody
ANA	antinuclear antibody
Anti-LKM1	anti-liver kidney microsomal antibody type 1
ASMA	anti-smooth muscle antibodies
AST	aspartate aminotransferase
BMI	body mass index
CBC	complete blood count
CHF	congestive heart failure
CMV	cytomegalovirus
CRP	C-reactive protein
CT	computerized tomography
DM	diabetes mellitus
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
EOI	end of intervention
GGT	gamma-glutamyltransferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HepB	hepatitis B virus
HEV	hepatitis E virus
IgM	immunoglobin M
INR	international normalized ratio
LT/LFT	liver tests/liver function tests
MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatography
NSAID	nonsteroidal anti-inflammatory drug
OTC	over the counter
PT	prothrombin time
PTT	partial thromboplastin time
RNA	ribonucleic acid
Tbili	total bilirubin

TIBC	total iron binding capacity
ULN	upper limit of normal
WBC	white blood count

10.10. Appendix 10: Mayo Score

Mayo scoring system for assessment of ulcerative colitis activity

Stool frequency[a]
- 0 Normal number of stools for this patient
- 1 1-2 stools more than normal
- 2 3-4 stools more than normal
- 3 5 or more stools more than normal

Rectal bleeding[b]
- 0 No blood seen
- 1 Streaks of blood with stool less than half the time
- 2 Obvious blood with stool most of the time
- 3 Blood alone passed

Findings of endoscopy
- 0 Normal or inactive disease
- 1 Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
- 3 Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment[c]
- 0 Normal
- 1 Mild disease
- 2 Moderate disease
- 3 Severe disease

[a] At the screening visit, each person indicates the number of stools he/she passed in a 24-hour period when in remission or before his/her UC diagnosis, thereby serving as his/her own control to establish the degree of abnormality of stool frequency.
[b] The daily bleeding score represents the most severe bleeding of the day.
[c] The physician's global assessment acknowledges the 3 other criteria, 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.

10.11. Appendix 11: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An adverse event that is not related to the use of the intervention.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant treatment(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the intervention. An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant treatment(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Special reporting situations must be reported by the investigator or site staff personnel to the sponsor or designee within 24 hours after being made aware of the event. Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without participant/patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, or intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number

- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a participant in a study within 12 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage, or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.12. Appendix 12: Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the CSR.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:

  remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures (eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration [including training where pertinent])

  procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at home administration

laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed

other procedures may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.

  other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in eCRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.

- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses may be outlined in study SAP(s).

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 2 (03 August 2021)

Overall Rationale for the Amendment: CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
	CCI	
CCI		
CCI		

Section Number and Name	Description of Change	Brief Rationale
CCI		

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol	Minor clarifying, grammatical, formatting, or spelling changes were made.	Minor errors were corrected.

Amendment 1 (08 January 2020)

Overall Rationale for the Amendment: CCI [redacted]

[redacted].

Section number and Name	Description of Change	Brief Rationale
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]

Section number and Name	Description of Change	Brief Rationale
CCI		
CCI		

Section number and Name	Description of Change	Brief Rationale
	CCI [redacted] s.	
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted] .
CCI [redacted]	[redacted]	[redacted]

Section number and Name	Description of Change	Brief Rationale
	CCI	
CCI		CCI
CCI		

Section number and Name	Description of Change	Brief Rationale
CCI	[redacted]	
CCI	[redacted]	
CCI	[redacted]	

Section number and Name	Description of Change	Brief Rationale
CCI	Maintenance Study.	
CCI		
CCI		

Section number and Name	Description of Change	Brief Rationale
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]

Section number and Name	Description of Change	Brief Rationale
	CCI	
CCI		
CCI		
CCI		
CCI		CCI
CCI		

Section number and Name	Description of Change	Brief Rationale
2.1.1 Unmet Need in Ulcerative [redacted]	CCI [redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section number and Name	Description of Change	Brief Rationale
		reasons and to prevent confounding.
CCI		
		CCI

Section number and Name	Description of Change	Brief Rationale
	7[redacted]CCI[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section number and Name	Description of Change	Brief Rationale
	CCI	
		CCI
	CCI	

Section number and Name	Description of Change	Brief Rationale
	• CCI [redacted] [redacted]	
CCI [redacted]	[redacted]	[redacted]
11 References	References were added and removed as necessary and the list of references was renumbered accordingly.	The updating of protocol text resulted in the addition and deletion of references.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

11. REFERENCES

Abraham BP (2012) and Kane S. Fecal Markers: Calprotectin and Lactoferrin. Gastroenterol Clin N Am. 2012;41:483-495.

Arora G (2009), Mannalithara A, Singh G, Gerson LB, Triadafilopoulos G. Risk of perforation from a colonoscopy in adults: a large population-based study. Gastrointest Endosc. 2009;69(3 Pt 2):654-664.

Baron JH (1964), Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. Brit Med J. 1964;1:89-92.

Côté-Daigneault J (2015), Bouin M, Lahaie R, Colombel J-F, Poitras P. Biologics in inflammatory bowel disease: what are the data? United European Gastroenterology Journal. 2015;3(5):419-428.

Cuffari C (2010). The genetics of inflammatory bowel disease: diagnostic and therapeutic implications. World J Pediatr. 2010;6(3):203-209.

Danese S (2019), Sands BE, O'Brien CD, et al. Efficacy and safety of ustekinumab through Week 16 in patients with moderate-to-severe ulcerative colitis randomised to ustekinumab: results from the UNIFI induction trial. Presented at: 14th Congress of ECCO; Mar. 6-9, 2019; Copenhagen, Denmark. Available at: https://www.ecco-ibd.eu/publications/congress-abstract-s/abstracts-2019/item/dop54-efficacy-and-safety-of-ustekinumab-through-week-16-in-patients-with-moderate-to-severe-ulcerative-colitis-randomised-to-ustekinumab-results-from-the-unifi-induction-trial.html

Danesh MJ (2016), Kimball AB. Brodalumab and suicidal ideation in the context of a recent economic crisis in the United States. J Am Acad Dermatol. 2016;74(1):190-192.

European Medicines Agency (2018). Guideline on the development of new medicinal products for the treatment of ulcerative colitis. 28 June 2018. Available at: https://www.ema.europa.eu/documents/scientific-guideline/draft-guideline-development-new-medicinal-products-treatment-ulcerative-colitis-revision-1 en.pdf

Feagan BG (2013), Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710.

Feagan BG (2016), Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016; 375(20):1946-1960.

Feagan BG (2017), Sandborn WJ, D'Haens G, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet. 2017;389(10080):1699-1709.

Feagan BG (2018), Panes J, Ferrante M, et al. Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. Lancet Gastroenterol Hepatol. 2018;3(10):671-680.

Food and Drug Administration (2016). Center for Drug Evaluation and Research. Ulcerative colitis: clinical trial endpoints guidance for industry. August 2016. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM515143.pdf

Food and Drug Administration (2019). Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009 Drug Safety. https://www.fda.gov/media/116737/download. Accessed 10 December 2019.

Furfaro F (2015), Bezzio C, Maconi G. Protein-losing enteropathy in inflammatory bowel diseases. Minerva Gastroenterol Dietol. 2015;61(4):261-265.

Geboes K (2000), Riddell R, Öst A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000;47:404-409.

Geert G (2019), D'Haens R, Sandborn WJ, et al. Maintenance treatment with mirikizumab, a p19-directed IL-23 antibody: 52-week results in patients with moderately-to-severely active ulcerative colitis. Presented at: 14th Congress of ECCO; Mar 6-9, 2019; Copenhagen, Denmark. Available at: https://www.ecco-ibd.eu/publications/congress-abstract-s/abstracts-2019/item/op38-maintenance-treatment-with-mirikizumab-a-p19-directed-il-23-antibody-52-week-results-in-patients-with-moderately-to-severely-active-ulcerative-colitis.html?highlight=WyJtaXJpa2l6dW1hYiJd

Glickman RM (1998). Inflammatory bowel disease: ulcerative colitis and Crohn's disease. In: Faluce AS, Braunwald E, eds. Harrison's Principles of Internal Medicine, 14th ed. New York, NY: McGraw-Hill;1998;1633-1645.

Gordon KB (2015), Duffin KC, Bissonnette R, et al. A Phase 2 Trial of Guselkumab versus Adalimumab for Plaque Psoriasis. N Engl J Med. 2015;373(2):136-144.

Guselkumab. (Phase 2/3 study in Crohn's Disease, Clinicaltrials.gov Identifier: NCT03466411). EudraCT Number 2017-002195-13. Available at: https://clinicaltrials.gov/ct2/show/NCT03466411

Guselkumab and Golimumab (Phase 2a Proof-of-Concept Study in Ulcerative Colitis, ClinicalTrials.gov Identifier: NCT03662542). Available at: https://clinicaltrials.gov/ct2/show/NCT03662542

Higgins PD (2005), Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. Gut. 2005;54(6):782-788.

Hochberg Y (1988). A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-802.

Irvine EJ (1994), Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology. 1994;106(2):287-296.

Kornbluth A (2010), Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010 Mar;105(3):501-23; quiz 524. Erratum in: Am J Gastroenterol. 2010;105(3):500.

Levitt DG (2017) and Levitt MD. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. Clin Exp Gastroenterol. 2017;10:147-168.

Li K (2016), Huang CC, Randazzo B, et al. HLA-C*06:02 allele and response to IL-12/23 inhibition: results from the ustekinumab phase 3 psoriasis program. J Invest Dermatol. 2016;136(12):2364-2371.

Loftus EV Jr (2004). Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004;126(6):1504-1517.

Machado Á (2018), Torres T. Guselkumab for the Treatment of Psoriasis. BioDrugs. 2018 Apr;32(2):119-128.

Marchal-Bressenot A (2017), Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. Gut. 2017;66(1):43-49.

Mirikizumab (Phase 3 Induction Study in Ulcerative Colitis, ClinicalTrials.gov Identifier: NCT03518086). Available at: https://clinicaltrials.gov/ct2/show/NCT03518086

Mirikizumab (Phase 3 Maintenance Study in Ulcerative Colitis, ClinicalTrials.gov Identifier: NCT03524092). Available at: https://clinicaltrials.gov/ct2/show/NCT03524092

Mosli MH (2017), Feagan BG, Zou G, et al. Development and validation of a histological index for UC. Gut. 2017;66(1):50-58.

Mundt JC (2013), Greist, JH, Jefferson, JW, et al. Prediction of suicidal behavior in clinical research by lifetime suicidal ideation and behavior ascertained by the electronic Columbia-Suicide Severity Rating Scale. J Clin Psych. 2013;74(9):887-893.

Ordás I (2012), Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380(9853):1606-1619.

Panaccione R (2015), Sandborn WJ, Gordon GL, et al. Briakinumab for treatment of Crohn's disease: results of a randomized trial. Inflamm Bowel Dis. 2015;21(6):1329-1340.

Posner K (2011), Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-1277.

Rabeneck L (2008), Paszat LF, Hilsden RJ, et al. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. Gastroenterology. 2008;135(6):1899-1906.

Reich K (2019), Rich P, Marri C, et al. Efficacy and safety of mirikizumab (LY3074828) in the treatment of moderate-to-severe plaque psoriasis: results from a randomized phase II study. Br J Dermatol. 2019 Feb 7. doi:10.1111/bjd.17628. [Epub ahead of print]

Risankizumab. (Phase 3 Maintenance Study in Ulcerative Colitis, ClinicalTrials.gov Identifier: NCT03398135). Available at: https://clinicaltrials.gov/ct2/show/NCT03398135

Risankizumab. (Phase 3 Induction Study in Ulcerative Colitis, ClinicalTrials.gov Identifier: NCT03398148). Available at: https://clinicaltrials.gov/ct2/show/NCT03398148

Rutgeerts P (2005), Sandborn WJ, Feagan BG et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462-2476.

Sandborn WJ (2012), Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012;367(16):1519-1528.

Sandborn WJ (2014), Feagan B, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):85-95.

Sandborn WJ (2016). The present and future of inflammatory bowel disease treatment. Gastroenterology and Hepatology. 2016;12(7):438-441.

Sandborn WJ (2017), Su C, Sands BE et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376(18):1723-1736.

Sandborn WJ (2018), Ferrante M, Bhandari BR, et al. Efficacy and safety of anti-interleukin-23 therapy with mirikizumab (LY3074828) in patients with moderate-to-severe ulcerative colitis in a phase 2 study. Gastroenterology. 2018;154(6)Suppl 1:S1360-S1361.

Sandborn WJ (2019a), Ferrante M, Bhandari BR, et al. Efficacy and safety of mirikizumab in a randomized phase 2 study of patients with ulcerative colitis. Gastroenterology. 2019 Sep 4. doi: 10.1053/j.gastro.2019.08.043. [Epub ahead of print]

Sandborn WJ (2019b), Sands BE, Panaccionne R, et al. Efficacy and safety of ustekinumab as maintenance therapy in ulcerative colitis: Week 44 results from UNIFI. Presented at: 14th Congress of ECCO; Mar 6-9, 2019; Copenhagen, Denmark. Available at: https://www.ecco-ibd.eu/publications/congress-abstract-s/abstracts-2019/item/op37-efficacy-and-safety-of-ustekinumab-as-maintenance-therapy-in-ulcerative-colitis-week-44-results-from-unifi.html

Sands BE (2017a), Chen J, Feagan BG, et al. Efficacy and safety of MEDI2070, an antibody against interleukin 23, patients with moderate to severe Crohn's disease: a Phase 2a study. Gastroenterology. 2017;153(1):77-86.

Sands BE (2017b), Sandborn W, Feagan BG, et al. DOP076 A phase 2B, multicenter, randomized, placebo-controlled dose-ranging trial of peficitinab, an oral JAK inhibitor, in patients with moderately to severely active ulcerative colitis. Abstract of the 12th Congress of ECCO. J Crohns Colitis. 2017;11(suppl 1):S71–S72. doi.org/10.1111/bjd.17628

Sands BE (2018), Sandborn WJ, Panaccione R et al. Safety and efficacy of ustekinumab induction therapy in patients with moderate to severe ulcerative colitis: results from the phase 3 UNIFI study (abstract). Presented at American College of Gastroenterology (ACG) Annual Scientific Meeting, 5-10 October 2018. Philadelphia, PA.

Sands BE (2019), Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for Ulcerative Colitis. N Engl J Med. 2019;381(13):1201-1214.

Smolen JS (2017), Agarwal SK, Ilivanova E, et al. A randomised phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate. Ann Rheum Dis. 2017;76(5):831-839.

Solem CA (2005), Loftus EV, Tremaine WJ, et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(8):707-712.

Stenson WF (2000). Inflammatory bowel disease. In: Goldman l, Bennett, JC, eds. Cecil Textbook of Medicine, 21st ed. Philadelphia, PA: WB Saunders Co; 2000;722-729.

Telesco SE (2018), Brodmerkel C, Zhang H, et al. Gene Expression Signature for Prediction of Golimumab Response in a Phase 2a Open-Label Trial of Patients With Ulcerative Colitis. Gastroenterology. 2018;155(4):1008-1011.

Travis SP (2012), Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012;61:535-542.

Truelove SC (1955), Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. Brit Med J. 1955;2:1041-1048.

Van Limbergen J (2008), Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135(4):1114-1122.

Vermeire S (2004), Van Assche G, Rutgeerts P. C-reactive protein as a marker of inflammatory bowel disease. Inflamm Bowel Dis. 2004;10(5):661-665.

Willert RP (2008), Lawrance IC. Use of infliximab in the prevention and delay of colectomy in severe steroid dependant and refractory ulcerative colitis. World J Gastroenterol. 2008;14(16):2544-2549.

Ye BD (2016), McGovern DP. Genetic variation in IBD: progress, clues to pathogenesis and possible clinical utility. Expert Rev Clin Immunol. 2016;12(10):1091-1107.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: *electronic signature appended at the end of the protocol*

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	12-Sep-2022 19:10:10 (GMT)	Document Approval