Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Ulcerative Colitis

ASTRO

Short Title

A Phase 3 Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Ulcerative Colitis

Protocol CNTO1959UCO3004; Phase 3

Version: Amendment 4

CNTO1959 (guselkumab)

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).
Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

Regulatory Agency Identifier Number(s)

IND: 140330
EU TRIAL NUMBER: 2023-504719-34

Status:	Approved
Document Date:	13 May 2025
Prepared by:	Janssen Research & Development, LLC
EDMS Number:	EDMS-RIM-583808, 5.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	13 May 2025
Amendment 3	21 October 2024
Amendment 2	16 August 2022
Amendment 1	2 May 2022
Original Protocol	11 February 2022

Amendment 4 (13 May 2025)

Overall Rationale for the Amendment:

To align with a health authority commitment to assess long-term safety outcomes, the protocol was updated to include additional hematology, chemistry, and endoscopy assessments.

The changes made to the clinical protocol CNTO1959UCO3004 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.12 Appendix 12: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.2 Schema	Updated schema to add endoscopy every 48 weeks beginning at Week 96.	Schema updated to reflect additional endoscopy assessments.
1.3 Schedule of Activities, Table 2: Schedule of Activities: Extension Treatment Period Week 28 Through Week 96	Added endoscopy assessment at Week 96 with corresponding footnote h, i, and j updated for endoscopy, partial Mayo score, and biopsy.	To align with the health authority commitment to assess long-term safety outcomes by adding hematology and chemistry every 16 weeks, and endoscopy assessments every 48 weeks beginning at Week 96.
1.3 Schedule of Activities, Table 3: Schedule of Activities: Extension Treatment Period Week 100 Through Week 248	• Added endoscopy assessment at Weeks 144, 192, 240, and ED. • Liver function tests replaced with hematology and chemistry assessments.	
4.1 Overall design	Endoscopy added to safety assessments.	
8.1.1 Mayo Score		
8.2 Safety assessments		
4.2.1 Study-Specific Ethical Design Considerations	Total blood volume collected changed from 308 mL to 326 mL.	Updated to reflect additional volume required for additional assessments.
8 Study Assessments and Procedures		
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made	Improve clarity in the protocol.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Ulcerative Colitis

IND: 140330
EU Trial Number: 2023-504719-34

A Phase 3 Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Ulcerative Colitis

DESCRIPTION OF COMPOUND

Guselkumab is a fully human immunoglobulin G1 lambda monoclonal antibody that binds to human IL-23 with high specificity and 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 mediated intracellular signaling, activation and cytokine production.

The term "study intervention" throughout the protocol, refers to study drug.

BENEFIT-RISK ASSESSMENT

Guselkumab, an IL-23 antagonist, has a well-defined long-term safety profile and has been extensively studied in the approved indications. Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with guselkumab are justified by the anticipated benefits that may be provided to participants with moderately to severely active UC. More detailed information about the known and expected benefits and risks of guselkumab may be found in the IB.

OBJECTIVES AND ENDPOINTS

The primary and secondary objectives and endpoints are listed below.

Objectives	Endpoints
Primary	
• To evaluate the efficacy, including clinical remission, of guselkumab SC induction compared to placebo in participants with moderately to severely active UC	• Clinical remission at Week 12 (defined as a CCI [redacted] CCI [redacted] and not increased from baseline, a rectal bleeding subscore of 0, and an CCI [redacted] with no friability present on the endoscopy)
Secondary	
• To further evaluate the efficacy of guselkumab SC induction compared to placebo across a range of outcome measures	• Symptomatic remission at Week 12 (defined as a CCI [redacted] and not increased from baseline, and a rectal bleeding subscore of 0) • Endoscopic improvement at Week 12 (defined as an endoscopy

Objectives	Endpoints
	subscore of 0 or 1 with no friability present on the endoscopy) • Clinical response at Week 12 (defined as a decrease from induction baseline in the CCI [redacted] 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) • Clinical remission at Week 24 • Symptomatic remission at Week 24 • Endoscopic improvement at Week 24 • Clinical response at Week 24 • Histologic-endoscopic mucosal improvement at Week 12 (defined as a combination of histologic improvement [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the CCI [redacted] and endoscopic improvement as defined above)
• To evaluate the safety of guselkumab SC induction compared to placebo	• Frequency and type of AEs (including SAEs)

HYPOTHESIS

The primary hypothesis of this study is that guselkumab SC induction is superior to placebo SC in achieving clinical remission at Week 12 among participants with moderately to severely active UC.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC induction therapy in adult participants with moderately to severely active UC who have demonstrated an inadequate response to or intolerance of conventional (ie, 6-MP, AZA, or corticosteroids) or advanced therapy (ADT; ie, TNFα antagonists, vedolizumab, ozanimod, or approved JAK inhibitors).

The main treatment period will evaluate guselkumab SC treatment through 24 weeks of therapy. Starting at Week 12, all participants who were taking corticosteroids at Week 0 must begin tapering their corticosteroid dose. This tapering is mandatory, unless not medically feasible. All participants who reach the Week 24 visit and are benefiting from study intervention in the opinion of the investigator are eligible for the study extension with treatment up to Week 248. At Week 24, participants entering the extension period will continue the same treatment regimen they were receiving prior to Week 24. The study will be unblinded after the last participant completes the Week 48 assessments and the Week 48 DBL and analyses

occur. Upon study unblinding, placebo participants who have not been rescued with guselkumab will be discontinued from study intervention and have a safety follow-up visit. All other participants will continue on guselkumab treatment up to Week 248.

Efficacy, safety, PK, immunogenicity, and biomarkers will be assessed according to the SoA.

Participants will complete an ED visit upon discontinuation of study intervention and before termination of study participation. All randomized and treated participants are to complete the safety follow-up visit 12 weeks after the last dose of study intervention.

Database locks are planned for Week 24, Week 48, and when the last participant completes the last scheduled assessment as shown in the SoA. Additional DBLs may be added as necessary.

End of Study

The end of study is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study or if a decision has been made by the sponsor not to pursue an indication in UC or SC induction and appropriate follow-up has been completed. 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 target sample size is 399 participants, with 133 participants per intervention group. Participants who have demonstrated an inadequate response to or intolerance of advanced therapy (ADT-IR) will comprise approximately 40% to 50% of the population.

INTERVENTION GROUPS AND DURATION

The overall study duration is up to 268 weeks. The study comprises of the following periods

- Screening period: up to 8 weeks
- Main treatment period: 24 weeks
- Extension treatment period: 224 weeks
- Safety Follow-up period: until approximately 12 weeks after the last dose of study intervention.

At Week 0, eligible participants will be randomly assigned in a 1:1:1 ratio to one of the following SC treatments:

- 133 participants to guselkumab CCI [redacted] at Weeks 0, 4, and 8 followed by guselkumab 200 mg SC q4w through Week 24
- 133 participants to guselkumab CCI [redacted] at Weeks 0, 4, and 8 followed by guselkumab 100 mg SC q8w through Week 24
- 133 participants to placebo SC q4w from Week 0 through Week 24

Participants will be allocated to an intervention group using permuted block randomization stratified by ADT-IR status (Yes/No) and CCI [redacted] at baseline (moderate [2] or severe [3]) obtained during central review of the video endoscopy.

All participants in the placebo group who meet rescue criteria at Week 16 will receive rescue treatment, ie, guselkumab CCI [redacted] at Weeks 16, 20, and 24 followed by guselkumab 100 mg SC q8w. Participants

randomized to guselkumab who meet rescue criteria at Week 16 will continue their assigned treatment regimen and receive blinded sham rescue with matching placebo SC injections at Weeks 16, 20, and 24.

Description of Interventions

Participants will receive the study interventions as described above in the Intervention Groups and Duration section.

Guselkumab will be provided in 2 dose strengths: guselkumab CCI in a single-dose PFS-Y and CCI in a single-dose PFS-U. Matching placebo will be provided as CCI in a single-dose PFS-Y and as CCI in a single-dose PFS-U.

EFFICACY EVALUATIONS

Efficacy evaluations will include the following:

- CCI
- Inflammatory PD markers including CRP and fecal calprotectin
- Histological assessments (eg, CCI
- Patient-reported outcome measures to assess CCI outcomes, fatigue, and UC symptoms and signs (ie, CCI

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 verify the stability of antibodies to guselkumab and/or 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 ulcerative colitis. Assessments will include the evaluation of relevant biomarkers in serum, whole blood, and endoscopic biopsy samples, where local regulations permit.

SAFETY EVALUATIONS

Safety assessments include AEs, clinical laboratory tests, vital signs and physical examinations, a screening electrocardiogram, suicidality assessment, concomitant medication review, monitoring for injection-site reactions and hypersensitivity reactions, a tuberculosis evaluation and other infection assessments.

STATISTICAL METHODS

Sample Size Determination

Sample size was determined by the power to detect significant differences in the primary endpoint of clinical remission at Week 12, and by the objective of maintaining at least 85% power across secondary endpoints at Week 12 between the combined guselkumab SC induction groups and the placebo SC group and secondary endpoints at Week 24 between each guselkumab group and the placebo group, using 2-sided

chi-square tests with significance level 0.05. The assumed rates are 22% versus 8% (guselkumab vs placebo) for clinical remission at Week 12. The study is sized such that the guselkumab therapy achieves a >95% power for the primary endpoint and a ≥85% power for all secondary endpoints.

Efficacy Analyses

Descriptive statistics (eg, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphical data displays (eg, line plots) may also be used to summarize data.

Analyses suitable for categorical data (eg, chi-square tests, CMH tests, or logistic regression, as appropriate) will be used to compare the proportions of participants achieving selected endpoints (eg, clinical response). In cases of rare events, the Fisher's exact test will be used for treatment comparisons. Continuous response parameters measured at more than one post-baseline visit will be compared using an MMRM model (unless otherwise specified). If the normality assumption is in question, an appropriate transformation may be implemented before fitting the MMRM model. Continuous response parameters measured at only one post-baseline visit will be compared using a ANOVA or ANCOVA, unless otherwise specified. In cases of small sample size, t-test will be used for treatment comparisons.

Efficacy analyses will be based on all randomized participants who received at least 1 dose of study intervention (the Full Analysis Set). Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment they received.

The primary endpoint (clinical remission at Week 12) will be analyzed based on the primary estimand, considering treatment groups, population, variable, ICE strategies, and population-level summary. After accounting for the ICEs, any participants who are missing any or all of the 3 subscores that comprise the primary endpoint at Week 12 will be considered not to be in clinical remission at Week 12 (ie, nonresponder imputation).

Summaries of the proportion of participants in clinical remission at Week 12 will be presented by treatment group. The common risk difference and the associated 95% confidence interval between the combined guselkumab SC induction group and the placebo group will be computed by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The primary endpoint will be tested by a two-sided Mantel-Haenszel test for the common risk difference. Stratification will be by the ADT-IR status (Yes/No), and CCI [redacted] at baseline (moderate [2], severe [3]) as obtained during central review of the video endoscopy. The study will be considered successful if the test for the primary endpoint is positive. While a multiplicity-controlled testing procedure will be implemented to control for the type I error rate at the 0.05 significance level (2-sided) across the primary and secondary endpoints, the primary endpoint will be tested at full significance level. Only if this test is significant, secondary endpoints will be tested in a confirmatory manner.

Safety Analyses

Safety data, including but not limited to, AEs, SAEs, infections, injection-site reactions, changes in laboratory parameters (hematology and chemistry), and suicidal ideation and behavior will be summarized. All reported AEs will be included in the analysis.

Other Analyses

Patient-reported Outcomes

Analysis of patient-reported outcomes will follow the general considerations. The testing of these endpoints will not be controlled for multiplicity and nominal p-values will be provided.

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 the population PK analysis are conducted, the results of these analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum guselkumab concentrations and efficacy measures will be analyzed graphically. If feasible, a suitable exposure-response model may be developed to describe the relationship between serum guselkumab exposure and efficacy. Results of the population PK/PD analysis will be presented in a separate technical report.

Immunogenicity Analyses

The incidence of antibodies to guselkumab will be summarized for all participants in the immunogenicity analysis set.

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.

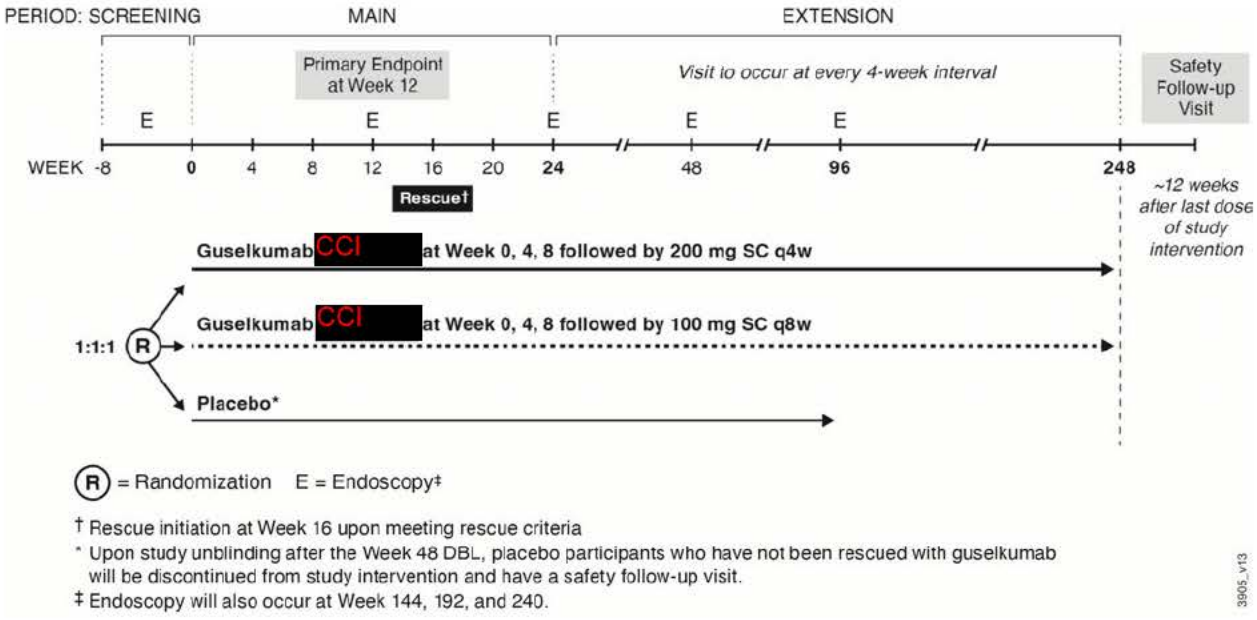
The incidence of neutralizing antibodies to guselkumab will be summarized for participants who are positive for antibodies to guselkumab and have samples evaluable for neutralizing antibodies to guselkumab.

Biomarker 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.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities: Screening and Treatment Period Through Week 24

Period	Screening	Treatment Period							ED[a]	Safety Follow-Up[b]	Notes
Week	(≤8 weeks)	0	4	8	12	16	20	24			
Visit Windows		±4 days				±7 days					
Study Assessments/ Procedures[c]											
Screening/Administrative											
Informed consent	X										ICF must be signed before first study-related activity.
Inclusion/exclusion criteria	X	X									
Medical history and demographics	X										
Review pre-study therapy	X										Pre-study therapies administered up to 30 days before the first dose of study intervention must be recorded. Any COVID-19 vaccines administered, regardless of timing, must be recorded on the eCRF.
Review preplanned surgery/procedure(s)	X										
ECG	X										
Chest radiograph	X										A historical chest radiograph or CT scan is acceptable if obtained within 12 weeks before the Week 0 visit. If unavailable, a chest radiograph must be obtained during the screening period.
IGRA	X										Either the QuantiFERON-TB® or T-SPOT® TB IGRA tests are acceptable. IGRA testing is not required at screening for participants with a history of treated latent TB or current treatment for latent TB.

Table 1: Schedule of Activities: Screening and Treatment Period Through Week 24											
Period	**Screening**	**Treatment Period**							**ED[a]**	**Safety Follow-Up[b]**	**Notes**
Week	**(≤8 weeks)**	**0**	**4**	**8**	**12**	**16**	**20**	**24**			
Visit Windows		**±4 days**				**±7 days**					
Study Assessments/ Procedures[c]											
Stool studies to evaluate for enteric pathogens	X										Stool studies for enteric pathogens may be performed at screening at either the central or a local laboratory and must include a stool culture and *Clostridioides difficile* (formerly known as *Clostridium difficile*) toxin assay. Although stool studies may be processed at either the central or local laboratory, the central laboratory is preferred when available. A stool study performed within 16 weeks before Week 0 will be accepted as a screening sample. *C. difficile* infection is presumed if screening EIAs for both glutamate dehydrogenase antigen and toxins A or B are positive OR reflexive NAAT performed on discordant EIAs is positive. Additional testing, such as ova and parasites or *Escherichia coli* O157:H7 assessment, may be performed at the investigator's clinical discretion.
HBV and HCV testing	X										
HIV test	X										
Provide participant diaries	X										Participants will be trained on how and when to complete required diary entries (for the 10 days immediately before Week 0, through Week 4, and the 10 days immediately before each visit thereafter) and will be reminded to bring the diaries to each study visit for review (ie, CCI [redacted]
Study Intervention											
Randomization		X									
Administer study intervention		X	X	X	X	X	X	X			All assessments/procedures should be completed before study intervention administration, unless otherwise specified.
Safety Assessments											
Physical examination	X	X	X	X	X	X	X	X	X	X	A complete physical examination should be performed at the screening visit. A targeted physical examination may be performed at all other visits per the discretion of the investigator.
Weight	X	X			X			X	X	X	
Height	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	Temperature (any method is acceptable), pulse/heart rate, respiratory rate, and blood pressure. Vital signs

Table 1: Schedule of Activities: Screening and Treatment Period Through Week 24											
Period	**Screening**	**Treatment Period**							**ED[a]**	**Safety Follow-Up[b]**	**Notes**
Week	**(≤8 weeks)**	**0**	**4**	**8**	**12**	**16**	**20**	**24**			
Visit Windows		**±4 days**				**±7 days**					
Study Assessments/ Procedures[c]											
											should be obtained prior to and approximately 30 minutes after the SC injection, or if the participant reports any symptoms.
Serum pregnancy test	X										
Urine pregnancy test		X	X	X	X	X	X	X	X	X	A urine pregnancy test must be performed before any study intervention administration for women of childbearing potential.
FSH	X										Consider testing in women with no menses for ≥52 weeks without an alternative medical cause.
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	
CCI	X	X	X	X	X	X	X	X	X		At the screening visit, the CCI should be completed as the first assessment, after signing the informed consent and before any other tests, procedures, or other consultations. For subsequent visits, the CCI should be completed after all PROs and before any other tests, procedures, or other consultations.
TB evaluation/other infection assessment	X	X	X	X	X	X	X	X	X	X	Screening TB assessment must include specific questions about 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 imaging, tuberculin skin, or other TB testing results. Additionally, investigators are required to evaluate participants for any signs or symptoms of active TB or other infections. If TB reactivation or new TB infection is suspected at any time during the study, study intervention must be withheld and an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.
Review of UC-related procedures and surgeries		X	X	X	X	X	X	X	X	X	

Table 1: Schedule of Activities: Screening and Treatment Period Through Week 24

Period	Screening	Treatment Period							ED[a]	Safety Follow-Up[b]	Notes
Week	**(≤8 weeks)**	**0**	**4**	**8**	**12**	**16**	**20**	**24**			
Visit Windows		**±4 days**				**±7 days**					
Study Assessments/ Procedures[c]											
Injection-site evaluation		X	X	X	X	X	X	X			Injection sites will be evaluated for reactions and any injection-site reaction should be recorded as an adverse event.
Efficacy Assessments											
CCI		X			X			X	X		
CCI	X		X	X		X	X				If endoscopy is not performed at the ED visit, the CCI should be assessed.
Endoscopy	X				X			X	X		A flexible sigmoidoscopy is generally acceptable for endoscopic assessments. A full colonoscopy should replace a sigmoidoscopy if screening for polyps or dysplasia is required or deemed clinically necessary by the investigator. Local pathology results from the screening endoscopy must be reviewed before the first dose of study intervention. The screening endoscopy should be performed within 2 weeks of the Week 0 visit and at least 4 days before the Week 0 visit to allow adequate time for central review of the endoscopy video. Endoscopy findings will be assessed by the investigator (ie, local endoscopist) during the procedure, and a video of the endoscopy will be submitted for central review. The CCI CCI as obtained during central review will be used for eligibility (ie, CCI ≥2, CCI 5 to 9) and assess rescue criteria.
Patient-reported Outcomes											
CCI		X			X			X	X		CCI should be completed before the CCI and before any other tests, procedures, or other consultations. CCI is a daily diary that should be collected for 10 consecutive days before the Week 0 visit.
CCI		X			X			X	X		
CCI		X	X	X	X	X	X	X	X		
Clinical Laboratory Tests											
Hematology and chemistry	X	X	X	X	X	X	X	X	X	X	

Table 1: Schedule of Activities: Screening and Treatment Period Through Week 24

Period	Screening	Treatment Period							ED[a]	Safety Follow-Up[b]	Notes
Week	(≤8 weeks)	0	4	8	12	16	20	24			
Visit Windows		±4 days				±7 days					
Study Assessments/ Procedures[c]											
CRP		X	X	X	X	X	X	X	X		
Fecal calprotectin		X	X		X			X	X		At visits where endoscopy is performed, stool sample collection (on-site or at home) must be obtained before the start of a bowel preparation or at least 48 hours after completing the endoscopy.
Pharmacokinetics and Immunogenicity Assessments											
Serum guselkumab concentration		X	X	X	X	X	X	X	X	X	Blood samples should be collected before the administration of study intervention. All reasonable attempts should be made to collect samples at the scheduled visits and record the actual times of sample collections.
Antibodies to guselkumab		X	X	X	X			X	X	X	
Pharmacodynamics and Biomarkers											
Whole blood (RNA) (where local regulations permit)		X			X			X			
Serum biomarkers (where local regulations permit)		X			X			X			
Biopsy samples for histology	X				X				X[d]		Biopsy samples for histology are not required at the Week 24 endoscopy.
Biopsy samples for exploratory biomarker analyses (where local regulations permit)	X				X				X[d]		Adjacent biopsy samples should be collected to support exploratory cellular and transcriptional biomarker analyses.

Footnotes:

a. If possible, the ED visit assessments/procedures should be performed at the time of the Week 12 visit for participants who discontinue study intervention prior to the Week 12 visit or at the time of the Week 24 visit for participants who discontinue between the Week 12 and 24 visits.

b. Participants who discontinue study intervention prior to Week 24 should have a safety follow-up visit approximately 12 weeks after the last dose of study intervention.

c. All assessments/procedures should be completed before study intervention administration, unless otherwise specified. PRO assessments should be completed first, followed by the CCI and then any other clinical procedures, tests, or consultations.

d. If the ED visit occurs after the Week 12 visit, this assessment/procedure should not be performed.

Table 2: Schedule of Activities: Extension Treatment Period Week 28 Through Week 96																				
Week[a,b]:	**28**	**32**	**36**	**40**	**44**	**48 c**	**52 d**	**56**	**60 d**	**64**	**68 d**	**72**	**76 d**	**80**	**84[d]**	**88**	**92 d**	**96**	**ED**	**SFU[e]**	**Notes**
Visit Window	**±10 days**																				
Study Assessments/ Procedures[f]																					
Study Intervention																					
Dispense study intervention	X	X	X	X	X	X		X		X		X		X		X		X			If applicable, study intervention for at-home administration at Weeks 52, 60, 68, 76, 84, and 92 will be supplied to participants during the on-site visits at Weeks 48, 56, 64, 72, 80, and 88 respectively. Study intervention for optional at-home administration will be supplied at Week 96 for participants continuing in the study.
Self-administration training	X	X																			At the Week 28 and 32 visits, participants who opt to self-administer will receive training (per investigator discretion and/or allowed per local regulation) on how to self-administer study intervention. A caregiver may also be trained to administer study intervention, if it was allowed per local regulation. If needed, participants (or their caregivers) can be trained at later visits.
Administer study intervention	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X			Upon completion of training and at the discretion of the investigator and participant, self-administration of study intervention (or administration by a caregiver) at the investigative site may begin at the Week 36 visit. From Week 52 to Week 92, participants (or their

																				caregivers) may administer study intervention at home for those weeks at which telemedicine visits occur. Refer to Section 6.1.1 for details.
Dispense at-home study medication diary						X		X		X		X		X		X		X			Eligible participants who opt to perform at-home administration will be provided a study medication diary to record the at-home administration of study intervention and bring it back at the next on-site visit. In the diary, participants will receive instructions on how to self-evaluate any injection-site reactions.
Study intervention accountability	X	X	X	X	X	X		X		X		X		X		X		X			
Safety Assessments																					
Physical examination	X	X	X	X	X	X	Tg	X	Tg	X	Tg	X	Tg	X	Tg	X	Tg	X	X	X	A targeted physical examination may be performed at the discretion of the investigator. Assessment is <u>not</u> required for telemedicine visits.
Vital signs	X	X	X	X	X	X	Tg	X	Tg	X	Tg	X	Tg	X	Tg	X	Tg	X	X	X	Temperature (any method is acceptable), pulse/heart rate, respiratory rate, and blood pressure. Vital signs should be obtained prior to and approximately 30 minutes after the SC injection, or if the participant reports any symptoms. Assessment is <u>not</u> required for telemedicine visits.
Urine pregnancy test	X	X	X	X	X	X	Tg	X	Tg	X	Tg	X	Tg	X	Tg	X	Tg	X	X	X	A urine pregnancy test must be performed before on-site study intervention administration in participants

																					who are women of childbearing potential. Assessment is not required for telemedicine visits.
TB evaluation/other infection assessment	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X	X	X	
Injection-site evaluation	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X			Injection sites should be evaluated for reactions and any injection-site reaction should be recorded as an adverse event.
CCI						X						X									The CCI should be completed after all PROs and before any other tests, procedures, or other consultations.
Concomitant therapy	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X	X	X	
AE review	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X	X	X	
Review of UC-related procedures and surgeries	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X	X	X	
Efficacy Assessments																					
Endoscopy						X												X[i]	X[h]		
CCI						X												X	X[h]		
CCI	X	X	X	X	X			X		X		X		X		X					If the endoscopy is not performed at ED visits prior to Week 96, the partial Mayo score should be assessed.
Patient-reported Outcomes																					
CCI						X						X						X	X		CCI and CCI should be completed before the CCI and before any other tests, procedures, or other consultations.
CCI						X						X						X	X		
CCI	X	X	X	X	X	X		X		X		X		X		X		X	X		
Clinical Laboratory Tests																					
Hematology and chemistry		X				X						X						X	X		
CRP		X				X						X						X	X		

Fecal calprotectin						X						X						X	X		At visits where endoscopy is performed, stool sample collection (on-site or at home) must be obtained before the start of a bowel preparation or at least 48 hours after completing the endoscopy.
Pharmacokinetics and Immunogenicity Assessments																					
Serum guselkumab concentration		X		X		X						X						X	X	X	All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of PK sample collections.
Antibodies to guselkumab		X				X						X						X	X	X	All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of sample collections.
Pharmacodynamics and Biomarkers																					
Biopsy samples for histology						X													X[j]		
Biopsy samples for exploratory biomarker analyses (where local regulations permit)						X													X[j]		Adjacent biopsy samples should be collected to support exploratory cellular and transcriptional biomarker analyses.

Footnotes:

a. If a participant discontinues study intervention prior to the Week 96 visit, the ED visit assessments/procedures should be completed. In addition, the participant should return for a safety follow-up visit approximately 12 weeks after their last dose of study intervention.
b. The visit window is ±10 days. Post-randomization scheduled study visit dates should be based on the participant's randomization date.
c. The study will be unblinded after the last participant completes the Week 48 visit assessments and the Week 48 DBL is completed. Upon study unblinding, placebo participants who have not been rescued with guselkumab will be discontinued from study intervention and have a safety follow-up visit. All other participants will continue study intervention up to Week 248.
d. Participants can opt to conduct this visit via telemedicine (T) visit (if allowed per local regulation and per investigator discretion). Otherwise, this visit should be conducted on-site.
e. Participants who discontinue study intervention prior to Week 96 should have a safety follow-up visit approximately 12 weeks after their last dose of study intervention.
f. All assessments/procedures should be completed before study intervention administration on-site, unless otherwise specified. PRO assessments should be completed first, followed by the CCI assessment, and then any other clinical procedures, tests, or consultations.
g. Assessment/procedure is not required for telemedicine visits.

h. This assessment/procedure is only required if the ED visit occurs at or after the Week 44 visit through Week 48. After Week 96, endoscopy is not recommended for the ED visit if the participant had a study-related endoscopy within 24 weeks.
i. A flexible sigmoidoscopy is generally acceptable for endoscopic assessments. A full colonoscopy should replace a sigmoidoscopy if screening for polyps or dysplasia is required or deemed clinically necessary by the investigator. PI must review local pathology results and report any abnormal findings to sponsor.
j. For ED visits prior to Week 48, biopsies are required to be performed.

Table 3: Schedule of Activities: Extension Treatment Period Week 100 Through Week 248

Week[a]:	112	128	144	160	176	192	208	224	240	248	ED	SFU[b]	Notes
Visit Window	±10 days												
Study Intervention													
On-site Visit	X	X	X	X	X	X	X	X	X	X	X	X	Participants that do not opt for at-home administration will have on-site visits either q4w or q8w according to their assigned treatment regimen.
Telemedicine Visit	q4w (between on-site visits)												Site to contact participants to remind them about at-home administration (as applicable) and perform safety assessments. On-site visits may replace telemedicine visits based on site/participant preference or per local regulation.
Dispense study intervention	X	X	X	X	X	X	X	X	X	X			Study intervention will be dispensed during on-site visits and supplied to participants for at-home administration (as applicable).
Dispense at-home study medication diary	X	X	X	X	X	X	X	X	X				
Administer study intervention	q4w or q8w (as applicable)												Study intervention will be self-administered (or administered on-site per local regulation) according to treatment regimen prior to Week 96. Retraining on self-administration (or administration by a caregiver) will be provided if needed.
Safety Assessments													
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	
Endoscopy[c]			X			X			X		X		Endoscopy is not recommended for the ED visit if the participant had

Week[a]:	112	128	144	160	176	192	208	224	240	248	ED	SFU[b]	Notes
Visit Window	±10 days												
Study Intervention													
													a study-related endoscopy within 24 weeks. .
Urine pregnancy test	q4w or q8w (as applicable)										X	X	Must be performed at least q8w (on-site or at home) in female participants of childbearing potential and a negative result must be available before study intervention administration.
Injection-site evaluation	q4w										X	X	Evaluations specified for q4w should be conducted during telemedicine and on-site visits (as applicable).
TB evaluation/other infection assessment													
Concomitant therapy											X	X	
AE review											X	X	
Review of UC-related procedures and surgeries											X	X	
Hematology and chemistry	X	X	X	X	X	X	X	X	X		X		

Footnotes:

a. If a participant discontinues study intervention prior to the Week 248 visit, the ED visit assessments should be completed. In addition, the participant should return for a safety follow-up visit approximately 12 weeks after their last dose of study intervention.

b. The safety follow-up visit should be completed approximately 12 weeks after the last dose of study intervention.

c. A flexible sigmoidoscopy is generally acceptable for endoscopic assessments. A full colonoscopy should replace a sigmoidoscopy if screening for polyps or dysplasia is required or deemed clinically necessary by the investigator. PI must review local pathology results and report any abnormal findings to sponsor.

2. INTRODUCTION

Guselkumab is a fully human immunoglobulin G1 lambda monoclonal antibody that binds to the p19 protein subunit of human IL-23 with high specificity and affinity. By binding to the p19 subunit of IL-23, guselkumab blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 mediated intracellular signaling, activation and cytokine production including IL-17A, IL-17F, and IL-22.

A rapidly growing body of literature suggests that the IL-23 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases including psoriasis, psoriatic arthritis, ankylosing spondylitis, and IBD. Susceptibility to psoriasis, psoriatic arthritis, and IBD has been shown to be associated with genetic polymorphisms in IL-23/IL-23 receptor components.

Guselkumab is currently being studied in participants with UC (see details in Section 2.2).

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the IB for guselkumab.

The term "study intervention" throughout the protocol, refers to study drug as defined in Section 6.1, Study Intervention(s) Administered.

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.

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 (Ordás 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 (Ordás 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).

Despite the availability of advanced therapies, many patients either inadequately respond (ie, primary nonresponse) or lose their initial response (ie, secondary nonresponse) to treatment, highlighting the significant unmet medical need for more effective therapies. Given the anal and safety of anti-IL-23 treatment demonstrated to date in both Crohn's disease and UC, there is strong rationale for the development of guselkumab in UC (Feagan 2018; Feagan 2017; Feagan 2016; Sandborn 2018; Sandborn 2012; Sands 2017).

Subcutaneous (SC) delivery of biologic agents has become a valuable alternative to IV administration across many disease areas. Although the pharmacokinetic profiles of SC and IV formulations differ, SC administration has proven effective, safe, well-tolerated, generally preferred by patients and healthcare providers due to the greater flexibility and ease of administration for patients or their caregivers at their preferred setting. For IBD patients, IV infusions represent an extra burden which takes time away from other activities (Buisson 2013). In addition, SC administration has resulted in reduced drug delivery-related healthcare costs and resource utilization (Bittner 2018). In short, SC administration has become an attractive alternative to more invasive, expensive, and time-consuming intravenous infusions. However, despite a growing number of therapeutic options for UC, few biologic therapies allow for SC induction and maintenance.

Considering the potential benefits of anti-IL-23 therapy and SC induction dosing, the aim of this study is to evaluate the efficacy, safety, and PK/PD profile of guselkumab SC induction compared to placebo in participants with moderately to severely active UC.

2.2. Background

Guselkumab 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 are presented in Section 3 of the guselkumab IB.

Guselkumab Clinical Studies

Guselkumab has received marketing approval in several countries and regions globally for the treatment of adults with moderate to severe plaque psoriasis and active PsA. The approved guselkumab dose for psoriasis and PsA is 100 mg by SC injection at Weeks 0, 4, and q8w thereafter. In the EU, for treatment of PsA, a dose of 100 mg q4w may also be considered for patients at high risk for joint damage according to clinical judgement.

Two global Phase 2/3 clinical programs are ongoing in Crohn's disease (CNTO1959CRD3001; GALAXI) and UC (CNTO1959UCO3001; QUASAR) evaluating induction dose regimens up to 1200 mg IV in GALAXI and CCI in QUASAR administered at Weeks 0, 4, and 8, as well as maintenance dose regimens of 100 mg SC q8w and 200 SC q4w in both programs. A separate Phase 3 SC induction study is planned for Crohn's disease (GRAVITI; CNTO1959CRD3004), evaluating the same CCI induction dose regimen included in this protocol.

As mentioned above, guselkumab is being investigated in several other indications. Details about these guselkumab clinical development programs are provided in Section 4 of the latest version of the guselkumab IB.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of guselkumab may be found in the Investigator's Brochure.

2.3.1. Risks for 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 6.8). • 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 6.8.2 and 7.1). • Participants in the placebo arm who meet rescue criteria will receive guselkumab (Section 6.5.1).
Risks Due to Study Intervention Guselkumab		
Serious infections and reactivation of latent infections	Available animal and human data suggest that blockade of IL-23 may be associated with an increased infection risk. Infections have been identified as adverse reactions for guselkumab, including respiratory infections, herpes simplex, tinea infections, and gastroenteritis.	• Participants with a history of, or ongoing, chronic or recurrent infectious disease, including HIV, HBV and HCV, will be excluded from the study. Similarly, participants with evidence of active or untreated latent TB will be excluded from the study (Section 5.2). • Participants who have received a live viral or live bacterial vaccination within 4 weeks before the first dose of study intervention will be excluded from the study. In addition, participants must agree not to receive a live viral or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention (Sections 5.2 and 5.3). • Participants will be instructed to seek medical attention if they develop signs or symptoms suggestive of an infection, and investigators are instructed in the protocol to monitor for signs or symptoms of infections, including tuberculosis (Sections 8.2.10 and 8.2.11). • Discontinuation of a participant's study intervention must be strongly considered if the participant develops a serious infection, including but not limited to sepsis or pneumonia. In addition, any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete (Sections 7.1 and 8.2.10).
Hypersensitivity reactions, including serious hypersensitivity reactions.	Serious hypersensitivity reactions including anaphylaxis have been reported in postmarketing experience with guselkumab in psoriasis patients.	• Participants with known allergy, hypersensitivity, or intolerance to guselkumab or its excipients will be excluded from the study (Section 5.2). • Sites are instructed that before any administration of study intervention, appropriately trained personnel and medications (eg, injectable

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. In addition, all participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, itching, hives) (Section 8.2.9). • Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1).
Malignancy	The preponderance of preclinical data suggests that blockade of endogenous IL-23 would not be detrimental and may in fact be beneficial in tumor immunosurveillance and host protection; however, a risk of malignancy cannot be excluded.	• Those participants who currently have a malignancy or have a history of malignancy within 5 years prior to screening (with exceptions noted in Section 5.2) will be excluded from the study. Additionally, participants who have a 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 will be excluded from the study (Section 5.2). • During the conduct of the study, participants will undergo regular clinical monitoring including routine safety labs to assess for any changes in health status that may indicate a possible malignancy. • Participants who develop a malignancy during the study (with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from study intervention (Section 7.1).
Liver injury	An SAE of 'toxic hepatitis' was reported in a participant in a Phase 2 Crohn's disease study who received guselkumab 1200 mg IV at Weeks 0, 4, and 8, and 200 mg SC at Week 12. This event may represent drug-induced liver injury possibly related to guselkumab (see Section 5.1.3 of IB [guselkumab]). Transaminase increases have been identified as an adverse reaction of guselkumab. In 2 Phase 3 PsA clinical studies, increased ALT and/or AST was observed more	• During the conduct of the study, liver function tests will be monitored at regular intervals in accordance with regulatory guidance (Food and Drug Administration 2019). In addition, the induction doses evaluated in this clinical program will not exceed CCI (systemic exposure comparable to guselkumab CCI • Participants with marked liver enzyme elevations or symptoms or signs of liver dysfunction (eg, jaundice), should undergo a thorough investigation for possible causes of liver injury (Appendix 10, Section 10.10). A participant must have their study intervention discontinued if the participant has severe liver test abnormalities that are not transient and are not explained by other etiologies (Section 7.1).

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	frequently in patients treated with guselkumab 100 mg SC q4w compared to patients treated with guselkumab 100 mg SC q8w or placebo.	
Immunosuppression	It is unknown if guselkumab in combination with other immunosuppressives increases the risk of diseases associated with immunosuppression, such as infections or malignancy.	• In order to minimize the theoretical increased risk of infection or malignancy with the combination of guselkumab with immunosuppressive therapy, the baseline dose of oral corticosteroids on study entry is limited to ≤20 mg prednisone or its equivalent per day, or 9 mg/day of budesonide, or 5 mg/day beclomethasone, which must be tapered during the from Week 12 onwards. Furthermore, participants receiving AZA, 6-MP, or MTX, must have been taking them for ≥12 weeks and been on a stable dose for at least 4 weeks before baseline. Additionally, participants are also excluded from the study if they have received cyclosporine, mycophenolate mofetil, tacrolimus, or sirolimus within 4 weeks, or anti-TNF α therapy within 8 weeks, or vedolizumab within 12 weeks prior to the first dose of study intervention. Further detail regarding concomitant medications is provided in Sections 5.1 and 5.2. • During study participation, the use of immunomodulators other than AZA, 6-MP, and MTX (eg, cyclosporine) as well as biologic immunomodulators (eg, TNFs α antagonists, vedolizumab) is prohibited. Participants initiating these treatments will be discontinued from further study intervention administration (see Section 6.8.2 for further details on prohibited concomitant medications).
Risks Due to Study Procedures		
Risks associated with the endoscopy procedure including bleeding and colonic perforation	These risks are well recognized but are considered rare (Arora 2009; Rabeneck 2008).	Trained and experienced endoscopists will be performing the procedure during this study.

2.3.2. Benefits for 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, 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

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with guselkumab are justified by the anticipated benefits that may be afforded to participants with ulcerative colitis.

Guselkumab has undergone extensive nonclinical and clinical development as summarized in the latest version of the IB and described briefly in Section 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 and psoriatic arthritis established a favorable benefit-risk profile for guselkumab in the treatment of plaque psoriasis and regulatory approval for both indications. This clinical experience provided support for the ongoing development of guselkumab in other inflammatory diseases such as UC and Crohn's disease.

In Crohn's disease, results from the GALAXI 1 study show that guselkumab IV induction demonstrated greater improvements compared to placebo across the key clinical efficacy and endoscopic outcome measures at Week 12 (Danese 2021; Sandborn 2020b). The safety profile of guselkumab in the GALAXI 1 study population is consistent with the safety profile of guselkumab established from clinical studies across investigational and approved indications.

In UC, animal and human data support the critical role of IL-23 in the disease pathogenesis. Clinical data from Phase 2 and Phase 3 studies of mirikizumab, an anti-IL-23 mAb, has demonstrated POC for this mechanism in UC (Geert 2019; Sandborn 2018). Importantly, in the QUASAR Phase 2b induction study, guselkumab has shown efficacy when compared with placebo at Week 12 and a consistent safety profile to that previously observed.

CCI [redacted] However, safety of these doses is supported by the available data from preclinical toxicology studies and ongoing clinical studies, including those in IBD (See Section 4.3). The Phase 2b portion of the QUASAR program in UC tested induction dose regimens up to CCI [redacted] the guselkumab induction dose for this study is based on favorable efficacy and safety data from the induction portion of that program.

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 summary, the collective preclinical and clinical evidence for guselkumab provide strong scientific and clinical rationale for the potential benefit in participants with moderately to severely

active UC. 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.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are as follows:

Objectives	Endpoints
Primary	
• To evaluate the efficacy, including clinical remission, of guselkumab SC induction compared to placebo in participants with moderately to severely active UC	• Clinical remission at Week 12 (defined as a CCI [redacted] and not increased from baseline, a rectal bleeding subscore of 0, and an CCI [redacted] with no friability present on the endoscopy)
Secondary	
• To further evaluate the efficacy of guselkumab SC induction compared to placebo across a range of outcome measures	• Symptomatic remission at Week 12 (defined as C [redacted] and not increased from baseline, and a rectal bleeding subscore of 0) • Endoscopic improvement at Week 12 (defined as an CCI [redacted] with no friability present on the endoscopy) • Clinical response at Week 12 (defined as a decrease from induction baseline in the CCI [redacted] 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) • Clinical remission at Week 24 • Symptomatic remission at Week 24 • Endoscopic improvement at Week 24 • Clinical response at Week 24 • Histologic-endoscopic mucosal improvement at Week 12 (defined as a combination of histologic improvement [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the CCI [redacted] and endoscopic improvement as defined above)
• To evaluate the safety of guselkumab SC induction compared to placebo	• Frequency and type of AEs (including SAEs)
Exploratory	
• To further evaluate the efficacy of guselkumab SC compared to placebo across a range of outcome measures	• Endoscopic normalization at Week 12 and at Week 48 (defined as an CCI [redacted] of 0)

Objectives	Endpoints
	• Histologic improvement at Week 12 and at Week 48 (defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the CCI [redacted] • Histologic remission at Week 12 and at Week 48 (defined as absence of neutrophils from the mucosa [both lamina propria and epithelium], no crypt destruction, and no erosions, ulcerations or granulation tissue according to the CCI [redacted] • Symptomatic remission over time • Corticosteroid-free clinical remission at Week 24 • Change from baseline in the modified CCI [redacted] at Week 12 • Change from baseline in the partial CCI [redacted] over time • Change from baseline in the stool frequency and CCI [redacted] at each visit over time • CCI [redacted] of 0 at each visit over time • CCI [redacted] of 0 or 1 at each visit over time • Change from baseline in the CCI [redacted] at Week 12 • Change from baseline in the full CCI [redacted] at Week 12 • Clinical remission at Week 48 • Endoscopic improvement at Week 48 • Clinical response at Week 48 • Histologic-endoscopic mucosal improvement at Week 48 • Corticosteroid-free clinical remission at Week 48
• To evaluate the impact of guselkumab SC on biomarkers	• Change from baseline in CRP and fecal calprotectin
• To evaluate the impact of guselkumab SC on patient-reported outcomes (PROs)	• Endpoints based on CCI [redacted] and CCI [redacted]

Objectives	Endpoints
• To evaluate the PK and immunogenicity of guselkumab SC	• Serum concentrations of guselkumab • Incidence and titers of antibodies to guselkumab

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints and Section 9 for further details on the analyses of the endpoints. Exploratory endpoints are not limited to those specified above. Refer to the SAP for further details.

HYPOTHESIS

The primary hypothesis of this study is that guselkumab SC induction is superior to placebo SC in achieving clinical remission at Week 12 among participants with moderately to severely active UC.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC induction therapy in adult participants with moderately to severely active UC who have demonstrated an inadequate response to or intolerance of conventional (ie, 6-MP, AZA, or corticosteroids) or advanced therapy (ADT; ie, TNFα antagonists, vedolizumab, ozanimod, or approved JAK inhibitors).

A target of 399 participants will be enrolled in this study with 133 participants planned per intervention group. Participants who had an inadequate response to or intolerance of advanced therapy (ADT-IR) will comprise a minimum of approximately 40% and a maximum of approximately 50% of the population. Consented participants will be screened for study eligibility within 8 weeks of the Week 0 visit. Eligible participants will be randomized in a 1:1:1 ratio to the following intervention groups:

- guselkumab CCI at Weeks 0, 4, and 8 followed by guselkumab 200 mg SC q4w through Week 24
- guselkumab CCI at Weeks 0, 4, and 8 followed by guselkumab 100 mg SC q8w through Week 24
- placebo SC q4w from Week 0 through Week 24

Participants will be allocated to an intervention group using permuted block randomization stratified by ADT-IR status (Yes/No) and CCI at baseline (moderate [2] or severe [3]) as obtained during central review of the video endoscopy.

All participants in the placebo group who meet rescue criteria at Week 16 will receive rescue treatment, ie, guselkumab CCI at Weeks 16, 20, and 24 followed by guselkumab 100 mg SC q8w. Participants randomized to guselkumab who meet rescue criteria at Week 16 will continue

their assigned treatment regimen and receive blinded sham rescue with matching placebo SC injections at Weeks 16, 20, and 24.

Rescue criteria are defined as:

- No improvement (ie, no decrease) in CCI [redacted] at Week 12 as obtained during central review, when compared with baseline

  AND

- A <2 point improvement (ie, <2 point decrease) in CCI [redacted] score at Weeks 12 and 16, when compared with baseline

All participants who reach the Week 24 visit and are benefiting from study intervention in the opinion of the investigator are eligible for the study extension with treatment up to Week 248. At Week 24, participants entering the extension period will continue the same treatment regimen they were receiving prior to Week 24 (either the treatment regimen assigned at randomization or the rescue regimen as described above).

The study will be unblinded after the last participant completes the Week 48 assessments and the Week 48 DBL and analyses occur. Upon study unblinding, placebo participants who have not been rescued with guselkumab will be discontinued from study intervention and have a safety follow-up visit. All other participants will continue on guselkumab treatment up to Week 248.

Participants who are receiving oral 5-ASA compounds, oral corticosteroids, or conventional immunomodulators (AZA, 6-MP, or MTX) for the treatment of UC at baseline should maintain a stable dose through Week 48; with the exception of oral corticosteroids which require mandatory tapering at Week 12. See Section 6.8.1 for instructions on concomitant medications.

Starting at Week 12, all participants who were taking corticosteroids at Week 0 must begin tapering their corticosteroid dose (for additional details, see Section 6.8.1.1, Table 4). This tapering is mandatory, unless not medically feasible.

Participants will complete an ED visit upon discontinuation of study intervention and before termination of study participation. All randomized and treated participants are to complete the safety follow-up visit 12 weeks after the last dose of study intervention.

Efficacy, safety, PK, immunogenicity, and biomarkers will be assessed according to the Schedule of Activities (SoA, Section 1.3).

Safety assessments include AEs, clinical laboratory tests (hematology and chemistry), vital signs, physical examination, screening ECG, suicidality assessment, and monitoring for hypersensitivity reactions, injection-site reactions, and early detection of active TB. Endoscopies will also be performed to assess long term safety.

Database locks are planned for Week 24, Week 48, and when the last participant completes the last scheduled assessment as shown in the SoA (Section 1.3). Additional DBLs may be added as necessary. An overview of the study design is presented in Section 1.2.

4.2. Scientific Rationale for Study Design

This SC induction study is intended to provide clinical evidence to support efficacy and safety of guselkumab SC induction dosing, compared to placebo. The safety and efficacy endpoints in this study are similar to those in the ongoing guselkumab Phase 3 UC program (QUASAR) designed to demonstrate the efficacy and safety of guselkumab IV induction. Additionally, the study population is generally consistent with the QUASAR population, which evaluates participants with moderately to severely active UC who demonstrated an inadequate response to or intolerance of conventional or advanced therapies. These similarities may enable indirect study comparison of guselkumab IV induction versus SC induction treatment.

Blinding, Control, Study Periods, Intervention Groups

Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints. A 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. To minimize risk to participants, they will be evaluated for rescue treatment and participants in the placebo group who meet the rescue criteria will receive guselkumab CCI at Weeks 16, 20, and 24 followed by guselkumab 100 mg SC q8w (see Section 6.5).

Participants initially randomized to either guselkumab groups who meet the rescue criteria will receive a blinded sham rescue at Weeks 16, 20, and 24. Published data from both IL-12/23 (ustekinumab) and IL-23 (mirikizumab) therapies suggest that participants may achieve a delayed induction response (Sands 2019; Sandborn 2020). Thus, participants undergoing sham rescue may still benefit from continued guselkumab therapy.

A study duration of 24 weeks is thought to be sufficient to evaluate efficacy and safety of SC induction followed by SC maintenance of guselkumab in UC. The guselkumab maintenance dosing regimen after Week 8 in this study is identical to that in the ongoing guselkumab Phase 3 UC program (QUASAR). After Week 24, no differences in guselkumab concentrations and exposures are expected between CCI induction (in this study) and CCI induction (QUASAR) dose regimens (see Section 4.3 for more details). Consequently, this study is a 24-week study with a 224-week extension, giving participants who are deemed by the investigator to be benefiting from study intervention access to treatment for approximately 5 years. The follow-up period (approximately 12 weeks after the last dose of study intervention) is designed to collect the final safety data.

Biomarker 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 may help 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 RNA expression profiles. Colonic biopsies will also be obtained from all participants to assess cellular and molecular changes within the intestinal mucosal tissue. 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 sample may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Patient-reported Outcomes on Health-related Quality of Life

Patient-reported outcome evaluations (ie, CCI [redacted] will be used to assess the benefits of guselkumab treatment on disease-specific and general CCI [redacted] Patient-reported outcome evaluations are only being collected in countries where translations of the evaluations are available. See Section 8.1, Efficacy Assessments for more details.

Oral Corticosteroids Tapering

Participants on corticosteroids will undergo mandatory tapering from Week 12 onwards according to pre-defined recommended tapering schedule given that obtaining corticosteroid-free clinical remission is an important goal of therapy (Lichtenstein 2018) (see Section 6.8).

4.2.1. 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. Written consent/assent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

The primary ethical concern is that one third of the participants in this study with moderately to severely active UC will receive placebo; however, these participants will be rescued upon meeting the rescue criteria (see Section 6.5). The use of placebo in participants with active disease is considered clinically acceptable in support of scientific research and is still considered necessary in IBD clinical trials (Danese 2016). A placebo-control period facilitates the evaluation of the efficacy and safety of a new treatment compared with placebo.

The total blood volume to be collected from each participant in this study (approximately 326 mL over 268 weeks) is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross (approximately 475 mL every 8 weeks).

4.3. Justification for Dose

Participants will be randomly assigned in a 1:1:1 ratio to receive the following dose regimens:

- Guselkumab CCI at Weeks 0, 4, and 8 followed by guselkumab 200 mg SC q4w
- Guselkumab CCI at Weeks 0, 4, and 8 followed by guselkumab 100 mg SC q8w
- Placebo SC q4w

A single SC induction guselkumab dose regimen CCI at Weeks 0, 4, and 8) was selected for this study based on data from the Phase 2 dose-ranging study of guselkumab IV in UC (QUASAR). The QUASAR Phase 2 Week 12 analyses demonstrated similar efficacy with guselkumab induction doses of CCI and CCI administered C at Weeks 0, 4, and 8, respectively. There was no clear dose/exposure-response within the range of guselkumab IV induction doses tested. As a result, the CCI induction dose regimen was selected for confirmatory evaluation in the guselkumab QUASAR Phase 3 studies.

With an estimated bioavailability of approximately 50% for guselkumab SC (TREMFYA® SmPC 2021; TREMFYA® USPI 2021), a CCI dose of guselkumab is expected to result in comparable overall guselkumab exposure (AUC) to theCCI dose. Population PK modeling and simulation demonstrate that while peak concentrations were higher with the CCI induction dose regimen, trough concentrations following the CCI induction dose regimen were non-inferior when compared with the IV induction dose regimen. Experience from biologics approved for both IV and SC administration demonstrate that achieving similar overall exposure (Cavg,ss) with non-inferior trough concentrations results in comparable efficacy for both routes of administration (Ji 2019; Sandborn 2020a). In addition, serum peak concentrations in the induction period may not be a dominant driver of efficacy for biologics in IBD (Rutgeerts 2015). Given this, a single guselkumab induction dose regimen of CCI at Weeks 0, 4, and 8 will be evaluated in participants with moderately to severely active UC. Of note, this same SC guselkumab induction dose regimen was selected for evaluation in the Crohn's disease indication.

Two guselkumab maintenance dose regimens (200 mg SC q4w and 100 mg SC q8w) will be evaluated in this study. These are the same doses being evaluated in the ongoing Phase 3 QUASAR study. The selection of the same maintenance dose regimens will enable cross-study comparison of SC induction followed by SC maintenance regimen (in this study) versus IV induction followed by SC maintenance regimen (in the QUASAR study). 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 of exposure that should support dose/exposure-response assessment of maintenance therapy in the treatment of UC.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study or if a decision has been made by the sponsor not to pursue an indication in UC or SC induction and appropriate follow-up has been completed. 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.

Participant Study Completion Definition

A participant will be considered to have completed the study if they have completed assessments at Week 248 and completed the safety follow-up visit.

Participants who prematurely discontinue study intervention for any reason before completion of the Week 248 visit can be considered to have completed the study if they have completed the safety follow-up visit assessments as indicated in 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, for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study 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 the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. 18 years of age or older (or the legal age of consent in the jurisdiction in which the study is taking place).

Type of Participant and Disease Characteristics

2. Documented diagnosis (histological and either endoscopic or radiographic) of UC at least 12 weeks prior to screening. A biopsy report supporting the diagnosis must be available in the source documentation.
3. Moderately to severely active UC, defined as baseline (Week 0) CCI [redacted] of 5 to 9, inclusive, using the CCI [redacted] obtained during central review of the screening video endoscopy.
4. CCI [redacted]
5. CCI [redacted]

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 (see Exclusion Criterion 2).

Concomitant or Previous Medical Therapies Received

8. Criterion modified per Amendment 1
   8.1 Criterion modified per Amendment 2
   8.2 A participant must:
   a. Have received treatment with 1 or more TNFα antagonists, vedolizumab, ozanimod, or approved JAK inhibitors at a dose approved for the treatment of UC, and have a documented history of inadequate response to or intolerance of such treatment as defined in Appendix 3 (Section 10.3) and Appendix 4 (Section 10.4);
      OR
   b. Be naïve to advanced therapy (ie, TNFα antagonists, vedolizumab, ozanimod, or approved JAK inhibitors) or not have demonstrated an inadequate response to or intolerance of advanced therapy **AND** have a prior or current UC medication history that includes at least 1 of the following:
      1) Inadequate response to or intolerance of current treatment with oral corticosteroids or immunomodulators (6-MP or AZA) as defined in Appendix 2 (Section 10.2).
         OR
      2) History of an inadequate response to or intolerance of at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA) as defined in Appendix 2 (Section 10.2).
         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 2 (Section 10.2).
9. Criterion modified per Amendment 1
   9.1 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 be ≤9 mg/day of budesonide, or ≤5 mg/day beclomethasone dipropionate and 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. Criterion modified per Amendment 1

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

a. TNFα-antagonist therapy (eg, infliximab, adalimumab, or golimumab [or approved biosimilars for these therapies]) for at least 8 weeks.
b. Vedolizumab for at least 12 weeks.

Note for a and b: If there is proper documentation of an undetectable drug level measured by the site using a commercially available assay for any of the approved biologics above, there is no minimum washout prior to baseline.

c. Tofacitinib, filgotinib, upadacitinib and other JAK inhibitors for at least 2 weeks or 5 half-lives, whichever is longer.
d. Ozanimod or other S1PR modulators for at least 4 weeks or 5 half-lives, whichever is longer.
e. Cyclosporine, mycophenolate mofetil, tacrolimus, or sirolimus for at least 4 weeks.
f. 6-thioguanine must have been discontinued for at least 4 weeks.
g. Rectal corticosteroids (ie, corticosteroids administered to the rectum or sigmoid colon via foam or enema or suppository) for at least 2 weeks.
h. 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.
i. Parenteral corticosteroids for at least 2 weeks.
j. Total parenteral nutrition for at least 2 weeks.
k. Antibiotics for the primary treatment of UC (eg, ciprofloxacin, metronidazole, or rifaximin) for at least 2 weeks.

Sex and Contraceptive/Barrier Requirements

11. Before randomization, a woman must be:

a. Not of childbearing potential

OR

b. Of childbearing potential and:

- Have a negative serum pregnancy test at screening and a negative urine pregnancy test at Week 0

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 of study intervention (ie, the end of relevant systemic exposure).

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.

12. 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.

13. Participants must agree not to donate eggs (ova, oocytes) or sperm for the purposes of reproduction during the study and for 12 weeks after the last dose of study intervention.

Informed Consent

14. Must sign an ICF indicating that participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.
    Note: In regions where a participant is ≥18 but has not yet reached the local legal age of consent, informed consent must be obtained from and signed by both the participant and his or her legally acceptable representative.
15. Criterion deleted per Amendment 1.
16. 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 the study:

Medical Conditions

1. Criterion modified per Amendment 1
   1.1 Severe extensive colitis as evidenced by:
   a. Current hospitalization for the treatment of UC.
      OR
   b. Investigator judgement that the participant is likely the 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:
      i. Diarrhea with >6 bowel movements/day with macroscopic blood in stool
      ii. Focal severe or rebound abdominal tenderness
      iii. Persistent fever (temperature >38°C)
      iv. Tachycardia (>100 beats/minute)
      v. Anemia (hemoglobin <8.5 g/dL [SI: <85.0 g/L])
2. Presence on screening endoscopy of adenomatous colonic polyps, if not removed before study entry, or history of adenomatous colonic polyps that have not been removed.
3. Diagnosis of indeterminate colitis, microscopic colitis, ischemic colitis, or Crohn's disease or clinical findings suggestive of Crohn's disease.
4. Positive stool culture or other examination for an enteric pathogen, including *Clostridioides difficile* (formerly known as *Clostridium difficile)* toxin, within 16 weeks before the first dose of study intervention, unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen. If time allows, treatment and repeat testing can occur in the current screening period. Note:

Participants with a history of cytomegalovirus colitis only remain eligible if, in the opinion of the investigator, the infection resolved at least 12 weeks prior to screening.

5. UC limited to the rectum only or to <20 cm of the colon.
6. Presence of a stoma.
7. Presence or history of a fistula.
8. Surgery within 8 weeks before screening or planned surgery during the study that may confound the evaluation of benefit from study intervention (eg, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage).
9. 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).

Malignancy or Increased Potential for Malignancy:

10. 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 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 12 weeks before the first dose of study intervention).
11. 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

12. 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.
13. History of a transplanted organ (with the exception of corneal transplant performed >12 weeks before screening).
14. Poor tolerability of venipuncture or lacks adequate venous access for required blood sample collections during the study period.
15. Active alcohol or substance abuse within 1 year before screening; use of marijuana is not necessarily exclusionary, unless deemed abuse by the investigator.
16. Suicidal ideation or suicidal behavior in the last 6 months (assessed at Screening). May be defined as a CCI rating of any of the following:
    a. CCI [redacted]
    b. CCI [redacted]
    c. 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.

    Participants with CCI [redacted] or non-suicidal

self-injurious behavior who are determined to be at risk by the investigator may not be randomized.

17. Known allergy, hypersensitivity, or intolerance to guselkumab or its excipients (refer to the guselkumab IB).
18. A woman who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 12 weeks after the last dose of study intervention.
19. A man who plans to father a child while enrolled in this study or within 12 weeks after the last dose of study intervention.

Prior/Concomitant Therapy

20. Has received the following 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 1 year of the first dose of study intervention.
    c. Agents that deplete B or T cells (eg, rituximab, alemtuzumab) within 24 weeks of the first dose of study intervention.
    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:

21. History of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Participants with radiographic evidence of possible prior histoplasmosis or coccidioidomycosis will be excluded. Note: See Exclusion Criterion 32 regarding tuberculosis-related granulomatous disease.
22. History of, or ongoing, chronic or recurrent infectious disease, including but not limited to, recurrent sinopulmonary infections, bronchiectasis, recurrent renal/urinary tract infection (eg, pyelonephritis, cystitis), an open, draining, or infected skin wound, or an ulcer.
23. Abnormal chest radiograph within 12 weeks before the first dose of study intervention with clinically significant findings such as malignancy, previously unrecognized pulmonary pathology, as well as active or latent infections from TB, histoplasmosis, or coccidiomycosis. A chest CT scan obtained outside of the protocol instead of a chest radiograph is also acceptable. Refer to Exclusion Criterion 32 for information regarding eligibility with a history of latent TB.
24. History of being HIV antibody positive, or tests positive for HIV at screening.
25. Seropositive for antibodies to HCV, unless they satisfy 1 of the following conditions:
    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 screening.
26. Tests positive for HBV infection. (Appendix 5 [Section 10.5])

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.

27. BCG vaccination within 1 year or any other live bacterial or live viral vaccination within 4 weeks of baseline or plans to receive such vaccines during the study.
28. History of nontuberculous mycobacterial infection or clinically significant opportunistic infection (eg, pneumocystosis, invasive aspergillosis, PML). See Exclusion Criterion 4 regarding cytomegalovirus colitis.
29. Clinically significant infection (eg, hepatitis, sepsis, pneumonia, pyelonephritis), hospitalization for an infection, or treatment with parenteral antibiotics for an infection within 8 weeks 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).
30. Evidence of a herpes zoster infection within 8 weeks before the first dose of study intervention.
31. During the 6 weeks prior to baseline (Week 0), have had ANY of the following (regardless of vaccination status): (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features 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

    a. 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

    b. With the 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: Those participants who may carry a higher risk for severe COVID-19 illness should follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study
32. Criterion modified per Amendment 2

    32.1 Meeting **ANY** of the following TB screening criteria is exclusionary:

    Note: IGRA testing includes either QuantiFERON-TB® or T-SPOT®.TB.

    a. History of active TB or shows signs or symptoms suggestive of active TB upon medical history and/or physical examination at screening.
    b. History of untreated latent TB prior to screening. An exception is made for participants who are receiving treatment or will initiate treatment for latent TB prior to first administration of study intervention.

Note: For participants with a history of treated latent TB there must be documentation of appropriate treatment prior to the first administration of study intervention. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation. IGRA testing is not required at screening for participants with a history of treated latent TB or ongoing treatment for latent TB.

c. Recent close contact with a person with active TB. An exception is made if such participants are referred to a physician specializing in TB to determine if treatment is warranted or not. This evaluation must be adequately documented and, if treatment is recommended, the participant must be receiving appropriate treatment prior to the first administration of study intervention.
d. Positive IGRA test result within 8 weeks before the first dose of study intervention. An exception is made for participants with:
   - History of adequately treated latent TB as described above.
   - Newly identified positive IGRA test result 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.
   - False-positive IGRA test as determined by the following:

     A suspected false-positive initial IGRA test must be repeated. If repeat testing is NOT positive, the participant must be referred to a physician specializing in TB to determine if the initial test can be considered a false-positive. This evaluation must be adequately documented prior to the first dose of study intervention. If repeat testing is positive, however, it will be considered a true-positive and the participant is only eligible if active TB has been ruled out and appropriate treatment for latent TB has been initiated as described above.
e. Chest radiograph or chest CT (if obtained outside of the protocol) within 12 weeks before the first dose of study intervention that shows abnormalities suggestive of active or inactive TB.

Screening Laboratory Tests

33. Screening laboratory test results outside the following parameters, and if 1 or more of the laboratory parameters are out of range, a single retest of laboratory values is permitted during the approximately 8-week screening period:
    a. Hemoglobin <8.0 g/dL (SI: <80.0 g/L)
    b. WBC $<3 \times 10^3$ cells/µL (SI: $<3.0 \times 10^9$ cells/L)
    c. Neutrophils <1.5 × 103 cells/µL (SI: $<1.5 \times 10^9$ cells/L)
    d. Platelets $<100 \times 10^3$ cells/µL (SI: $<100 \times 10^9$ cells/L)
    e. eGFR <30 mL/min/1.73 m^2 using the CKD-EPI formula (Levey 2009)
    f. Alanine aminotransferase or aspartate aminotransferase concentrations >2 times the ULN range
    g. TBili >1.5 times the ULN range (Isolated total bilirubin >1.5 times the ULN range is allowed for those participants with known Gilbert's syndrome. Note: Gilbert's syndrome is suggested by direct bilirubin <30% [Palmer 2020])

Other Exclusions

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

35. 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.
36. 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.

Note: Investigators must 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 the participant no longer meets all eligibility criteria, then the participant must 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 6, Regulatory, Ethical, and Study Oversight Considerations (Section 10.6).

5.3. Lifestyle Considerations

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

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

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

3. It is recommended that participants are up to date on age-appropriate vaccinations prior to screening as per routine local medical guidelines. It is strongly recommended that participants will have completed a locally-approved (or emergency use-authorized) COVID-19 vaccination regimen at least 2 weeks prior to study-related visits or procedures. Study participants should follow applicable local vaccine labeling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.8, Concomitant Therapy).

4. Willing and able to complete a daily diary 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. This study will use IWRS. The investigator will not generate screening and enrollment logs directly from IWRS.

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 screening window of approximately 8 weeks is required. If any delay leads to the expiration of time-specific assessments (eg, IGRA testing, chest radiograph, endoscopy), the participant will be considered a screen failure because they will not meet eligibility criteria, and the expired assessment(s) (along with the non-time-specific laboratory tests) will have to be repeated on rescreening. Additional criteria for retesting and rescreening are outlined below.

Retesting

Retesting of abnormal screening laboratory results that may lead to exclusion will be allowed once. A second retest of abnormal screening laboratory results may be allowed upon consultation and approval by the sponsor's medical monitor. Retesting can occur at an unscheduled visit during the screening period, as long as this is done within the specified screening window.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then start a new screening period including the collection and testing of new laboratory specimens. Previous TB evaluation results (including an IGRA test and chest imaging), and endoscopy results from the first screening event may be used if they meet the specified protocol criteria as described in Section 5.1. Medical monitor approval is required prior to the study site obtaining a new informed consent for rescreening.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.11 (Appendix 11, Study Conduct During a Natural Disaster). Criteria for temporary discontinuation of study intervention are described in Section 7.1.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Designation	Product
Investigational Medicinal Product(s)	Authorization status in the EU/EEA: Authorized: N/A Unauthorized: Guselkumab, Placebo

Study intervention administration must be captured in the source documents and the CRF. Study-site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

Guselkumab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

For details on rescue medications, refer to Section 6.5.1, Rescue Medication. For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

Description of Interventions

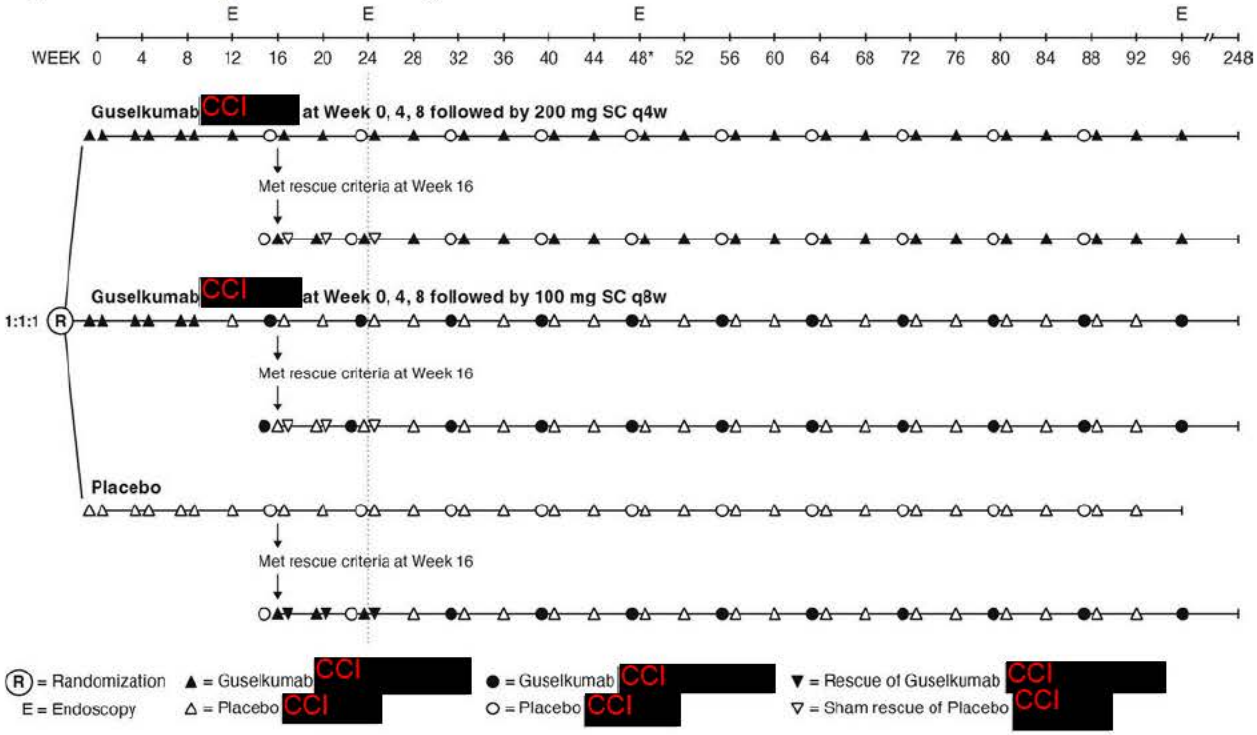
Arm Name	Arm A	Arm B	Arm C
Intervention Name	Guselkumab	Guselkumab	Placebo
Dose Formulation	Active guselkumab CCI [redacted]	Active guselkumab CCI [redacted] Active guselkumab CCI [redacted]	Matching placebo of CCI [redacted] Matching placebo of CCI [redacted]
Unit Dose Strength(s)	CCI [redacted]	CCI [redacted] SC 100 mg	Placebo
Dosage Level(s)	Guselkumab CCI [redacted] at Weeks 0, 4, and 8 followed by guselkumab 200 mg q4w SC at Week 12.	Guselkumab CCI [redacted] at Weeks 0, 4, and 8 followed by guselkumab 100 mg q8w SC at Week 16.	Placebo SC (2 placebo CCI [redacted] at Weeks 0, 4, and 8 followed by placebo q4w SC at Week 12.
Route of Administration	SC	SC	SC
Use	Experimental	Experimental	Placebo
Investigational Medicinal Product (IMP)	Yes	Yes	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No	No	No

Delivery Instructions[a]	Must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. The sterile product does not contain preservatives and is designed for single use only. It should be clear to slightly yellow and may contain tiny white or clear particles. Do not use 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. Aseptic procedures must be used during the preparation and administration of the study intervention material.

[a] Labels will contain information to meet the applicable regulatory requirements.

The dosing schedules with and without rescue are presented on the following figure.

Figure 2: Dosing Schedule Through Week 248



* Upon study unblinding after the Week 48 DBL, placebo participants who have not been rescued with guselkumab will be discontinued from study intervention and have a safety follow-up visit. All other participants will continue guselkumab treatment through Week 248, following their assigned dosing regimen (either q4w or q8w) without receiving sham injections.

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When multiple SC injections are administered at a visit, each injection of study intervention should be given at a different location of the body. Detailed instructions on the preparation and administration of study intervention will be provided in the site IPPM and the IFU.

6.1.1. Self-administration of Study Intervention

On-site

Beginning at Week 36, at the discretion of the investigator and participant, and after appropriate and documented training at Weeks 28 and 32, participants may self-administer study intervention at the study site. A caregiver may also be trained to administer study intervention. The self-administration of study intervention on-site should be done in the presence of study site staff. If needed, participants (or their caregivers) can be trained at later time points.

At-home

Starting from Week 52 up to Week 92, participants may self-administer (or their caregivers may administer) study intervention at home every 8 weeks, according to the visits outlined in the SoA (Section 1.3), if allowed per local regulation.

After Week 96, participants may self-administer (or their caregivers may administer) study intervention doses at home q4w or q8w (based on their assigned treatment regimen prior to Week 96). As study unblinding will have occurred, all sham injections will cease. A medication supply will be provided during on-site study visits.

Participants who are unable or unwilling to have study injections administered at home will be required to return to the site for administration of study intervention injection. Participants will receive instructions on compliance with study intervention, dosing instructions and instructions for study intervention storage at-home for when they begin self-administration of study intervention. Participants are provided a study medication diary to record at-home study intervention administration and will receive instructions on how to self-evaluate any injection-site reaction. Participants will also be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding.

6.1.2. Combination Products

The sponsor-manufactured combination products (or those manufactured for the sponsor by a third party) provided for use in this study are the CCI [redacted]) and the CCI [redacted]

The sponsor manufactures the 100 and 200 mg guselkumab PFS. The sponsor also assembles the PFS with the devices to form the PFS-U and PFS-Y combination products. The YpsoMate device (Y) is manufactured by Ypsomed. The UltraSafe device (U) is manufactured by medical device manufacturer Becton-Dickinson.

Picture-based instructions for the CCI [redacted] will be provided for participants as part of training on how to use the device.

All combination product deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error and inadequate labeling) shall be documented and reported by the investigator throughout the study. For studies in combination product, these deficiencies will be reported as PQC (see Appendix 7: Adverse Events Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Guselkumab will be supplied as a CCI [redacted] Matching placebo will be supplied as a 1 CCI [redacted] respectively.

All study intervention must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. Do not freeze the study interventions. The products are designed for single-use only.

Guselkumab and matching placebo should be clear and colorless to slightly yellow solution that may contain small translucent particles. Do not use guselkumab or matching placebo 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.

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

Accountability

The investigator is responsible for ensuring that all study intervention (study drug) received at the site is inventoried and accounted for throughout the study. All study intervention will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study intervention containers.

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 and used study intervention with empty outer box/carton must be available for verification by the sponsor's study site monitor during on-site monitoring visits for study intervention accountability.

Potentially hazardous materials containing hazardous liquids, such as used needles and syringes, 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 study intervention 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 neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

For at-home administration if permitted by local regulation, participants will receive instructions for at-home storage and handling of used and unused study intervention materials. Participants who self-administer (or whose caregiver administers) at home will record study intervention administration with time and date information in the study medication diary. Participants will be instructed to return the outer box/carton from the prefilled syringe/autoinjector and/or any unused study intervention at the next on-site visit. The actual used syringe/autoinjector should be disposed in the provided sharps container which should only be returned to the site as needed at the last study visit. Intervention accountability will be based upon the returned outer box/carton for used study intervention and any unused study intervention if not administered.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Randomization minimizes 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. Participants will be randomly assigned to 1 of 3 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by ADT-IR status (ie, inadequate response to or intolerance of approved TNFα antagonists, vedolizumab, ozanimod, or approved JAK inhibitors) (Yes/No), and CCI at baseline (moderate [2] or severe [3]) as obtained during central review of the video endoscopy.

The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

To maintain the study blind, the study intervention container will have a label containing study name, study intervention number, and reference number. The study intervention number will be entered in the eCRF when the study intervention is dispensed. Each active study intervention and its matching placebo will be identical in appearance and will be packaged in identical containers. All participants will receive the same device(s), which could be either active or matching placebo at 4-week intervals (double-dummy; see Figure 2) in order to maintain treatment blinding.

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 intervention assignment (eg, study intervention serum concentrations, anti-guselkumab antibodies) 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 time of unblinding.

At the Week 24 DBL, data will be unblinded for analysis to the sponsor only. Treatment assignment will remain blinded to the study sites, site monitors, and participants until the full study unblinding following the Week 48 DBL. Identification of sponsor personnel who will have access to the unblinded participant-level data at the Week 24 DBL will be documented before the unblinding.

Under normal circumstances, the blind should not be broken until the Week 48 DBL is completed and the database is finalized. Otherwise, the blind should be broken only if specific emergency intervention/course of action would be dictated by knowing the intervention status of the participant. In such cases, the investigator may in an emergency determine the identity of the intervention by contacting 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. In the event 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/or 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.

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

6.4. Study Intervention Compliance

When study intervention is administered by qualified staff, the details of each administration (including date and time of SC injection) will be recorded in the eCRF.

Throughout the study, the investigator or designated study research personnel will be responsible for providing additional instruction to re-educate any participant who is not compliant with taking study intervention.

Compliance with the treatment schedule is strongly encouraged. Study site personnel will keep a log of all study intervention dispensed and will compare the amount of study intervention dispensed with the amount returned. Additional details may be provided in the site IPPM and IFU that is provided separately.

6.5. Dose Modification

6.5.1. Rescue Medication

All participants in the placebo group who meet rescue criteria at Week 16 will receive rescue treatment, ie, guselkumab CCI at Weeks 16, 20, and 24 followed by guselkumab 100 mg SC q8w. Participants randomized to guselkumab who meet rescue criteria at Week 16 will continue their assigned treatment regimen and receive blinded sham rescue with matching placebo SC injections at Weeks 16, 20, and 24.

Rescue criteria are defined below.

- No improvement (ie, no decrease) in CCI at Week 12 as obtained during central review, when compared with baseline

  AND

- A <2 point improvement (ie, <2 point decrease) in CCI at Weeks 12 and 16, when compared with baseline

The above rescue criteria are not applicable after Week 16. As described in Section 7.1, discontinuation of a participant's study intervention must be strongly considered if they have a persistent inadequate response or worsening of UC based on signs, symptoms, and/or laboratory values.

6.6. Continued Access to Study 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; however, local regulations on continued access will take precedence.

6.7. Treatment of Overdose

For this study, any dose of guselkumab 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 treatment for an overdose.

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

- Closely monitor the participant for adverse event/serious adverse event and laboratory abnormalities.
- Contact the medical monitor immediately.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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.

6.8. Concomitant Therapy

Pre-study 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 also be recorded throughout the study, from signing of the informed consent to the last study visit. This includes all prescription or over-the-counter medications (eg, vaccines, vitamins, herbal supplements) different from the study intervention.

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.

6.8.1. UC-related Concomitant Therapies

Week 0 through Week 48

Participants who are receiving oral 5-ASA compounds, oral corticosteroids, or conventional immunomodulators (AZA, 6-MP, or MTX) for the treatment of UC at baseline should maintain a stable dose through Week 48; with the exception of oral corticosteroids which require mandatory tapering at Week 12 as described in Section 6.8.1.1.

From Week 0 through Week 48, enrolled participants should not initiate any of the following concomitant UC-specific medical therapies at any time:

- 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 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. This does not represent a deviation from the study protocol and the participants may remain on their assigned therapy (guselkumab or placebo).

Week 48 through Week 248

Concomitant therapies for UC, including 5-ASA compounds, corticosteroids, antibiotics, immunomodulators (ie, AZA, 6-MP, or MTX), and/or total parenteral nutrition, may be administered and changed at the discretion of the investigator.

6.8.1.1. Oral Corticosteroids and Tapering

Participants who are receiving oral corticosteroids for the treatment of UC at baseline (Week 0) should maintain a stable dose through Week 12. The oral corticosteroid dose should not be increased above the baseline dose unless due to medical necessity.

At Week 12, all participants who were taking corticosteroids at Week 0 must begin tapering corticosteroids. This tapering is mandatory (unless medically not feasible) and should follow the recommended schedule shown in Table 4. If participants experience worsening disease activity while tapering corticosteroids, further dose decreases may be suspended, and/or their oral corticosteroid dose may be temporarily increased up to their baseline corticosteroid dose per the discretion of the investigator. For participants whose corticosteroid taper is interrupted, investigators are encouraged to resume tapering within 4 weeks. Tapering may exceed this schedule only if warranted by medical necessity (eg, participant experiencing corticosteroid-related side effects). After Week 48, corticosteroids may be administered and dose changed at the discretion of the investigator.

Table 4: 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 at 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 at 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 or 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.	

6.8.2. Prohibited Concomitant 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 (eg, 6-thioguanine, cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus, ozanimod, and JAK inhibitors).

- Immunomodulatory biologic agents (eg, TNFα antagonists, ustekinumab, vedolizumab, abatacept, anakinra).

- Experimental IBD medications (eg, etrolizumab, brazikumab, mirikizumab, risankizumab) or other investigational medications/therapies.

- Thalidomide or related agents.

The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered or planned to be administered.

Participants must not receive guselkumab outside of the protocol or participate in any other clinical study with an investigational agent while in this study and must terminate study participation if they do. Prior to termination of study participation, participants should complete evaluations for an ED visit as described in Section 1.3.

6.8.3. Vaccinations (including COVID-19)

Participants must not receive a live virus, live bacterial, or BCG vaccination during the study and for 12 weeks after receiving the last dose of study intervention.

When considering use of locally-approved (including emergency use-authorized) COVID-19 vaccines in study participants, consider protocol life style considerations (Section 5.3) and follow applicable local vaccine labeling, guidelines, and standards of care for patients receiving immune-targeted therapy. Additionally, 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.

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).

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant or plans a pregnancy within the study period. Refer to Appendix 8 (Section 10.8), Contraceptive and Barrier Guidance.
- The participant initiates treatment with a prohibited therapy (Section 6.8.2).
- The participant receives a live viral, live bacterial, or BCG vaccination.
- The participant has a colectomy.

- The participant develops an opportunistic infection as determined by the investigator.
- The participant meets ANY of the following TB related conditions:
  - 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 chest imaging with evidence of current active TB and/or a positive IGRA test result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study intervention and continued to completion. Indeterminate/borderline results should be handled as outlined in Section 8.2.11.
  - A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The participant has a serious adverse reaction that is temporally related to an injection 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.
- 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.
- The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allowing participants who develop ≤2 localized basal cell skin cancers that are adequately treated with no evidence of recurrence or residual disease to continue to receive study intervention.
- 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 10 (Section 10.10; Guideline Algorithm for Monitoring, Assessment and Evaluation of Abnormal Liver Tests).

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

- 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.
- 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.

- The participant reports suicidal ideation with intention to act CCI [redacted] on a post-baseline CCI [redacted] 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.
- The participant develops a severe injection-site reaction.

If a participant discontinues study intervention for any reason before the end of the treatment period, then the assessments as specified in the SoA (Section 1.3) must be obtained. If the reason for discontinuation of study intervention is withdrawal of consent, every effort should be made to conduct the ED visit assessment, as indicated in the SoA, prior to terminating the study participation. After termination of study participation, no additional assessments are allowed. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered to replace participants who discontinue study intervention or withdraw from the study.

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
- Withdrawal of consent
- Death
- Sponsor decision (eg, participating in any other clinical study with an investigational agent)

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document. 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 (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion,) as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

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 6, 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 the participant 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.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information may be transferred to another study site if feasible.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA (Section 1.3) summarizes the frequency and timing of scheduled visits, and the timing of efficacy, safety, PK, immunogenicity, PRO, and other assessments applicable to this study.

The visit window should be ±4 days for each visit up to and including Week 12; after Week 12 to Week 24, the visit window should be ±7 days, after Week 24 to the end of study the visit window should be ±10 days (as described in the SoA). All post-randomization visits should be scheduled relative to the participant's randomization date. If a study visit cannot be held within the recommended visit window, the subsequent visit should be conducted as closely as possible to the study visit schedule and the site should bring the participant in gradually closer to the expected visit date by applying the allowable ± visit window.

All PRO assessments should be conducted/completed before any tests, procedures, or other

consultations to prevent influencing participant responses. Refer to the PRO completion guidelines for instructions on the administration of PROs.

The CCI should be completed after all PRO assessments and before any other 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 and eCRF.

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.

Screening

The screening period 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 randomized 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 and/or instructions for use of a personal device will be provided to each participant. A CCI diary will be completed from recall at screening and will be used to assess the participant's eligibility for further screening and to train the participant on the use of the diary. Participants with a combined stool frequency and CCI can proceed with endoscopy.

Participants will be instructed to complete the CCI and CCI daily diary entries for the 10 days immediately before Week 0 through Week 4, and for the 10 days immediately before each visit thereafter, as per SoA (Section 1.3).

The screening endoscopy should be performed within 2 weeks (and at least 4 days) before the baseline 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 0 visit. Local pathology results from the screening endoscopy must be reviewed before the first dose of study intervention.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF 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 found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

The total blood volume to be collected from each participant will be approximately 326 mL.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IB)
- ICF
- IFU
- IPPM
- IWRS manual
- Participant diaries (and/or instructions for use of a personal device) and study medication diaries
- eCRF completion instructions
- Central laboratory manual
- Laboratory kits
- Biopsy manual
- Endoscopy kit
- Imaging manual
- Electronic patient-reported outcome equipment
- Patient recruitment materials
- At home stool collection kits
- Ancillary supplies as required

8.1. Efficacy Assessments

Efficacy evaluations will include the following:

- CCI [redacted]
- Inflammatory PD markers including CRP and fecal calprotectin
- Histological assessments (eg, CCI [redacted]

- Patient-reported outcome measures to assess CCI outcomes, fatigue, and UC symptoms and signs (eg, CCI

8.1.1. CCI

CCI

8.1.2. Histologic Assessments

Histologic assessments will be performed using biopsy samples collected during endoscopy (see endoscopy manual for biopsy details). Histologic assessments will be conducted by a central reader who is blinded to treatment groups and visit. The CCI will be used to evaluate histologic activity. Analyses will be specified in the SAP.

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 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. CCI

CCI [redacted]

8.1.6. CCI

CCI [redacted]

8.1.7. CCI

CCI [redacted]

8.2. Safety Assessments

Safety assessments will include the monitoring of AEs, injection-site reactions, symptoms of a hypersensitivity reaction, UC-related surgeries and procedures, and any signs or symptoms of infection or TB. In addition, vital signs, physical examinations, ECGs, clinical safety laboratory tests, and CCI [redacted] will be performed, as well as review of concomitant medication. Endoscopies will be performed every 48 weeks beginning at Week 96 to assess long term safety.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting and Appendix 7, 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.

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 (any method is acceptable), pulse/heart rate, respiratory rate, blood pressure will be assessed.

Blood pressure and pulse/heart rate measurements should be assessed with a completely automated device. Manual techniques should be used only if an automated device is not available. 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 and approximately 30 minutes after the SC injection, or if the participant reports any symptoms.

8.2.3. Electrocardiograms

A 12-lead ECG will be performed locally at screening.

During the collection of ECGs, 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 the SoA (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 AE section of the eCRF. Any clinically significant laboratory abnormality should be assessed and repeated as warranted. 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.

- **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, ALP, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, blood urea nitrogen/urea, and creatinine).

  A medical monitor or delegate and the clinical site will be notified if prespecified 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. Additional details regarding HBV are provided in Appendix 5 (Section 10.5).
- **Liver chemistry:** If laboratory testing for a participant who is enrolled in the study and receiving study intervention reveals a possible Hy's Law case (Section 8.3.1), study intervention should be suspended immediately. In addition, laboratory tests for ALT, AST, ALP, and TBili 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 10 (Section 10.10) for additional information on monitoring and assessment of abnormal liver function tests.
- **FSH**: Refer to Appendix 8 (Section 10.8) for instances when a screening FSH test should be considered.

Details on the laboratory tests that will be performed are provided in the laboratory manual.

8.2.5. Pregnancy Testing

Women participants of childbearing potential will undergo pregnancy testing as indicated in the SoA (Section 1.3). 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.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

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 CCI [redacted] will be used as a screening tool to prospectively evaluate suicidal ideation and behavior among study participants.

CCI [redacted]

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

At screening, the CCI will be the first assessment performed after signing informed consent, before any other study procedure. At all subsequent visits, the CCI will be performed according to the assessment schedule as outlined in the SoA (Section 1.3) 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 CCI 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 CCI has been reviewed by the investigator and the participant's risk has been assessed and follow-up is determined, as appropriate.

At screening (within the last 6 months) and Week 0, participants with a CCI 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 CCI 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 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.
- CCI Participant risk is assessed by the investigator.
- CCI 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 CCI or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a postbaseline CCI 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 CCI 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 7 [Section 10.7], Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting).

8.2.7. Concomitant Medication Review

Concomitant medications will be reviewed and recorded at each visit.

8.2.8. 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.

Participants are provided a study medication diary to record at-home study intervention administration (see Section 6.1) and will receive instructions on how to self-evaluate any injection-site reaction. Participants will also be instructed to report AEs related to injection-site reactions to the site promptly.

8.2.9. 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).

8.2.10. Infections

Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits (see SoA, Section 1.3). Study intervention should not be administered 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). 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

Initial Tuberculosis Evaluation

Participant 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 imaging results and responses to tuberculin skin or other TB testing. Investigators have the option to use the tuberculin skin test in addition to IGRA testing to screen for latent TB if preferred by local health authorities, or if they

believe based on their judgment that both tests are clinically indicated to evaluate a participant at high risk for latent TB.

Participants with a negative IGRA test result are eligible to continue with prerandomization procedures. Participants with a newly identified positive IGRA test result must undergo an evaluation for active or latent TB, or suspected false-positive initial testing, and initiate appropriate treatment if needed (see Section 5.2). 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 must be followed.

Participants with indeterminate/borderline IGRA test results should have the test repeated. Participants with persistently indeterminate/borderline IGRA test results may be randomized or continued in the study without treatment for latent TB, if active TB is ruled out, chest imaging shows no abnormality suggestive of TB (active or inactive), and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the participant's source documents and initialed by the investigator.

Ongoing Tuberculosis Evaluation

To aid in the early detection of TB infection or exposure during study participation, participants must be evaluated for TB signs, symptoms, and close contacts at scheduled visits (refer to Section 1.3) or by telephone 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 for TB infection or the participant has had a close contact exposure to TB, study intervention must be withheld and an immediate and thorough investigation must be undertaken, including consultation with a physician specializing in TB to determine if treatment is warranted prior to any further study intervention. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol.

Note: Investigators should be aware that TB reactivation in immunocompromised participants may also present as extrapulmonary or disseminated disease.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, serious AEs, and PQCs, 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 study intervention that meets the definition of a combination product, malfunctions or deficiencies of a device constituent will be reported as a PQC.

Further details on AEs, SAEs, and PQCs can be found in Appendix 7, 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 AEs 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

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately.

Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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, even before all other possible causes of liver injury have been excluded.

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

Information regarding SAEs will be transmitted to the sponsor using an SAE form which must be completed and reviewed by a physician from the study site and transmitted to the sponsor

immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be made per sponsor reporting process.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events and the special reporting situation of pregnancy will be followed by the investigator as specified in Appendix 7, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of the Safety Information to the Regulatory Authorities/IECs/IRBs in each respective country/territory, as applicable.

An anticipated event is an AE 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 ulcerative colitis
- Adverse events related to worsening or progression of ulcerative colitis

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 intervention 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 in which the studies are conducted.

8.3.5. 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 SAEs 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 for female participants who become pregnant, or where the pregnancy was the result of male participant and his partner, and any postnatal sequelae in the infant will be required.

8.3.6. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study intervention must be reported by the investigator according to the procedures in Appendix 7 (Section 10.7). Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of a serious adverse event.

8.4. Pharmacokinetics

Serum samples will be used to evaluate the PK of guselkumab at time points 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. Participant confidentiality will be maintained.

8.4.1. Evaluations

At visits where only serum concentrations 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 concentrations 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 biological samples can be found in the laboratory manual.

8.4.2. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of guselkumab using a 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.

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

Serum samples will be used to evaluate guselkumab PK parameters 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.

8.5. Pharmacogenomics

Pharmacogenomics are not evaluated in this study.

8.6. 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 and endoscopic biopsy samples collected as specified in the SoA (Section 1.3), where local regulations permit. Digital images of biopsy histology slides and endoscopy videos may be used to support exploratory research to develop artificial intelligence algorithms to aide in the evaluation of mucosal changes in UC.

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 an individual may respond differently to guselkumab
4. To understand the impact of treatment with guselkumab on intestinal mucosal inflammation in participants with moderately to severely active UC
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.

8.6.1. Serum-based Biomarkers

Blood samples for serum-based biomarker analyses will be collected from all participants where local regulations permit. 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 will not be limited to IL-17A and IL-22. Proprietary algorithms and standard statistical techniques, such as ANOVA and 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 biologic response relating to UC or the mechanism of action of guselkumab.

8.6.2. Whole Blood-based Biomarkers

Whole blood samples will be collected from all participants to assess the effect of study intervention on RNA expression profiles where local regulations permit. Whole blood analyses may also examine RNA expression associated with the pathogenesis of UC. Transcriptome studies may be conducted using RNA sequencing, 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 biologic response relating to UC or the action of guselkumab.

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

8.6.3. Biopsy-based Biomarkers

Mucosal biopsy samples will be collected during endoscopy to evaluate the effect of study intervention on histologic activity. Biopsies will also be analyzed for exploratory gene and protein expression analysis where local regulations permit.

8.6.4. Pharmacodynamics

Inflammatory PD markers (CRP and fecal calprotectin [see Section 8.1]) will be evaluated using blood and fecal samples collected at visits as indicated in the SoA (Section 1.3)

8.7. Immunogenicity Assessments

Antibodies to guselkumab will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

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.

Serum samples will be used to evaluate the immunogenicity of anti-guselkumab antibodies. 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.

8.8. Medical Resource Utilization and Health Economics

UC-related surgeries and procedures will be collected and reviewed in this study.

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. Further details will be provided in the SAP.

9.1. Statistical Hypotheses

The primary hypothesis is that guselkumab SC induction is superior to placebo SC as measured by clinical remission at Week 12 among participants with moderately to severely active UC.

9.2. Sample Size Determination

Sample size was determined by the power to detect significant differences in the primary endpoint of clinical remission at Week 12, and by the objective of maintaining at least 85% power across secondary endpoints at Week 12 between the combined guselkumab SC induction groups and the placebo SC group as well as for secondary endpoints at Week 24 between each guselkumab group and the placebo group, using 2-sided chi-square tests with significance level 0.05. Combination of guselkumab SC induction groups for the primary endpoint and other Week 12 endpoints is warranted by the fact their treatment is identical through the induction period, and only differs after assessment of the primary endpoint at Week 12.

With assumed clinical remission rates of 8% for placebo and 22% for the combined guselkumab groups (based on data from Phase 2b guselkumab UC IV induction study [CNTO1959UCO3001]) and Phase 3 ustekinumab UC program [CNTO1275UCO3001], a total of 399 participants (randomized 1:1:1 for guselkumab CCI q4w (Weeks 0, 4, and 8) followed by guselkumab 200 mg SC q4w: guselkumab CCI q4w (Weeks 0, 4, and 8) followed by guselkumab 100 mg SC q8w: Placebo, yielding a 2:1 guselkumab:placebo randomization ratio for Week 12 comparisons) will ensure >95% power for the primary endpoint. This sample size also protects against a slightly lower remission rate of 20% for the combined guselkumab groups or a slightly

higher remission rate of 9.5% in the placebo group (as observed in CNTO1959UCO3001), yielding a power of 90% in both cases.

Individual power values (ie, without consideration of an adjustment for multiplicity) achieved for secondary endpoints at Week 12 are described in Table 5.

Table 5: Power for Secondary Endpoints at Week 12 with a Total of 399 Participants (2:1 Guselkumab:Placebo)

Endpoints	Proportion achieving endpoint in Placebo group	Proportion achieving endpoint in combined Guselkumab group	Power
Symptomatic remission	20%	45%	>99%
Endoscopic improvement	13%	28%	94%
Clinical response	30%	60%	>99%
Histologic-endoscopic mucosal improvement	8%	19%	85%
Assumed rates were based on data from Phase 2b guselkumab UC IV induction study and Phase 3 ustekinumab UC program			

For the secondary endpoints at Week 24, power is determined by the pairwise comparison of individual guselkumab groups to placebo (see Table 6).

Table 6: Power for Secondary Endpoints at Week 24 with a Total of 399 Participants (133 per Treatment Group)

Endpoints	Proportion achieving endpoint in Placebo group	Proportion achieving endpoint in an individual Guselkumab group	Power
Clinical remission	10%	27%	95%
Symptomatic remission	30%	60%	>99%
Endoscopic improvement	13%	28%	86%
Clinical response	35%	70%	99%

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Table 7: Analysis Populations

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All participants who were randomized in the study.
Full analysis set	All randomized participants who received at least 1 dose of study intervention
Safety analysis set	All randomized participants who received at least 1 dose of study intervention.
PK analysis set	All randomized participants who received at least 1 dose of study intervention and have at least one valid blood sample drawn post-baseline for PK analysis
Immunogenicity analysis set	All randomized participants who received at least 1 dose of study intervention and have appropriate samples for anti-drug antibody detection

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to the Week 24 DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including the primary and secondary endpoints.

9.4.1. General Considerations

Descriptive statistics (eg, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphical data displays (eg, line plots) may also be used to summarize data.

Analyses suitable for categorical data (eg, chi-square tests, CMH chi-square tests, or logistic regression, as appropriate) will be used to compare the proportions of participants achieving selected endpoints (eg, clinical response). In cases of rare events, the Fisher's exact test will be used for treatment comparisons. Continuous response parameters measured at more than one post-baseline visit will be compared using a MMRM model (unless otherwise specified). If the normality assumption is in question, an appropriate transformation may be implemented before fitting the MMRM model. Continuous response parameters measured at only one post-baseline visit will be compared using an ANOVA or ANCOVA, unless otherwise specified. In cases of small sample size, t-test will be used for treatment comparisons.

The overall Type I error rate will be controlled at the significance level of 0.05 (2-sided). Methods for multiplicity control over primary and secondary endpoints are described in Section 9.4.3.2.

Unless otherwise specified, the analysis of endpoints related to the endoscopy subscore, including the CCI [redacted] will be based on the final reported CCI [redacted] (Section 8.1.1).

9.4.2. Primary Endpoint

The primary endpoint is clinical remission at Week 12, defined as a CCI and not increased from baseline, a CCI and an CCI with no friability present on the endoscopy.

9.4.2.1. Primary Estimand of Clinical Remission at Week 12

The primary estimand (ie, a precise definition of the primary targeted treatment effect) is defined by the following 5 attributes:

i) Treatment through Week 12:

- Experimental: Combined guselkumab CCI induction dose group (ie, both guselkumab groups who received CCI at Weeks 0, 4, and 8; see Section 4.1)
- Control: Placebo SC q4w (Weeks 0, 4, 8)

ii) Population: Participants with moderately to severely active ulcerative colitis as reflected in the inclusion/exclusion criteria (Section 5).

iii) Variable (Endpoint): A binary response variable (response/nonresponse) where response is defined as achieving a CCI a CCI and an CCI with no friability present on the endoscopy at Week 12, where the CCI has not increased from baseline and none of the ICEs in categories 1 to 3 and 5 outlined in Table 8 has occurred prior to the Week 12 visit.

iv) Intercurrent Events and Corresponding Strategies: ICEs and the corresponding analysis strategies are defined in Table 8. Note that meeting rescue criteria at Week 12/Week 16 is not an intercurrent event for the primary endpoint and is therefore not contained in Table 8.

Table 8: Intercurrent Events and Respective Analysis Strategies

ICE (between Baseline and Week 12)	Analysis strategy for ICE
1. An ostomy or colectomy (partial or total)	**Composite strategy:** Occurrence of these ICEs will be treated as an unfavorable outcome
2. A prohibited change in medications for UC	
3. Discontinuation from study intervention due to lack of efficacy or an AE of UC worsening	
4. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)	**Treatment policy strategy**: Observed values will be used if available
5. Discontinuation of study intervention due to reasons other than ICEs 3 or 4 as described above	**Composite strategy:** Occurrence of these ICEs will be treated as an unfavorable outcome

v) Population-level summary: Difference in proportions of participants who achieved the binary response at Week 12 as defined in the variable attribute above between the combined guselkumab group and the placebo group.

9.4.2.2. Estimator for the Primary Endpoint

The analysis of the primary endpoint will be based on the Full Analysis Set. Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment they received.

After accounting for the ICE strategies, any participants who are missing any or all of the 3 CCI that comprise the primary endpoint at Week 12 will be considered not to be in clinical remission at Week 12 (ie, nonresponder imputation).

Summaries of the proportion of participants in clinical remission at Week 12 will be presented by treatment group. The common risk difference and the associated 95% confidence interval between the combined guselkumab SC induction group and the placebo group will be computed by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The primary endpoint will be tested by a two-sided Mantel-Haenszel test for the common risk difference. Stratification will be by the ADT-IR status (Yes/No), and CCI at baseline (moderate [2] or severe [3]) as obtained during central review of the video endoscopy. The study will be considered successful if the test for the primary endpoint is positive. While a multiplicity-controlled testing procedure will be implemented to control for the Type I error rate at the 0.05 significance level (2-sided) across the primary and secondary endpoints, the primary endpoint will be tested at full significance level. Only if this test is significant, secondary endpoints will be tested in a confirmatory manner.

To evaluate the robustness of the primary analysis results, sensitivity analyses using alternative missing data handling rules may be performed and supplementary estimands will be evaluated; these analyses will be described in the SAP. In particular, this includes the use of the treatment policy strategy for ICEs 3, 4, and 5 in Table 8 while continuing to use the composite strategy for ICEs 1 and 2.

In addition, 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-IR status).

9.4.3. Secondary Efficacy Endpoints

The following are the secondary endpoints:

- Symptomatic remission at Week 12 (defined as a CCI and not increased from baseline, and a CCI
- Endoscopic improvement at Week 12 (defined as an CCI with no friability present on the endoscopy)
- Clinical response at Week 12 (defined as a decrease from baseline in the CCI 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)
- Clinical remission at Week 24

- Symptomatic remission at Week 24
- Endoscopic improvement at Week 24
- Clinical response at Week 24
- Histologic-endoscopic mucosal improvement at Week 12 (defined as a combination of histologic improvement [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the CCI and endoscopic improvement as defined above)

9.4.3.1. Estimands and Estimators

Secondary endpoints at Week 12

For secondary endpoints at Week 12, the same estimand that is specified for the primary endpoint will be used (except for the "variable attribute"). The variable attributes are given in Table 9 below:

Table 9: Variable Attributes of Secondary Endpoints at Week 12

Endpoint	Variable attribute
Symptomatic remission at Week 12	A binary response variable (response/nonresponse) where response is defined as achieving a CCI and not increased from baseline, and a rectal bleeding subscore of 0 at Week 12 and none of the ICEs in categories 1 to 3 and 5 outlined in Table 8 has occurred prior to the Week 12 visit.
Endoscopic improvement at Week 12	A binary response variable (response/nonresponse) where response is defined as achieving an CCI with no friability present on the endoscopy at Week 12, where none of the ICEs in categories 1 to 3 and 5 outlined in Table 8 has occurred prior to the Week 12 visit.
Clinical response at Week 12	A binary response variable (response/nonresponse) where response is defined as achieving a decrease from induction baseline in the CCI 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 at Week 12, where none of the ICEs in categories 1 to 3 and 5 outlined in Table 8 has occurred prior to the Week 12 visit.
Histologic-endoscopic mucosal improvement at Week 12	A binary response variable (response/nonresponse) where response is defined as a combination of histologic improvement [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the CCI and endoscopic improvement CCI with no friability present] at Week 12, where none of the ICEs in categories 1 to 3 and 5 outlined in Table 8 has occurred prior to the Week 12 visit

Secondary endpoints at Week 24

The estimand (ie, a precise definition of the targeted treatment effect) is defined by the following 5 attributes:

i) Treatment through Week 24:

- Experimental 1: Guselkumab CCI q4w [Weeks 0, 4, and 8] followed by guselkumab 200 mg SC q4w (see Section 4.1)

- Experimental 2: Guselkumab CCI q4w [Weeks 0, 4, and 8] followed by guselkumab 100 mg SC q8w (see Section 4.1)

- Control: Placebo SC q4w (Weeks 0, 4, 8, 12, 16, 20)

ii) Population: Participants with moderately to severely active ulcerative colitis as defined by the inclusion/exclusion criteria (Section 5).

iii) Variable (Endpoint): The variable attributes for secondary endpoints at Week 24 are given in Table 10 below.

Table 10: Variable Attributes of Secondary Endpoints at Week 24

Endpoint	Variable attribute
Clinical remission at Week 24	A binary response variable (response/nonresponse) where response is defined as achieving a CCI and not increased from baseline, a rectal bleeding subscore of 0, and an CCI with no friability present on the endoscopy at Week 24, where none of the ICEs in categories 1 to 4 and 6 outlined in Table 11 has occurred prior to the Week 24 visit.
Symptomatic remission at Week 24	A binary response variable (response/nonresponse) where response is defined as achieving a CCI and not increased from baseline, and a rectal bleeding subscore of 0 at Week 24, and none of the ICEs in categories 1 to 4 and 6 outlined in Table 11 has occurred prior to the Week 24 visit.
Endoscopic improvement at Week 24	A binary response variable (response/nonresponse) where response is defined as achieving an CCI with no friability present on the endoscopy at Week 24, where none of the ICEs in categories 1 to 4 and 6 outlined in Table 11 has occurred prior to the Week 24 visit.
Clinical response at Week 24	A binary response variable (response/nonresponse) where response is defined as achieving a decrease from induction baseline in the CCI 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 at Week 24, where none of the ICEs in categories 1 to 4 and 6 outlined in Table 11 has occurred prior to the Week 24 visit.

iv) Intercurrent Events and Corresponding Strategies: ICEs and the corresponding analysis strategies are defined in Table 11.

Table 11: Intercurrent Events and Respective Analysis Strategies

ICE (between Baseline and Week 24)	Analysis strategy for ICE
1. An ostomy or colectomy (partial or total)	**Composite strategy:** Occurrence of these ICEs will be treated as an unfavorable outcome
2. A prohibited change in medications for UC	
3. Discontinuation from study intervention due to lack of efficacy or an AE of UC worsening	

ICE (between Baseline and Week 24)	Analysis strategy for ICE
4. Meeting rescue criteria according to Section 6.5.1	
5. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)	**Treatment policy strategy**: Observed values will be used if available
6. Discontinuation of study intervention due to reasons other than ICEs 3 or 5 as described above	**Composite strategy:** Occurrence of these ICEs will be treated as an unfavorable outcome

v) Population-level summary: Difference in proportions of participants who achieved the binary response at Week 24 as defined in the variable attribute above between each of the guselkumab groups and the placebo group.

Estimator for Secondary Efficacy Endpoints

The analysis of the secondary endpoints will be based on the Full Analysis Set. Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment they received.

After accounting for the ICE strategies, any participants who are missing any or all of the components that define the secondary endpoints at Week 12/Week 24 will be considered not to meet the respective endpoint (ie, nonresponder imputation).

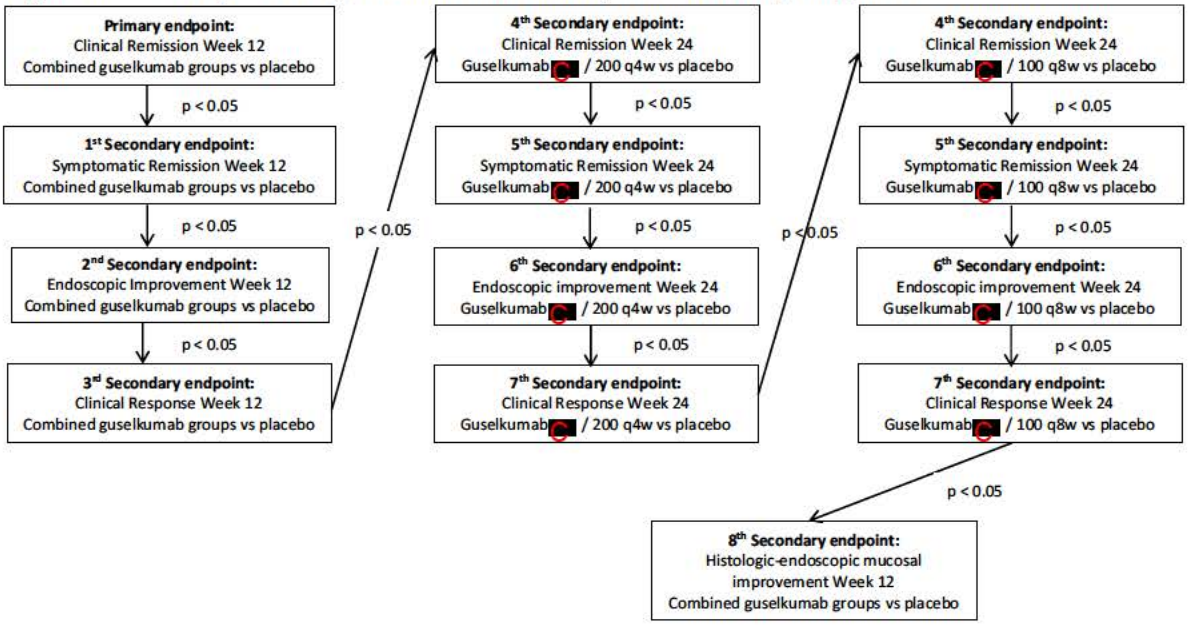
Summaries of the proportion of participants achieving each secondary endpoint will be presented by treatment group. The common risk difference and the associated 95% confidence interval between the combined guselkumab SC induction group (Week 12 endpoints) / individual guselkumab SC induction groups (Week 24 endpoints) and the placebo group will be computed by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The secondary endpoints will be tested by a two-sided Mantel-Haenszel test for the common risk difference. Stratification will be by the ADT-IR status (Yes/No), and CCI [redacted] at baseline (moderate [2] or severe [3]) obtained during central review of the screening video endoscopy.

9.4.3.2. Confirmatory Testing Procedure

A multiple testing procedure is planned to control the overall Type 1 error rate in the study at the 2-sided 0.05 significance level. The planned procedure is depicted in Figure 3. It follows a fixed sequence approach, where the primary endpoint and the Week 12 secondary endpoints (with the exception of histologic-endoscopic mucosal improvement) for the combined guselkumab groups vs placebo are tested prior to the secondary endpoints at Week 24. For the Week 24 endpoints, the testing sequence continues with testing all 4 endpoints in the guselkumab CCI [redacted] q4w (Weeks 0, 4, and 8) followed by guselkumab 200 mg SC q4w group against placebo and then testing all 4 endpoints in the guselkumab CCI [redacted] q4w (Weeks 0, 4, and 8) followed by guselkumab 100 mg SC q8w group against placebo. Histologic-endoscopic mucosal improvement at Week 12 is the last element of the testing sequence and is tested for the combined guselkumab groups against placebo.

This testing procedure may be revised prior to Week 24 database lock and unblinding if warranted by emerging external data. For example, the position of testing individual guselkumab groups against placebo may be changed based on QUASAR (CNTO1959UCO3001) maintenance data, which are expected to become available prior to any data unblinding in this study. Any such changes will be documented in the SAP. No changes to the testing procedure based on CNTO1959UCO3004 (this study) results will be made.

Figure 3: Multiple Testing Procedure for Primary and Secondary Endpoints



Note 1: All p-values are 2-sided

9.4.4. Exploratory Efficacy Endpoints

The exploratory endpoints include but are not limited to the endpoints described in Section 3. Further details will be provided in the SAP. The testing of these endpoints will not be controlled for multiplicity and nominal p-values will be provided.

Statistical methods will follow the general considerations given in Section 9.4.1.

9.4.5. Safety Analyses

All safety analyses will be based on the Safety Analysis Set. In general, participants will be analyzed according to their assigned treatment. However, participants assigned to placebo who incorrectly received guselkumab at any time will be analyzed in the guselkumab group; participants assigned to guselkumab who received only placebo during the study will be analyzed in the placebo group.

9.4.5.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the final safety visit (approximately 12 weeks

following the last dose) is considered to be treatment emergent. 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 related AEs as assessed by the investigator;
- Frequency and type of AEs leading to discontinuation of study intervention;
- 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 an SAE.

9.4.5.2. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics for changes from baseline in clinical laboratory results will be summarized by treatment group.

9.4.5.3. Suicidal Ideation and Behavior

Suicidal ideation and behavior based on the CCI and AEs will be summarized descriptively.

9.4.6. Other Endpoints

9.4.6.1. Patient-reported Outcomes

Analysis of patient-reported outcomes will follow the general considerations as given in Section 9.4.1. The testing of these endpoints will not be controlled for multiplicity and nominal p-values will be provided. These endpoints include but are not limited to the endpoints described below. A complete list of the PRO endpoints will be provided in the SAP.

- CCI remission at Week 12 and Week 24 (defined as total CCI score ≥170)
- Proportion of participants with >20 points change in CCI total score at Week 12 and Week 24
- Change from baseline in Domains T-scores of CCI and pain intensity at Week 12 and Week 24
- Proportion of participants with clinically meaningful change in Domains T-scores of CCI and pain intensity (as defined in SAP) at Week 12 and Week 24

- Change from baseline in CCI functional domain score and bowel domain score at Week 12 and Week 24
- Proportion of participants with clinically meaningful change (as defined in SAP) in CCI functional domain score and bowel domain score at Week 12 and Week 24
- Change from baseline in score of urgency of bowel movement by CCI at Week 12 and Week 24
- Proportion of participants with clinically meaningful change in score of urgency of bowel movement (as defined in SAP) by CCI at Week 12 and Week 24

9.4.6.2. Pharmacokinetic Analyses

Unless otherwise noted, PK analyses will be based on the PK analysis set. 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 time point. 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.

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.

9.4.6.3. Immunogenicity Analyses

The incidence of antibodies to guselkumab will be summarized for all participants in the immunogenicity analysis set.

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.

9.4.6.4. 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.

9.4.6.5. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum guselkumab concentrations and efficacy measures will be analyzed graphically. If feasible, a suitable exposure-response model may be developed to describe the relationship between serum guselkumab exposure and efficacy. Details will be provided in a population PK/PD analysis plan and results of the population PK/PD analysis will be presented in a separate technical report.

9.5. Interim Analysis

No interim analysis is planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADT	advanced therapy
ADT-IR	inadequate response to or intolerance of advanced therapy
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
AUC	area under the concentration time curve
AZA	azathioprine
BCG	Bacille Calmette-guerin
Cavg,ss	average steady-state serum study intervention concentration
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRO	contract research organization
CRP	C-reactive protein
CCI	[redacted]
CT	Computed Tomography
CTM	clinical trial manager
DBL	database lock
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
ED	Early Discontinuation
eDC	electronic data capture
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EU	European Union
EU-CTR	European Union Clinical Trials Regulation
FSH	Follicle Stimulating Hormone
GCP	good clinical practice
GI	gastrointestinal
GPSP	good post-marketing study practice
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
CCI	[redacted]
IB	Investigator's Brochure
IBD	inflammatory bowel disease
CCI	[redacted]
ICE	intercurrent events
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IGRA	Interferon-gamma release assay
IL	interleukin
IMP	Investigational Medicinal Product
IND	Investigational New Drug

INR	International Normalized Ratio
IPPM	Investigational Product Procedure Manual
IQ	interquartile
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
JAK	janus kinase
LTM	local trial manager
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measures
MTX	methotrexate
N/A	not applicable
PD	pharmacodynamic
PFS	Prefilled syringe
PFS-U	PFS-UltraSafe Plus Passive Needle Guard
PFS-Y	PFS-ypsomate autoinjector
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
POC	proof of concept
PQC	product quality complaints
PRO	Patient-reported Outcomes
CCI	[redacted]
PsA	psoriatic arthritis
q4w	every 4 weeks
q8w	every 8 weeks
RNA	ribonucleic acid
S1PR	sphingosine-1-phosphate receptor
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory coronavirus syndrome coronavirus 2
SC	subcutaneous
SD	standard deviation
SF	stool frequency
SFU	safety follow-up
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reactions
T	Telemedicine Visit
TB	tuberculosis
Tbili	total bilirubin
TNF	tumor necrosis factor
UC	ulcerative colitis
CCI	[redacted]
ULN	upper limit of normal
WBC	white blood cells

Definitions of Terms

COA	An umbrella term encompassing different types of outcomes assessments.
Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.
PRO	Reports directly from the patient without interpretation by clinician or anybody else.

10.2. Appendix 2: 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 12 weeks of starting therapy, or if a relapse occurs within 12 weeks after stopping corticosteroids or if they are unable to discontinue these agents without flare within 12 weeks 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 12 weeks 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 within the past 5 years.

  OR

- They have a medical condition that precludes the use of 6-MP or AZA.

10.3. Appendix 3: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNFα 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 or 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).

10.4. Appendix 4: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to Tofacitinib, Filgotinib, Upadacitinib, or Ozanimod

The criteria for inadequate initial response, response followed by loss of response, or intolerance to tofacitinib, filgotinib, upadacitinib, or ozanimod are described in items I, II, and III, below.

I. Inadequate initial response to induction therapy with tofacitinib, filgotinib, upadacitinib, or ozanimod (primary nonresponse)

Eligible participants must satisfy criteria A, B, and C.

A. Have received the following induction therapy (or other approved regimen):

- **Tofacitinib 10 mg by mouth (PO) twice daily for at least 8 weeks**

  or

- **Filgotinib 200 mg PO once daily for at least 10 weeks**

  or

- **Upadacitinib 45 mg PO once daily for at least 8 weeks**

  or

- **Ozanimod 0.92 mg PO once daily for at least 9 weeks after induction dose titration/escalation**

AND

B. Did not initially respond to induction therapy with tofacitinib, filgotinib, upadacitinib, or ozanimod, 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, filgotinib, upadacitinib, or ozanimod.

AND

C. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the dates and doses of the failed tofacitinib, filgotinib, upadacitinib, or ozanimod induction therapy
- Documents that the participant had persistence of disease activity following tofacitinib, filgotinib, upadacitinib, or ozanimod 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, filgotinib, upadacitinib, or ozanimod (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 the following (or other approved regimen):

- **Tofacitinib at a dose ≥5 mg PO twice daily**

  or

- **Filgotinib 200 mg PO once daily**

  or

- **Upadacitinib 15 mg or 30 mg PO once daily**

  or

- **Ozanimod at a dose of 0.92 mg daily**

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, filgotinib, upadacitinib, or ozanimod therapy.

AND

D. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the dates and doses of the failed tofacitinib, filgotinib, upadacitinib, or ozanimod maintenance therapy
- Documents that the participant had recurrence of UC disease activity despite adequate tofacitinib, filgotinib, upadacitinib, or ozanimod 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, filgotinib, upadacitinib, or ozanimod

Eligible participants must satisfy criteria A and B.

A. Have developed a clinically significant adverse event unresponsive to dose reduction that, in the judgment of the investigator, precluded continued use of tofacitinib, filgotinib, upadacitinib, or ozanimod to treat UC

- Examples of clinically significant adverse events associated with tofacitinib include serious infection, thrombosis, gastrointestinal perforation, lymphopenia, neutropenia, anemia, or persistently elevated liver enzymes.
- Examples of clinically significant adverse events associated with filgotinib include infections, neutropenia, anemia, or VTE.
- Examples of clinically significant adverse events associated with upadacitinib include serious infections, thrombosis, gastrointestinal perforation, major adverse cardiac events, lymphopenia, neutropenia, anemia, or persistently elevated liver enzymes.
- Examples of clinically significant adverse events associated with ozanimod include serious infection, bradyarrhythmias and Atrioventricular Conduction Delays, increased blood pressure, a decline in pulmonary function and respiratory effects, macular edema, persistently elevated liver enzymes, or Posterior Reversible Encephalopathy Syndrome.

AND

B. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the date of discontinuation of tofacitinib, filgotinib, upadacitinib, or ozanimod.

- Documents that the participant had intolerance to tofacitinib, filgotinib, upadacitinib, or ozanimod

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

10.5. Appendix 5: 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):

- 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.

Note: Additional HBV DNA testing at screening and/or HBV DNA monitoring during the study may be recommended regionally and should be performed according to local guidelines.

These eligibility criteria based on HBV test results are also represented in Table 12 below.

Table 12: Eligibility Based on Hepatitis B Virus Test Results

Hepatitis B Test Result			
HBsAg	**Anti-HBs**	**Anti-HBc total**	**Status**
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.
Abbreviations: DNA=deoxyribonucleic acid; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; anti-HBs=hepatitis B surface antibody; anti-HBc=hepatitis B core antibody

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.

10.6. Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

10.6.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current 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.

Post-marketing Study

In countries where, as required by local regulation, an ongoing clinical study may be considered a post-marketing study after new drug approval, instances of 'clinical trial' and 'clinical study' in this protocol can be considered synonymous with 'post-marketing study.' The studies will continue to be performed in accordance with the protocol for the post-marketing study, GCP/GPSP, and applicable regulatory and country-specific requirements following new drug approval for the corresponding study indication.

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) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, 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 must 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 CRF 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)
- IB (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.

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 IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs 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 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 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.6.2. 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 study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.6.3. Informed Consent Process

Each participant (or a legally acceptable representative) must give 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 or their legally acceptable representatives 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 or legally acceptable representative 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 or legally acceptable representative 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 must be appropriately recorded by means of either the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

10.6.4. Recruitment Strategy

Not applicable. Recruitment has stopped, and no further enrollment is planned, therefore the recruitment strategy is not further described. However, this section is being added to be compliant with EU-CTR as part of the transition to EU-CTR.

10.6.5. 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 (or his or her legally designated representative) 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.

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 PD, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. 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.

10.6.6. 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. Samples will only be used to understand guselkumab, to understand UC, to understand differential intervention responders, and to develop tests/assays related to guselkumab and UC. 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 Samples in Future Research).

10.6.7. Use of Information and Publication

All information, including but not limited to information regarding guselkumab supplied by the sponsor to the study site or investigator and not previously published, and any data or analysis generated as a result of this study, are considered confidential and remain the sole property of the sponsor. Study site and investigator shall not use this information except in the performance of this study and shall not disclose this information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

Study site and investigator shall not publish study results except as required by law or as specified in a separate, written agreement between the sponsor and the study site or investigator.

The sponsor will register the study and publish the study results in compliance with applicable law and may register the study or publish study results when not required.

Authorship of any peer-reviewed publications will be determined by mutual agreement in line with International Committee of Medical Journal Editors authorship guidelines.

In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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.

10.6.8. 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 CRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor may review the CRF 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.

10.6.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms must be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to CRF are needed after the initial entry into the CRF, 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.

10.6.10. 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 AEs and follow-up of AEs; 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 must 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
- 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 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 CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

10.6.11. Monitoring

The sponsor 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. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor may compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). At these visits, the monitor will compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF 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 as requiring central review.

10.6.12. 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 must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.6.13. 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. For trials performed under Regulation [EU] No. 536/2014, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

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.

10.6.14. Study and Site Start and Closure

First Act of Recruitment

The first participant 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 intervention.

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

10.7. Appendix 7: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.7.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE 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 International Council on Harmonisation [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 AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information, for time of last AE recording).

For combination products with a device constituent, AEs include those resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any AE resulting from use error or from intentional misuse of the investigational device.

Serious Adverse Event

An SAE 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 was 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 must 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.

For combination products with a device constituent, SAEs include adverse device effects that resulted in any of the consequences characteristic of an SAE. An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3, Benefit-Risk Assessment).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an AE will be determined by whether or not it is listed in the IB. In countries where, as required by local regulation, an ongoing clinical study may be considered a post-marketing study after new drug approval, the expectedness of an AE will be determined by whether it is listed in an appropriate document (eg, package insert).

10.7.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is assessed by the Investigator. The following selection must be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term “reasonable causal relationship” means there is evidence to support a causal relationship.

10.7.3. 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 must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.7.4. Special Reporting Situations

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 patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

Special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the CRF.

10.7.5. Procedures

All Adverse Events

All AEs, 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 AE to study therapy. All measures required for AE 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 SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from 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)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

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 an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.7.6. Product Quality Complaint Handling

Definition

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.

This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the study intervention or the comparator. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

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.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.7.7. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.8. Appendix 8: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 7: 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, or 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 woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman 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 men or women must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

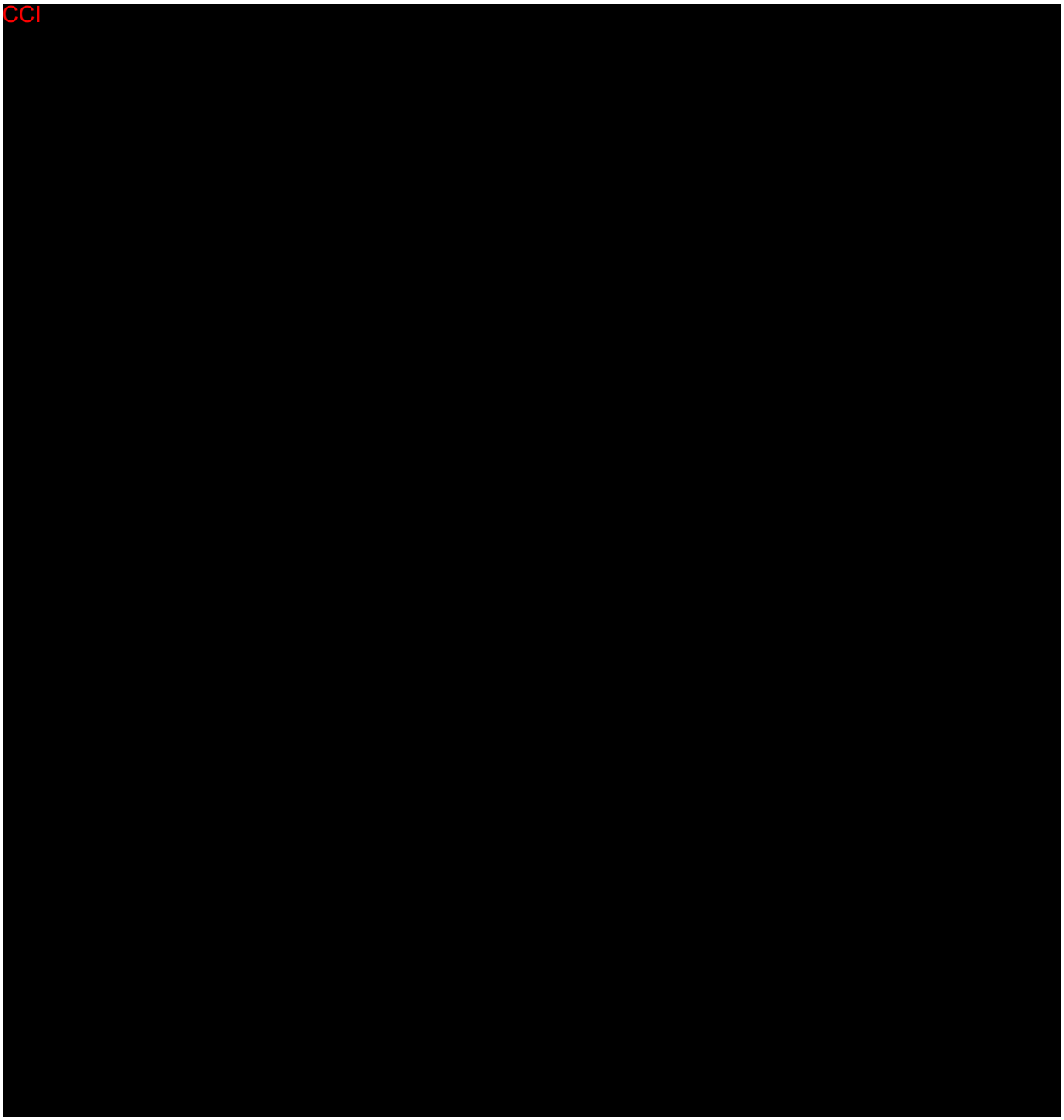
Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives for Female Participants

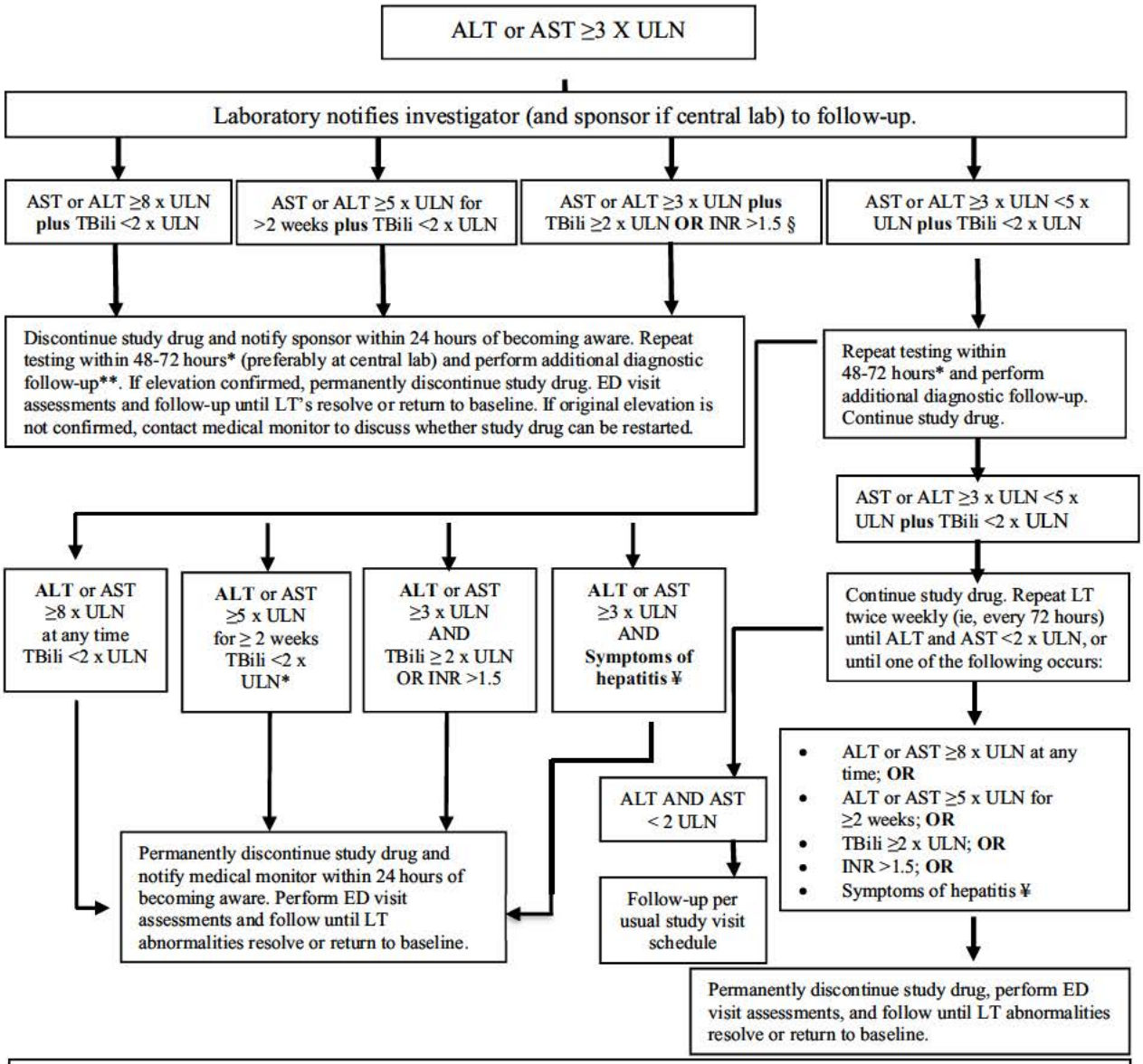
EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
•Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
•Intrauterine 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 woman 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 must not be used together (due to risk of failure with friction).

10.9. Appendix 9: CCI



10.10. Appendix 10: Guideline Algorithm for Monitoring, Assessment and Evaluation of Abnormal Liver Tests



Abbreviations: LT= Liver tests that include ALT, AST, TBili, direct bilirubin, ALP, and gamma-glutamyltransferase

* Repeat testing within 48-72 hours in participants with initial ALT or AST elevation. NOTE: ALT is considered a more liver-specific aminotransferase enzyme than AST.

¥ ALT or AST ≥3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)

§ Any ALT or AST ≥3 AND TBili ≥2 x ULN OR INR >1.5 results (Potential Hy's Law cases) must be reported to the sponsor within 24 hours from investigator awareness using an SAE form and while repeat test and additional work up is being performed. If initial results are confirmed and no obvious alternatives have been identified at the time of expedited reporting timelines, these liver function test elevations will be reported as SUSARs.

If the investigator feels that the participant cannot safely continue administration of study intervention regardless of algorithm, participant should discontinue study intervention and continue to the ED visit.

** SEE NEXT PAGE FOR TESTS AND EVALUATIONS TO BE OBTAINED

- **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 CONTINUED MONITORING RESULTS OF THE DIAGNOSTIC WORK-UP.**
- **CONSULT MEDICAL MONITOR FOR ANY QUESTIONS ON WORK -UP RECOMMENDATIONS, INCLUDING WHEN OPTIONAL TEST MAY BE INDICATED.**
- **A HEPATOLOGIST CONSULTATION SHOULD BE CONSIDERED IF CLINICALLY INDICATED FOR THE DIAGNOSIS AND MANAGEMENT OF POTENTIAL DRUG INDUCED LIVER INJURY (DILI).**

Steps 1-6 should be performed for liver work-up when meeting the liver test algorithm (ie, ALT ≥ 3 x ULN) in which DILI is a possibility.

1. Obtain detailed history of present illness (abnormal liver tests [LTs]) including (if not already obtained at baseline) height, weight, body mass index. 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, occupational exposure to hepatotoxins, diabetes mellitus, gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other medications including acetaminophen, nonsteroidal anti-inflammatory drugs, over-the-counter 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 body mass index, 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).
2. Imaging is strongly recommended to exclude other liver injury causes, particularly if TBili or ALP is >2 x ULN, or when clinically indicated based on medical history (eg, to exclude non-alcoholic hepatic steatosis). Imaging is mandatory if participant meets criteria for study intervention discontinuation according to the liver tests algorithm. Liver ultrasound is the recommended initial imaging modality with consideration of further imaging (eg, CT, MRI, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation).
3. If TBili is ≥2 x ULN, 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.

4. Complete blood count with WBC, eosinophil, and platelet count (to further scrutinize potential immune-mediated mechanism of injury)
5. INR, and total protein and albumin (compute globulin fraction) should also be documented (to further scrutinize potential severity of the liver damage). If INR is abnormal, prothrombin time, partial thromboplastin time 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.
6. 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 (Ig)M, anti-hepatitis A virus total, HBsAg, anti-HBs, anti-HBc total, anti-HBc IgM, anti-HCV, anti-hepatitis E virus IgM (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus, and cytomegalovirus screen.
    - If participant is immunosuppressed, test for HCV RNA and hepatitis E virus RNA by polymerase chain reaction.
    - If HBsAg or anti-HBc IgM or anti-HBc IgG positive, also get HBV DNA to detect active Hepatitis B, 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.

Steps 7-12 are optional; In consultation with the medical monitor, additional clinical and laboratory studies may be performed to evaluate the underlying etiology of abnormal findings.

7. Based on potential baseline confounders of the disease target population consider (optionally): gamma-glutamyl transferase (to confirm the liver origin of elevated ALP levels), serum creatine phosphokinase (to confirm the liver origin of elevated AST levels], lactate dehydrogenase (to help exclude hemolysis), glutamate dehydrogenase (if muscle injury is suspected or if muscle disease is target population).
8. 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: antinuclear antibody, anti-liver kidney microsomal antibody type 1, anti-liver-kidney microsomal antibodies, anti-smooth muscle antibodies (to screen for additional immune-related etiologies), erythrocyte sedimentation rate, and CRP (to screen for potential systemic inflammatory causes).
9. If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in Table 13), then gamma-glutamyl transferase, anti-mitochondrial antibody and anti-neutrophil cytoplasmic antibody 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 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.

Table 13: Patterns of DILI Based on Elevations of Liver Tests

Histopathology	LT	Ratio (ALT/ULN) / (ALP/ULN)
Hepatocellular	**ALT ≥3 × ULN**	**≥5**
Cholestatic	**ALT ≥3 × ULN**	**≤2**
Mixed	**ALT ≥3 × ULN and AP ≥2 × ULN**	**>2 to <5**

10. 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 ALP 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.

11. If pertinent, copies of hospital discharge summary, radiology, pathology and autopsy reports should be obtained.

10.11. Appendix 11: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the 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 requirements or the clinical judgement 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 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 via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. 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.

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 responsible medical officer 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 clinical study report.

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 (including the potential for self-administration of study intervention)
    - 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 will be outlined in study SAP.

10.12. Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 3 (21 October 2024)

Overall Rationale for the Amendment: Extend the overall duration of the study from approximately 112 weeks (92 weeks of treatment) to 268 weeks (248 weeks of treatment), to align with a Health Authority commitment. Time points for assessments were added/updated accordingly. In addition, edits were made to bring this protocol into compliance with EU-CTR requirements (Regulation [EU] 536/2014).

The changes made to the clinical protocol CNTO1959UCO3004 as part of Protocol Amendment 3 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.12 Appendix 12: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.3 Schedule of Activities Table 2 (footnote c), 4.1 Overall Design, 4.2 Scientific Rationale for Study Design	Updated the study duration to reflect the extension of the overall treatment period and to clarify that participants will continue on guselkumab treatment up to Week 248.	The study was extended to align with a Health Authority commitment.
1.1 Synopsis	Updated overall study duration from up to 112 weeks to 268 weeks. Updated the extension treatment period duration from 72 weeks to 224 weeks. Removed the statement that the last scheduled dose of study intervention will be at Week 92.	
1.2 Schema	Updated the study schema to reflect the extended treatment duration. Added a clarifying footnote.	
1.3 Schedule of Activities, Table 1	Edited footnote b to clarify that participants who discontinue study intervention prior to Week 24 should have a safety follow-up visit approximately 12 weeks after the last dose of study intervention.	
1.3 Schedule of Activities, Table 2	Updated the table title (“Week 28 Through Week 96”). Added “Dispense study intervention”, “Administer study intervention”, “Dispense at-home study medication diary”, and “Injection-site evaluation” at the Week 96 visit, and updated the note for the “Dispense study intervention” row. Edited footnote e to clarify that participants who discontinue study intervention prior to Week 96 should have a safety follow-up visit approximately 12 weeks after their last dose of study intervention.	
1.3 Schedule of Activities, Table 3	Added a new SoA covering the extension treatment period from Week 100 through Week 248.	
3 Objectives and Endpoints, 9 Statistical Considerations, 9.4.4 Exploratory Efficacy Endpoints	Edited the sentence referring to the SAP to state that further details will be provided in the SAP.	
4.2 Scientific Rationale for Study Design	In the final paragraph in the subheading “Blinding, Control, Study Periods, Intervention Groups”, clarified that, with the extension of the overall treatment period, the study will provide access to treatment for approximately 5 years. Also edited the final statement regarding the follow-up period.	
4.2.1 Study-Specific Ethical Design Considerations,	Updated the total blood volume to be collected (and where necessary, the timing for collection) from each participant.	

Section Number and Name	Description of Change	Brief Rationale
8 Study Assessments and Procedures		
4.4 End of Study Definition	Updated instances of Week 96 to Week 248 in the "Participant Study Completion Definition" section.	
6.1 Study Intervention(s) Administered	Updated title of Figure 2 to "Dosing Schedule Through Week 248". Updated the figure to include guselkumab dosing at Week 96 and extended the duration of the study to Week 248. Added a footnote to Week 48.	
6.1.1 Self-administration of Study Intervention	Added language on at-home administration from Week 96.	
6.8.1 UC-related Concomitant Therapies	Updated the subheading "Week 48 through Week 96" to "Week 48 through Week 248."	
8 Study Assessments and Procedures	In the paragraph on CCI and CCI daily diary entries (under the "Screening" subheading), added a reference to the SoA (Section 1.3).	
8.2.5 Pregnancy Testing	Edited first sentence to refer the reader to the SoA for details on pregnancy testing for women participants of childbearing potential.	
Title page	Added sentence on new EU regulation.	To comply with EU-CTR requirements and comply with the Sponsor's protocol template.
Title page, 1.1 Synopsis	Deleted EudraCT number (from title page) and added the EU Trial Number.	
1.1 Synopsis	Added a summary of Benefit/Risk Assessment.	
5.4 Screen Failures	Added text to specify usage of IWRS and its relationship to the generation of screening and enrollment logs.	
6.1 Study Intervention(s) Administered	Added a table of IMPs and authorization status to the start of this section.	
8.3.4 Regulatory Reporting Requirements for SAEs and Anticipated Events	Updated safety reporting text.	
10.6.4 Recruitment Strategy	Added section and text indicating that it is not applicable to this study, because recruitment for this study has stopped.	
10.6.5 Data Protection	Changed "legally acceptable representative" to "legally designated representative".	
10.6.7 Use of Information and Publication	Updated text to match recent template update.	
10.6.13 Record Retention	Sentence on trials performed under EU Regulations added to the end of the second paragraph.	
Title page, 1.1 Synopsis	Added IND number.	To comply with the Sponsor's protocol template.
6.1.1 Self-Administration of Study Intervention	Edited the first sentence under the subheading "At-home" to clarify that self-administration of study intervention should occur as outlined in the SoA (Section 1.3).	For clarity.
8.2.6 Suicidal Ideation and Behavior Risk Monitoring	Added a reference to the SoA (Section 1.3) in the fourth paragraph.	For clarity.
10.6.1 Regulatory and Ethical Considerations	Added post-marketing study paragraph.	To comply with local regulations.
10.7.1 Adverse Event Definitions and Classifications	Added final sentence to text in "Unlisted (Unexpected) Adverse Event/Reference Safety Information" subheading specifying that an AE will be determined by whether it is listed in an appropriate document.	

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

Amendment 2 (16 August 2022)

Overall Rationale for the Amendment: The overall reason for the amendment is to align with requests received from Health Authorities. In addition, revisions were made to improve clarity and consistency in the protocol. The changes made to the clinical protocol CNTO1959UCO3004 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in the previous protocol amendment are listed in Section 10.12 Appendix 12: Protocol Amendment History.

Section number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	• Added endoscopy at Week 24 • Removed endoscopy, CCI as well as adjacent biopsy samples at Week 96	Addresses health authority request
1.1 Synopsis, 3. Objectives and Endpoints, 9.2 Sample Size Determination, 9.4.3 Secondary Endpoints, 9.4.3.2 Confirmatory Testing Procedure	Week 24 endoscopy was added to enable inclusion of clinical remission at Week 24 as a secondary endpoint. Along with clinical remission at Week 24, endoscopic improvement at Week 24 and clinical response at Week 24 were also added as secondary endpoints. These secondary endpoints were incorporated in the confirmatory testing sequence which now follows a purely hierarchical approach. Individual power for the additional secondary endpoints was added into the sample size calculation section.	Addresses health authority request
1.2. Schema, 6.1 Study Intervention(s) Administered	Modified Figures 1 and 2: • Added endoscopy at Week 24 • Removed endoscopy at Week 96	Addresses health authority request
1.3 Schedule of Activities	Urine pregnancy test added at ED and SFU visits following the main treatment period.	Inadvertently omitted from prior protocol versions
1.1 Synopsis, 9.4.2.2 Estimator for the Primary Endpoint, 9.4.3.1 Estimands and Estimators	Changed CMH test to Mantel-Haenszel test for common risk difference with Mantel-Haenszel weights and Sato variance estimator.	Addresses health authority request
9.4.5.1 Adverse Events	Removed frequency and type of infections and serious infections analyses	These analyses are redundant as they will be included in summaries of frequency and type of AEs and SAEs, respectively
1.1 Synopsis, 4.2.1 Study-specific Ethical Design Consideration	Updated duration of the study from 116 to 112 weeks	SFU visit is 12 weeks after the last study medication dose, which is at Week 92
1.3 Schedule of Activities, 8. Study Assessments and Procedures	Added details on how to complete daily diary entries	Improve clarity in the protocol
5.1 Inclusion Criteria,	Updated inclusion criterion 8 and exclusion criterion 32	Improve clarity in the protocol

5.2 Exclusion Criteria		
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made	Improve clarity in the protocol
Throughout the protocol	Updated "country" to "country/territory" when referring to country-specific regulations and requirements.	To clarify that the text specifying country-specific regulations and requirements are also applicable to territories.

Amendment 1 (2 May 2022)

Overall Rationale for the Amendment: The overall reason for the amendment is to align with requests received from the Health Authorities. In addition, revisions were made to improve clarity and consistency in the protocol.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.2 Schema, 1.3 Schedule of Activities, 4.1 Overall Design, 6.1.1 Self-Administration of Study Intervention, 6.3 Measures to Minimize Bias: Randomization and Blinding, 6.8.1 UC-related Concomitant Therapies	Timing of endoscopy procedure moved from Week 56 to Week 48. Updated the study assessments and text to allow for unblinding at Week 48 instead of Week 56, and for optional at-home study administration to begin at Week 52 instead of Week 60.	Addresses health authority request.
1.1 Synopsis, 4.1 Overall Design, 5.1 Inclusion Criteria, 6.3 Measures to Minimize Bias: Randomization and Blinding, 6.8.2 Prohibited Concomitant Therapies, 10.4 Appendix 4: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to Tofacitinib, Filgotinib, Upadacitinib or Ozanimod	Upadacitinib and filgotinib were added as approved JAK inhibitors to the list of advanced therapies. Appendix was updated to define primary nonresponse, secondary loss of response, and intolerance to upadacitinib and filgotinib.	Upadacitinib and filgotinib have recently been approved to treat moderately to severely active UC.
1.1 Synopsis, 1.3 Schedule of Activities, 4.2 Scientific Rationale for Study Design,	Optional genetic research sampling was removed from the study.	Reduces participant burden.

Section number and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria, 7.2.1 Withdrawal From the Use of Research Samples, 8.5 Pharmacogenomics, 9.4.6.6 Pharmacogenomic Analyses, 10.6 Appendix 6 Regulatory, Ethical, and Study Oversight Considerations		
1.3 Schedule of Activities, 8 Study Assessments and Procedures	Updated the visit window in the extension phase from ±7 days to ±10 days.	To provide greater flexibility to schedule study visits during the extension phase.
3 Objectives and Endpoints	Added exploratory endpoints at Week 48, including clinical response, clinical remission, and endoscopic improvement.	Addresses health authority request.
5.1 Inclusion Criteria	Updated the dose of budesonide or beclomethasone dipropionate allowed prior to receiving study intervention.	Addresses health authority request.
8.1.1 CCI	Updated the days that will be used to calculate the CCI	Addresses health authority request.
9.2 Sample Size Determination	Added Phase 3 ustekinumab UC program [CNTO1275UCO3001], to rationale of sample size determination.	Clarify assumption for sample size determination.
9.4.2.1 Primary Estimand of Clinical Remission, 9.4.2.2 Estimator for the Primary Endpoint, 9.4.3.1 Estimands and Estimators	Changed analysis strategy for intercurrent events.	Intercurrent event handling strategies were updated to address health authority request.
9.4.3.2 Confirmatory Testing Procedure	Updated the testing procedure for the endpoint of symptomatic remission at Week 24.	Testing procedure for 4th secondary endpoint was updated to address health authority request.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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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] Date: _____
(Day Month Year)

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	13-May-2025 21:11:34 (GMT)	Document Approval