Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 2a Randomized, Double-blind, Active-controlled, Parallel-group, Multicenter, Proof-of-concept Clinical Study to Evaluate the Efficacy and Safety of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis

VEGA

Short Title

A Proof-of-concept Study of the Efficacy and Safety of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis

Protocol CNTO1959UCO2002; Phase 2a
Amendment 2

TREMFYA® (guselkumab)
SIMPONI® (golimumab)

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

EudraCT NUMBER: 2018-001510-15

Status: Approved
Date: 7 March 2019
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-155505739, 3.0

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 2	07 March 2019
Amendment 1	24 Sep 2018
Original Protocol	21 June 2018

Amendment 2- 07 March 2019

Overall Rationale for the Amendment: The overall reason for the amendment is to update the procedure for single cell isolation to be collected from all participants during mucosal biopsy sample collection and to collect peripheral blood mononuclear cells (PBMCs) from whole blood. Additional clarifications were made throughout the protocol based on feedback from health authorities, ethics committees, and investigative sites.

The changes to the protocol are outlined in the table below. Additions to the text are indicated by underline; deletion of text is shown in ~~strikethrough~~.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	The following footnote from Table 1 (footnote u.) and from Table 2 (footnote l.) was modified: Mucosal biopsy samples will be collected from all participants during endoscopy for RNA expression analysis, ~~and~~ histologic assessment, and single cell isolation. ~~Additional biopsy samples for single cell isolation will be collected from a subset of approximately 75 participants at pre-defined study sites capable of performing biopsy collection procedure for single cell isolation~~. Footnote v. on Table 1 was modified: The screening biopsy samples for histology, RNA analyses, and single cell isolation ~~(at selected study sites)~~ will be collected from all participants during the screening endoscopy performed within 2 weeks of the baseline (W0) visit.	The protocol was updated to collect mucosal biopsy samples from all participants for single cell isolation.
8.8.4 Mucosal Biopsy (RNA, Histology, and Single Cell Isolation)	The section was modified as follows: Mucosal biopsy samples will be collected from all participants during endoscopy at the times specified in the SoA for RNA expression analysis, ~~and~~ histologic assessment, and single cell isolation. Total RNA will be isolated and used for differential gene expression analyses to identify mRNA or microRNA expression patterns that are relevant to guselkumab or golimumab treatment and/or UC, and to evaluate markers that can predict therapeutic response. The biopsy samples collected will also be used for the	

Section Number and Name	Description of Change	Brief Rationale
	histologic and immunohistochemical assessment of disease and healing. ~~Additional biopsy samples will be collected from a subset of up to approximately 75 participants at selected study sites capable of performing biopsy collection procedure for single cell isolation.~~ Protein and gene expression will be measured at higher resolution in various immune cell populations isolated from these biopsy samples.	
1.1. Synopsis	Peripheral blood mononuclear cells (PBMCs) was added to the subsection of "Pharmacodynamic and Biomarker Evaluations."	The protocol was updated to include procedures and timing for whole blood collection for PBMC isolation.
1.3. Schedule of Activities	Whole blood (PBMC) collection was added to the SoA under Pharmacodynamics and Biomarkers in Table 1 and Table 2. Whole blood (PBMCs) will be collected at screening, Week 4 (only those who consent to participate in the optional endoscopy and biopsy sub-study), and Week 12 during the combination phase and at Week 38 and the early termination visit during the monotherapy phase. The following footnote from Table 1 (footnote w.) and Table 2 (footnote m.) was modified: Serum biomarkers and whole blood RNA <u>and PBMCs</u> will be ~~measured in~~ <u>collected from</u> all participants to evaluate the molecular effects of each study intervention in UC. Footnote p. on Table 1 was modified: Only those participants who consent to participate in the optional <u>endoscopy and biopsy</u> sub-study will undergo Week 4 endoscopy and mucosal biopsy collection <u>and whole blood PBMC collection.</u> The following footnote was added to Table 1 (footnote cc.) and Table 2 (footnote q.): <u>Whole blood (PBMC) samples are to be collected ideally within ±2 days of the endoscopy visit.</u>	
1.3. Schedule of Activities; 10.1. Appendix 1: Abbreviations and Trademarks	The following abbreviation was added to Table 1 and Table 2 of the SoA, and to the Abbreviation list in Appendix 1: PBMC= peripheral blood mononuclear cell	
4.2.2. DNA and Biomarker Collection	The following was added as the second to last sentence in the bullet for Optional Week 4 endoscopy and biopsy sub-study: <u>Whole blood (PBMCs) will also be collected.</u>	

Section Number and Name	Description of Change	Brief Rationale
4.2.5 Study-Specific Ethical Design Considerations; 8. Study Assessments and Procedures 8.8.5 Whole blood (PBMCs)	The maximum total blood volume to be collected from each participant in the study was updated from approximately 310 mL to approximately 350 mL. Section 8.8.5 was added to describe the collection of whole blood (PBMCs) and the subsequent subsection was renumbered accordingly: Whole blood samples will be collected from all participants as specified in the SoA. Peripheral blood mononuclear cells (PBMCs) will be isolated and used for single cell isolation. Protein and gene expression that are relevant to study intervention and/or UC will be measured at higher resolution in PBMCs isolated from whole blood. To match with single cell analysis in colonic biopsies, whole blood samples will also be obtained at Week 4 from participants who agree to participate in the optional endoscopy and biopsy sub-study.	
1.1. Synopsis, Statistical Methods; 9.4.2 Safety Analyses	The first sentence in the subsection of "Safety Analyses" in the Synopsis and in section 9.4.2 was modified: Safety data, including but not limited to, AEs, serious adverse events (SAEs), infections, serious infections, and changes in laboratory assessments~~, and changes in vital signs~~ will be summarized.	To clarify that vital signs will be collected as indicated on the SoA but will not be summarized.
1.3. Schedule of Activities	The following footnote was added to the line item for "Injection-site evaluation" in both Table 1 (footnote bb.) and Table 2 (footnote p.): An injection-site reaction is any adverse reaction at any SC study intervention injection site. Injection sites will be evaluated for reactions and any injection-site reaction should be recorded as an adverse event.	To clarify how injection-site reactions should be recorded if noted.
4.2.3. Patient-Reported Outcomes on Health-Related Quality of Life	The following sentence was added to the paragraph: Patient-reported outcomes will only be collected in countries where translations of the evaluations are available.	Translations of the PRO evaluations are currently available in all participating countries. However, in the event that additional sites are needed in additional countries, it is possible that translations of the PRO evaluation may not be available.
5.1. Inclusion Criteria; Appendix 2: Definition of Inadequate Response to or Intolerance of	Appendix 2, Definition of Inadequate Response to or Intolerance of Corticosteroids or AZA/6-MP and Corticosteroid Dependence, was added to the protocol. The subsequent appendices were renumbered accordingly. Inclusion criterion #5 a., b., and c., remain the same	This appendix was inadvertently not included in the prior version of the protocol.

Section Number and Name	Description of Change	Brief Rationale
Corticosteroids or AZA/6-MP and Corticosteroid Dependence	but were updated to include the statement "as defined in Appendix 2 (Section 10.2)" for each.	
5.1. Inclusion Criteria 8.2.12.1 Initial Tuberculosis Evaluation	Inclusion Criterion #11 d. was modified: Within 8 weeks prior to the first administration of study intervention, has a negative QuantiFERON®-TB test result. ~~For the purposes of this study, an indeterminate QuantiFERON® -TB test result is exclusionary as outlined in Section 8.2.12~~. For a participant with an indeterminate QuantiFERON®-TB test, the test may be repeated once. If the result is indeterminate on repeat testing, the participant is considered a screen failure as outlined in Section 8.2.12.1. The last sentence of the second paragraph was modified as follows: ~~For the purposes of this study, participants with an indeterminate QuantiFERON® -TB test result are excluded.~~ For a participant with an indeterminate QuantiFERON®-TB test, the test may be repeated once. If the result is indeterminate on repeat testing, the participant is considered a screen failure.	To clarify the retesting procedure for the QuantiFERON-TB test with respect to participant eligibility during screening.
5.1. Inclusion Criteria	Inclusion Criterion #17 was modified: Be willing and able to adhere to all specified requirements, including but not limited to completion of required assessments, adherence to visit schedule, and compliance with the lifestyle restrictions as specified in this protocol.	Added specific examples of what may be considered critical barriers for a potential study participant to be eligible for enrollment.
5.1. Inclusion Criteria	Inclusion Criterion #20 was added: Each participant must sign a separate ICF if he or she agrees to participate in the optional Week 4 endoscopy and biopsy sub-study. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the participant and his or her legally acceptable representative. Refusal to give consent for the optional Week 4 endoscopy and biopsy sub-study does not exclude a participant from participation in the study.	The inclusion criterion for participants to sign a separate ICF for the optional Week 4 endoscopy and biopsy sub-study was inadvertently not included in the prior version of the protocol.
5.2. Exclusion Criteria	Exclusion Criterion #11 was modified: Has a stool culture or other examination positive for an enteric pathogen, including *Clostridium difficile* toxin, ~~in the previous~~ within 4 months before the first administration of study intervention, unless a repeat examination is negative and there are no signs	To clarify the timeframe of a positive test for an enteric pathogen is within 4 months before the first administration of study intervention, which aligns with footnote l. in Table 1 of the SoA.

Section Number and Name	Description of Change	Brief Rationale
	of ongoing infection with that pathogen.	
5.2. Exclusion Criteria	Exclusion Criterion #31 was deleted: ~~31. Has previously undergone allergy immunotherapy for prevention of anaphylactic reactions (eg, venom immunotherapy).~~	This exclusion criterion was included in the original protocol in error and is not relevant for guselkumab or golimumab.
7.1. Discontinuation of Study Intervention	The following sentences were removed from Criterion #7 under the section entitled "A participant's study treatment must be discontinued under the following conditions:" The participant has a serious adverse reaction that is related to an injection or an infusion, including an injection-site or infusion reaction, 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. ~~This may include events of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grade ≥3. In general, discontinuation of study intervention administration must be considered for participants who develop a severe injection-site or infusion reaction.~~	The first statement on NCI-CTCAE criteria was removed because grading of adverse events is not being performed in this study. The second statement on injection site reactions was removed because injection site or infusion reactions are not mandatory discontinuation requirements.
7.1. Discontinuation of Study Intervention	The following criterion was relocated from Criterion #4 in the section entitled "Discontinuation of a participant's study intervention must be strongly considered under the following conditions" to become Criterion #14 in the section entitled "A participant's study treatment must be discontinued under the following conditions": The investigator believes that for safety or tolerability reasons, it is in the best interest of the participant to discontinue study intervention.	Relocation of the specified statement is necessary because the criterion is clearly indicative of the need to mandate discontinuation.
7.1. Discontinuation of Study Intervention	The following note was added to Criterion 2 under "Discontinuation of a participant's study intervention must be strongly considered under the following conditions": 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.	To clarify that study intervention should be withheld until a clinical assessment is complete for any serious infection.
7.1. Discontinuation of Study Intervention	The following criterion was relocated from #7 in the section entitled "A participant's study treatment must be discontinued under the following conditions" to become criterion #6 in the section entitled "Discontinuation of a participant's study	Relocation of the specified criterion was necessary since injection site or infusion reactions are not mandatory discontinuation requirements.

Section Number and Name	Description of Change	Brief Rationale
	intervention must be strongly considered under the following conditions:" The participant develops a severe injection-site or infusion reaction.	
8. Study Assessments and Procedures	The following sentence was added to the second paragraph of the subsection "Screening Phase": Participants will be instructed to complete a daily Mayo diary for 7 days immediately before each visit and bring them to every visit for data collection and review by the investigator/study coordinator. The following sentence was added to the third paragraph of the subsection "Screening Phase": Participants will complete the BSFS as a daily diary entry from Week 0 through Week 12. The fourth paragraph of the subsection "Screening Phase" was deleted: ~~Participants will be instructed to complete Mayo and BSFS diaries 7 days immediately before each visit and bring them to every visit for data collection and review by the investigator/study coordinator. Bristol Stool Form Scale diaries are required only during the combination comparison phase of the study (ie, through Week 12).~~	To clarify that the diary for the Bristol Stool Form Scale will only need to be completed from Week 0 through Week 12.
8. Study Assessments and Procedures	The following sentence was added to the fifth paragraph of the subsection "Screening Phase": Histology results from the polypectomy must be available to confirm absence of colonic mucosal dysplasia before first administration of study intervention (Section 5.1, Exclusion Criterion #8).	To clarify Exclusion Criterion #8 that absence of colonic mucosal dysplasia must be confirmed before first administration of study intervention.
8.1.6. PROMIS-29	The following sentences were added to the paragraph: Norm-based scores have been calculated for each domain on the PROMIS measures, with a score of 50 representing the mean or average of the reference population. On symptom-oriented domains of PROMIS-29 (anxiety, depression, fatigue, pain interference, and sleep disturbance), higher scores represent worse symptomatology. On the function-oriented domains (physical functioning and social role), higher scores represent better functioning.	To clarify how the PROMIS-29 is scored and how the scores should be interpreted.
8.2.9 Hypersensitivity Reactions	The third paragraph was modified: Participants who experience serious adverse reactions related to an injection or infusion ~~should~~	The text was updated to align with the changes made to the discontinuation criteria regarding hypersensitivity reactions in

Section Number and Name	Description of Change	Brief Rationale
	must strongly be considered to be discontinued from further study intervention administrations. The fourth paragraph was modified: Participants who experience reactions following an injection or infusion that result in bronchospasm with wheezing and/or dyspnea that requires ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm Hg or blood pressure <90/60 mm Hg ~~will not be permitted to receive~~ must be discontinued from additional study intervention administration (see Section 7). The first sentence of the fifth paragraph was modified: Participants who experience reactions suggestive of serum sickness (resulting in symptoms such as myalgia and/or arthralgia with fever and/or rash that are not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after administration of study intervention, ~~should~~ must be discontinued from further study intervention administration.	Section 7 and to clarify when study intervention must be discontinued or must be strongly considered to be discontinued for hypersensitivity reactions.
8.3.5 Events of Special Interest 10.9 Appendix 9: Adverse Events: Definitions and procedures for Recording, Evaluating, Follow-up, and Reporting	The first sentence of the section was modified as follows: Any newly identified malignancy or case of active TB occurring after the first study intervention administration(s) in subjects participating in this clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the event, according to the procedures in Appendix 9 (Section 10.9), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting for SAEs. The following sentence was added as the first sentence to the subsection for "Special Reporting Situations": Special reporting situations must be reported by the investigator or site staff personnel to the sponsor or designee within 24 hours after being made aware of the event.	To specify the time period in which investigators or site personnel must report an event of special interest and special reporting situations.
Section 10.6, Appendix 6: Regulatory, Ethical, and Study Oversight Considerations	The subsection for "Investigator Responsibilities" was revised as follows: The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), the latest version of the Declaration of	Clarification to specify that investigators are required to comply with the principles of Declaration of Helsinki.

Section Number and Name	Description of Change	Brief Rationale
	Helsinki, and applicable regulatory and country-specific requirements.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2a Randomized, Double-blind, Active-controlled, Parallel-group, Multicenter, Proof-of-concept Clinical Study to Evaluate the Efficacy and Safety of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis

Protocol number: CNTO1959UCO2002

EudraCT Number: 2018-001510-15

Guselkumab (CNTO 1959 or TREMFYA®) is a fully human immunoglobulin G1 lambda monoclonal antibody (mAb) that binds to the p19 subunit of human interleukin (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-specific intracellular signaling and subsequent activation and cytokine production. Guselkumab is currently approved in the United States, European Union, Canada, and several other countries for the treatment of moderate to severe plaque psoriasis. In addition, guselkumab is also being evaluated in psoriatic arthritis (PsA) and Crohn's disease globally.

Golimumab (CNTO 148 or SIMPONI®) is a fully human anti-tumor necrosis factor alpha (TNFα) mAb that binds to TNFα with high affinity. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα. Golimumab is approved for treatment of moderately to severely active ulcerative colitis (UC) in over 90 countries worldwide. Additionally, golimumab is approved for 1 or more of the following indications around the world: rheumatoid arthritis (RA), PsA, ankylosing spondylitis (AS), nonradiographic axial spondyloarthritis (nr-Axial SpA), and polyarticular juvenile idiopathic arthritis (pJIA).

OBJECTIVES AND ENDPOINTS

This study will consist of 2 distinct phases: a 12-week combination comparison phase followed by a 26-week monotherapy phase.

Objectives

Primary Objectives

Combination Comparison Phase

- To evaluate the clinical efficacy of combination therapy with guselkumab and golimumab in participants with moderately to severely active UC.
- To evaluate the safety of combination therapy with guselkumab and golimumab in participants with moderately to severely active UC.

Secondary Objectives

Combination Comparison Phase

- To evaluate the effect of combination therapy with guselkumab and golimumab on endoscopic improvement.
- To evaluate the impact of combination therapy with guselkumab and golimumab on disease-specific health-related quality of life (HRQOL), including fatigue.
- To evaluate the efficacy of combination therapy with guselkumab and golimumab by negative response signature status at baseline.

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

Monotherapy Phase

- To evaluate the clinical efficacy of combination therapy followed by guselkumab monotherapy.
- To evaluate the safety of combination therapy followed by guselkumab monotherapy.
- To evaluate the effect of combination therapy followed by guselkumab monotherapy on endoscopic improvement.
- To evaluate the impact of combination therapy followed by guselkumab monotherapy on disease-specific HRQOL, including fatigue.
- To evaluate the efficacy of combination therapy followed by guselkumab monotherapy by negative response signature status at baseline.
- To evaluate the PK, immunogenicity, and PD of combination therapy followed by guselkumab monotherapy, including changes in CRP, fecal calprotectin, and other PD biomarkers.

Exploratory Objectives

- To explore the effect of combination therapy on patient-reported outcome (PRO) instruments (eg, Bristol Stool Form Scale [BSFS] and Patient's Global Impression of Change [PGIC] of Severity of UC).

Endpoints

Primary Endpoint

- Clinical response at Week 12, defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points with either a decrease in rectal bleeding subscore (RBS) ≥1 or a RBS of 0 or 1.

Major Secondary Endpoint

- Clinical remission at Week 12, defined as a Mayo score ≤ 2 with no individual subscore >1.

Note: Other remission definitions may be considered and will be fully described in the Statistical Analysis Plan (SAP).

Hypothesis

Combination therapy with guselkumab and golimumab will result in a rate of clinical response at Week 12 that is superior to both monotherapy arms.

OVERALL DESIGN

This is a Phase 2a, randomized, double-blind, active-controlled, parallel-group, multicenter, interventional proof-of-concept (POC) clinical study designed to evaluate the efficacy and safety of combination therapy with guselkumab and golimumab in adults with moderately to severely active UC. The target population is men or women 18 to 65 years old with moderately to severely active UC, as defined by a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopy subscore ≥2 as obtained during the central review of the video endoscopy. Participants must be naïve to TNF antagonists and have failed or not tolerated conventional therapy with oral or intravenous (IV) corticosteroids or immunomodulators (6-mercaptopurine [6-MP] or azathioprine [AZA]).

Immunomodulators (6-MP, AZA, and methotrexate [MTX]) must be discontinued for at least 2 weeks before the first dose of study intervention. For participants who are receiving oral corticosteroids at baseline, the investigator must begin tapering the daily dose of corticosteroids at Week 6. All participants will be evaluated for clinical worsening of UC throughout the study. In general, doses of concomitant therapies for UC should remain stable through Week 38 (except for oral corticosteroid tapering beginning at Week 6), and concomitant therapies for UC should not be initiated unless considered medically necessary by the investigator. Initiation of prohibited therapies will result in discontinuation of study intervention.

Endoscopy with central read is planned for screening/baseline, Week 12, and Week 38. Consenting participants will have an additional endoscopy at Week 4, which will also be assessed by a central reader. Efficacy, PK and PD parameters, biomarkers, and safety will be assessed according to the Schedule of Activities (SoA). A pharmacogenomic blood sample will be collected from participants who consent to this component of the protocol (where local regulations permit). Participation in pharmacogenomic research is optional.

An interim analysis is planned to inform future clinical development. Database locks (DBLs) are planned at Weeks 12 and 38, and a final DBL is planned after all participants complete the safety follow-up visit.

An independent Data Monitoring Committee (DMC) will be commissioned for this study.

NUMBER OF PARTICIPANTS

A target of 210 participants will be enrolled in this study with 70 participants planned per intervention group.

INTERVENTION GROUPS AND DURATION

This study will consist of 2 distinct phases: a 12-week combination comparison phase followed by a 26-week monotherapy phase. At Week 0, a target of 210 participants will be randomized in a 1:1:1 ratio to either combination therapy with guselkumab and golimumab, guselkumab monotherapy, or golimumab monotherapy, stratified by the concomitant use of corticosteroids at baseline (Y/N). Participants randomized to combination therapy will receive guselkumab monotherapy after Week 12. Participants randomized to a monotherapy group will continue on their originally randomized monotherapy after Week 12. The combination therapy arm will employ the same dose regimens of guselkumab and golimumab being used in the respective monotherapy intervention groups to facilitate scientific interpretation of the results. The following is a description of the 3 intervention groups:

- **Combination therapy**: guselkumab 200 mg IV and golimumab 200 mg subcutaneous (SC) at Week 0; golimumab 100 mg SC at Weeks 2, 6, and 10; guselkumab 200 mg IV at Weeks 4 and 8 followed by guselkumab 100 mg SC q8w
- **Guselkumab monotherapy**: guselkumab 200 mg IV at Weeks 0, 4, and 8 followed by guselkumab 100 mg SC q8w
- **Golimumab monotherapy**: golimumab 200 mg SC injection at Week 0, followed by golimumab 100 mg at Week 2 and then golimumab 100 mg every 4 weeks (q4w)

In addition, placebo administrations (IV or SC) will be given, as appropriate, to maintain the blind throughout the duration of the study.

Overall participant duration will be up to 58 weeks total (screening: up to 8 weeks; treatment duration: 38 weeks [12 weeks for the combination comparison phase; 26 weeks for the monotherapy phase]; safety follow-up: approximately 16 weeks after the last administration of study intervention at Week 34). The end of the study will be defined as when the last participant completes his or her final safety follow-up visit.

EFFICACY EVALUATIONS

Efficacy evaluations will include the following:

- Mayo score and Partial Mayo score
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS)
- Inflammatory PD markers including CRP and fecal calprotectin
- Patient-reported outcome measures to assess HRQOL outcomes and fatigue (ie, Inflammatory Bowel Disease Questionnaire [IBDQ], Patient-Reported Outcomes Measurement Information System [PROMIS]-29, and PROMIS Fatigue 7-item Short Form [7a])
- Exploratory patient-reported symptom measures including BSFS and PGIC of Severity of UC

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

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

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 and/or golimumab in the treatment of UC. Assessments will include the evaluation of relevant biomarkers in serum, stool, whole blood, and mucosal biopsy samples (RNA [ribonucleic acid], peripheral blood mononuclear cells (PBMCs), histology, and single cell isolation).

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic whole blood sample of approximately 5 mL will be collected (where local regulations permit) for genetic analyses as specified in the SoA. Only participants who sign the consent form to participate in the genetic assessment will have whole blood deoxyribonucleic acid (DNA) samples collected. Participation in the pharmacogenomic sub-study is optional.

SAFETY EVALUATIONS

Safety evaluations conducted at each study visit will include the assessment of adverse events (AEs, at the visit and those occurring between evaluation visits), a tuberculosis (TB) evaluation and other infection assessment, clinical laboratory blood tests (hematology and chemistry), vital signs, suicidality assessment, concomitant medication review, observations for injection-site reactions, AEs temporally associated with infusion, and/or hypersensitivity reactions.

STATISTICAL METHODS

Sample Size Determination

A sample size of 210 participants (70 per intervention group) was determined by the power to detect a significant difference in the proportion of participants in clinical response at Week 12 (primary endpoint) between the combination therapy and both monotherapies using a 1-sided chi-square test with 0.1 significance level for each comparison. The study is sized such that the combination therapy has approximately 80% power based on simulations to achieve both comparisons to monotherapy for the primary endpoint. The proportion of participants in clinical response at Week 12 is assumed to be 75% for the combination therapy, which is based on the additive effect from both monotherapies (20% improvement from each monotherapy relative to a historical placebo response of 35%).

Efficacy Analyses

All randomized participants who receive at least 1 dose of study intervention will be included in the efficacy analyses. Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment they received.

For testing of the primary endpoint, the efficacy of combination therapy versus each monotherapy will be compared. For both statistical comparisons of the primary endpoint, a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by concomitant use of corticosteroids at baseline (Y/N) will be used. The testing will be done simultaneously at the 1-sided 0.1 level of significance for each comparison. The study will be considered positive if the combination therapy group is significantly different from both monotherapy groups for the primary endpoint.

If both tests of the primary endpoint are positive, a CMH chi-square test (1-sided) stratified by concomitant use of corticosteroids at baseline (Y/N) will be used to compare the efficacy of the combination therapy to each monotherapy for the major secondary endpoint. The testing will be done simultaneously at the 1-sided 0.1 level of significance for each comparison.

Analyses for other efficacy endpoints will be performed with no adjustments made for multiple comparisons and nominal p-values will be provided.

Safety Analyses

Safety data, including but not limited to, AEs, serious adverse events (SAEs), infections, serious infections, and changes in laboratory assessments will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

Other Analyses

Pharmacokinetic Analyses

Serum guselkumab and golimumab concentrations over time will be summarized for each treatment group using descriptive statistics.

Population PK modeling may be conducted when appropriate. If these population PK analyses are conducted, the results of these analyses will be presented in a separate report.

Immunogenicity Analyses

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

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum concentrations of guselkumab and golimumab and the efficacy measures and/or relevant biomarker(s) may be explored graphically when appropriate. Additional analysis may be conducted if deemed necessary.

Biomarkers Analyses

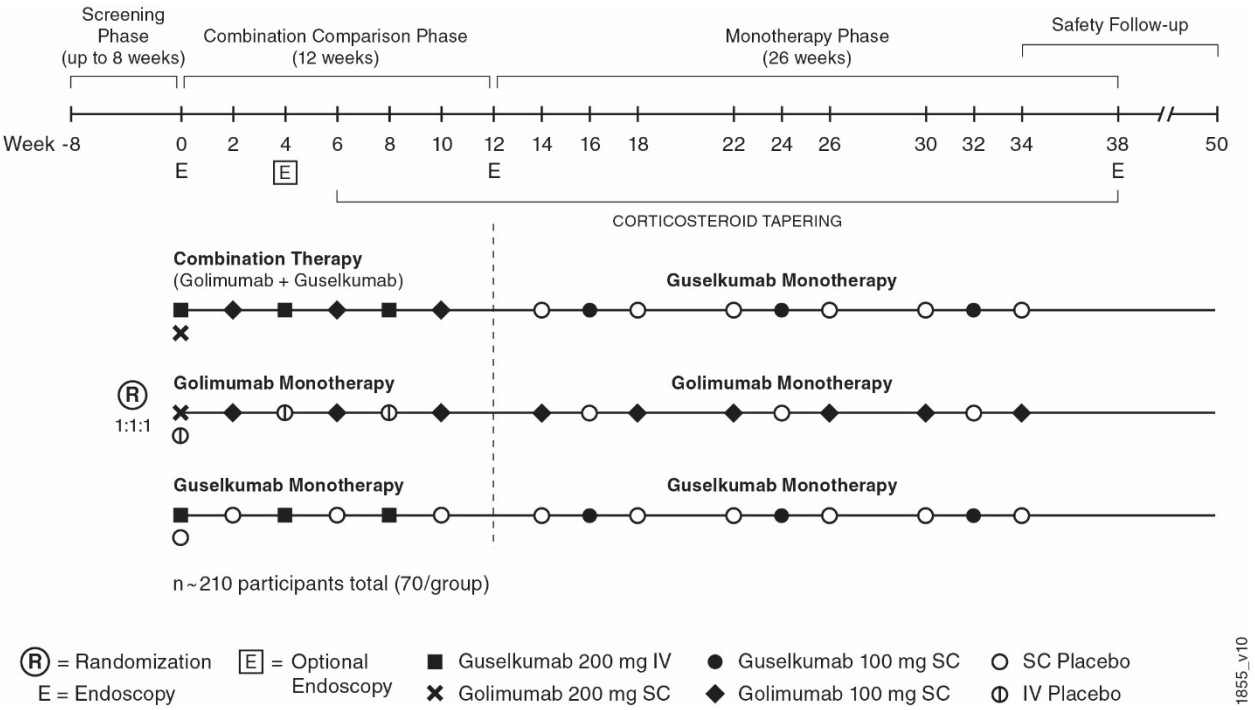
Changes in serum protein analytes, fecal biomarkers, and biopsy and whole blood RNA obtained over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and response to treatment will be explored. Biomarker analyses will be summarized in a separate technical report.

Pharmacogenomic Analyses

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

1.2. Schema

Figure 1: Schematic Overview of Study CNTO1959UCO2002



1.3. Schedule of Activities (SoA)

Table 1: SoA - Combination Comparison Phase (ie, through Week 12)

Phase	Screening	Treatment						
Week	Within 8 weeks	W0	W2	W4	W6[e]	W8	W10	W12[f]
Study Procedures[a,b,c,d]								
Screening/Administrative								
Informed consent (ICF)[g]	X							
ICF for optional pharmacogenomic sub-study[g]	X							
ICF for optional Week 4 endoscopy and biopsy sub-study[g]	X							
Review medical history requirements	X							
Inclusion/exclusion criteria[h]	X	X						
Demographics	X							
Prestudy therapy	X							
Preplanned surgery/procedure(s)	X							
QuantiFERON®-TB test[i]	X							
HBV and HCV testing	X							
HIV test	X							
Chest radiograph[j]	X							
Serum pregnancy test[k]	X							
Stool for enteric pathogens[l]	X							
Training on Mayo diary and BSFS diary completion[m]	X	X						
Study Intervention Administration								
Randomization		X						
Administer study intervention		X[z]	X	X	X	X	X	
Efficacy Evaluations								
Endoscopy[n]	X[o]			(X)[p]				X
Mayo score		X						X
Partial Mayo score	X		X	X	X	X	X	
BSFS		X	X	X	X	X	X	X
Patient-Reported Outcomes (PROs)[b]								
IBDQ		X			X			X
PROMIS-29		X			X			X

Table 1: SoA - Combination Comparison Phase (ie, through Week 12)								
Phase	**Screening**	**Treatment**						
Week	Within 8 weeks	W0	W2	W4	W6[e]	W8	W10	W12[f]
Study Procedures[a,b,c,d]								
PROMIS Fatigue Short Form 7a		X			X			X
PGIC					X			X
Safety Evaluations								
Physical examination	X							X
12-lead ECG	X							
TB evaluation[i]/Other infection assessment[q]	X	X	X	X	X	X	X	X
Vital signs[r]	X	X	X	X	X	X	X	X
Weight	X	X						X
Height	X							
Urine pregnancy test[k]		X	X	X	X	X	X	X
Concomitant therapy review	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
UC-related emergency department visits, hospitalizations, and surgeries		X	X	X	X	X	X	X
Injection-site evaluation[bb]		X	X		X		X	X
C-SSRS[s]	X	X	X	X	X	X	X	X
Clinical Laboratory Tests								
Hematology and chemistry[aa]	X	X	X	X	X	X	X	X
CRP		X	X	X	X	X	X	X
Fecal calprotectin		X	X	X		X		X
Pharmacokinetics/Immunogenicity[t]								
Serum guselkumab/golimumab concentration		X	X	X	X	X	X	X
Antibodies to guselkumab/golimumab		X	X	X		X		X
Pharmacodynamics and Biomarkers								
Biopsy (RNA, histology, single cell isolation)[u]	X[v]			(X)[p]				X
Serum biomarkers[w]	X		X	X				X
Whole blood (RNA)[w]	X		X	X				X
Whole blood (PBMC)[w,cc]	X			(X)[p]				X
Fecal biomarkers[x]		X	X	X				X
Pharmacogenomics								
Whole blood (DNA)[y]		X						

BSFS=Bristol Stool Form Scale; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; DNA=deoxyribonucleic acid; ECG=electrocardiogram; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IBDQ=Inflammatory

Table 1: SoA - Combination Comparison Phase (ie, through Week 12)

Phase	Screening	Treatment						
Week	Within 8 weeks	W0	W2	W4	W6[e]	W8	W10	W12[f]
Study Procedures[a,b,c,d]								

Bowel Disease Questionnaire; IV=intravenous; PBMC= peripheral blood mononuclear cell; PK=pharmacokinetic; PGIC=Patient's Global Impression of Change (of Severity of UC); PRO=patient-reported outcome; PROMIS=Patient-Reported Outcomes Measurement Information System; RNA=ribonucleic acid; SC=subcutaneous; TB=tuberculosis; UC=ulcerative colitis; W=Week.

a. Screening should occur within 8 weeks before the W0 visit. Visit dates are based on the participant's original randomization date; visit windows are as follows: day of the scheduled visit ±4 days (ie, plus or minus 4 days).
b. All assessments are to be completed before study intervention administration, unless otherwise specified; PRO assessments should be completed first. At the screening visit, the C-SSRS should be completed as the first assessment after signing informed consent and before any other tests, procedures, or other consultations. When blood samples are to be collected for safety, PK, efficacy, and biomarkers evaluations at the same time point, the order of blood draws will be samples for CRP, hematology and chemistry, PK/immunogenicity, serum biomarkers, whole blood DNA (for those participating in the optional pharmacogenomic sub-study at Week 0), and whole blood RNA.
c. Participants who discontinue study intervention (but have not terminated study participation) before W12 visit should complete the W12 assessments at the time of discontinuation and a safety follow-up visit (see Table 2) approximately 16 weeks after their last study intervention administration.
d. Subjects who terminate their study participation before the W12 visit should complete the W12 assessments at the time of termination (which will serve as the early termination visit).
e. For participants who are receiving oral corticosteroids, the investigator must begin tapering the daily dose of corticosteroids at W6.
f. Participants randomized to combination therapy will receive guselkumab monotherapy after W12. Participants randomized to a monotherapy group will continue on their originally randomized monotherapy after W12.
g. Must be signed before first study-related activity.
h. The required source documentation to support meeting the enrollment criteria are noted in Appendix 6 [Section 10.6], Regulatory, Ethical, and Study Oversight Considerations. Check clinical status again before first dose of study intervention.
i. All participants will undergo QuantiFERON®-TB testing. If the QuantiFERON®-TB test is not approved/registered in the country in which this protocol is being conducted or the tuberculin skin test is mandated by local health authorities, a negative tuberculin skin test result (see Appendix 3 [Section 10.3]) is also required. In Ukraine, while the QuantiFERON®-TB test is not approved/registered, it is accepted, and a tuberculin skin test is not required.
j. Chest radiograph (posterior-anterior and lateral views, or per country regulations where applicable) must be obtained within 3 months before the W0 visit. Note: A chest CT scan is also acceptable in place of a chest radiograph.
k. Must be performed before any study intervention administration for female participants of childbearing potential.
l. Stool studies for enteric pathogens may be performed at either the central or local laboratory and must include a stool culture and *Clostridium difficile* toxin assay. These tests must be performed during screening or have been performed during the current episode of disease exacerbation (as long as the stool studies were performed within 4 months before the first administration of study intervention). Additional testing (eg, ova and parasites or *Escherichia coli* O157:H7

Table 1: SoA - Combination Comparison Phase (ie, through Week 12)									
Phase	**Screening**	**Treatment**							
Week	Within 8 weeks	W0	W2	W4	W6[e]	W8	W10	W12[f]
Study Procedures[a,b,c,d]									

assessments) may be performed at the investigator's clinical discretion.

m. Participants should be instructed to bring their diaries to each study visit for review.

n. Endoscopy findings will be assessed by the investigator (ie, local endoscopist) during the procedure and a video of the endoscopy must be submitted to the central reader.

o. The screening endoscopy must be performed within 2 weeks of the baseline (W0) visit. The interval from the endoscopy procedure to the availability of the Mayo endoscopy subscore is approximately 4 days; therefore, the screening endoscopy must be performed at least 4 days before the baseline (W0) visit. The Mayo endoscopy subscore obtained during the central review of the video endoscopy will be used to determine eligibility (ie, Mayo endoscopy subscore ≥2) and to calculate the baseline Mayo score. A full colonoscopy will replace a sigmoidoscopy if screening for polyps or dysplasia is required. At least 48 hours must elapse between a colonoscopy with polypectomy and the W0 visit.

p. Only those participants who consent to participate in the optional endoscopy and biopsy sub-study will undergo Week 4 endoscopy and mucosal biopsy collection and whole blood PBMC collection.

q. If TB is suspected at any time, a chest radiograph (or chest CT scan if obtained instead) and QuantiFERON®-TB test should be performed. In countries where the QuantiFERON®-TB test is not registered/approved or the tuberculin skin test is mandated by local health authorities, TB skin testing (see Appendix 3 [Section 10.3]) should also be performed. Note: In Ukraine, while the QuantiFERON®-TB test is not approved/registered, it is accepted and a tuberculin skin test is not required.

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

s. At the screening visit, the C-SSRS should be completed as the first assessment after signing informed consent and before any other tests, procedures, or other consultations. For subsequent visits, the C-SSRS should be completed after all PROs and before any other tests, procedures, or other consultations.

t. For all visits where study intervention will be administered, 1 blood sample should be collected prior to study intervention administration for evaluation of serum concentrations and/or antibodies to interventions. In addition, for IV infusion-related visits (ie, Weeks 0, 4, and 8), another blood draw should be taken approximately 60 minutes after completion of the infusion for serum concentration measurement. All reasonable attempts should be made to collect samples at the scheduled timepoints and record the actual dates and times of PK sample collections.

u. Mucosal biopsy samples will be collected from all participants during endoscopy for RNA expression analysis, histologic assessment, and single cell isolation.

v. The screening biopsy samples for histology, RNA analyses, and single cell isolation will be collected from all participants during the screening endoscopy performed within 2 weeks of the baseline (W0) visit.

w. Serum biomarkers and whole blood RNA and PBMCs will be collected from all participants to evaluate the molecular

Table 1: SoA - Combination Comparison Phase (ie, through Week 12)								
Phase	**Screening**	**Treatment**						
Week	Within 8 weeks	W0	W2	W4	W6[e]	W8	W10	W12[f]
Study Procedures[a,b,c,d]								

effects of each study intervention in UC.

x. Fecal biomarkers (including microbiome) and associated products will be collected from all participants to evaluate the association between microbial activities, study intervention, and/or UC.

y. Whole blood for genetic analyses will be collected (where local regulations permit) only from participants who sign a separate ICF to participate in the optional pharmacogenomic sub-study. The pharmacogenomic (DNA) sample should be collected at the specified time point; however, if necessary it may be collected later without constituting a protocol deviation.

z. For the baseline (W0) visit, the IV study intervention should be administered first. The SC study intervention should be administered approximately 30 minutes after the IV study intervention infusion is complete.

aa. Certain laboratory abnormalities require re-testing and potential discontinuation of study intervention (See Sections 8.2.5 and 7.1, respectively).

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

cc. Whole blood (PBMC) samples are to be collected ideally within ±2 days of the endoscopy visit.

Table 2: SoA- Monotherapy Phase (ie, after Week 12)

Phase	Treatment										Early Term[c,e]	Safety Follow-Up[d,e]
Week	W14	W16	W18	W22	W24	W26	W30	W32	W34	W38		
Study Procedure[a,b]												
Study Intervention Administration												
Administer study intervention	X	X	X	X	X	X	X	X	X			
Efficacy Evaluations												
Endoscopy[f]										X	X	
Mayo score										X	X	
Partial Mayo score	X	X	X	X	X	X	X	X	X			
Patient-Reported Outcomes (PROs)[b]												
IBDQ					X					X	X	
PROMIS-29					X					X	X	
PROMIS Fatigue Short Form 7a					X					X	X	
PGIC					X					X	X	
Safety Evaluations												
Physical examination										X	X	X
TB evaluation[g]/Other infection assessment	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X
Weight										X	X	X
Urine pregnancy test[i]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
UC-related emergency department visits, hospitalizations, and surgeries	X	X	X	X	X	X	X	X	X	X	X	X
Injection-site evaluation[p]	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[j]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests												
Hematology and chemistry[o]	X	X	X	X	X	X	X	X	X	X	X	
CRP		X			X			X		X	X	
Fecal calprotectin					X					X	X	
Pharmacokinetics/Immunogenicity[k]												
Serum guselkumab/golimumab concentration	X	X			X			X	X	X	X	X

Table 2: SoA- Monotherapy Phase (ie, after Week 12)

Phase	Treatment										Early Term[c,e]	Safety Follow-Up[d,e]
Week	W14	W16	W18	W22	W24	W26	W30	W32	W34	W38		
Study Procedure[a,b]												
Antibodies to guselkumab/golimumab		X			X			X		X	X	X
Pharmacodynamics and Biomarkers												
Biopsy (RNA, histology, single cell isolation)[l]										X	X	
Serum biomarkers[m]										X	X	
Whole blood (RNA)[m]										X	X	
Whole blood (PBMC)[m,q]										X	X	
Fecal biomarkers[n]										X	X	

CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; Early Term=early termination visit; IBDQ=Inflammatory Bowel Disease Questionnaire; PBMC= peripheral blood mononuclear cell; PK=pharmacokinetic; PGIC=Patient's Global Impression of Change (of Severity of UC); PRO=patient-reported outcome; PROMIS=Patient-Reported Outcomes Measurement Information System; RNA=ribonucleic acid; TB=tuberculosis; UC=ulcerative colitis; W=Week.

a. Visit dates are based on the participant's original randomization date; visit windows are as follows: day of the scheduled visit ±4 days (ie, plus or minus 4 days).
b. All assessments are to be completed before study intervention administration, unless otherwise specified; PRO assessments should be completed first. When blood samples are to be collected for safety, PK, efficacy, and biomarkers evaluations at the same time point, the order of blood draws will be samples for CRP, hematology and chemistry, PK/immunogenicity, serum biomarkers, and whole blood RNA.
c. Participants who discontinue study intervention or terminate study participation after Week 12 should undergo the procedures indicated for an Early Term visit.
d. Participants, including those who discontinue study intervention administration (but have not terminated study participation), will have a final safety follow-up visit approximately 16 weeks after the last administration of study intervention.
e. At their last study visit, each study participant will be invited to complete an Independent Ethics Committee/Institutional Review Board approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and provided anonymously to the sponsor.
f. Endoscopy findings will be assessed by the investigator (ie, local endoscopist) during the procedure and a video of the endoscopy must be submitted to the central reader.
g. If TB is suspected at any time, a chest radiograph (or chest CT scan if obtained instead) and QuantiFERON®-TB test should be performed. In countries where the QuantiFERON®-TB test is not registered/approved or the tuberculin skin test is mandated by local health authorities, TB skin testing (see Appendix 3 [Section 10.3]) should also be performed. Note: In Ukraine, while the QuantiFERON®-TB test is not approved/registered, it is accepted and a tuberculin skin test is not required.
h. Temperature, pulse/heart rate, respiratory rate, and blood pressure. At a study intervention administration visit, vital sign measurements should be obtained before and approximately 30 minutes after study intervention administration or if the participant reports any symptoms.
i. Must be performed before any study intervention administration for female participants of childbearing potential.
j. The C-SSRS should be completed after all PROs and before any other tests, procedures, or other consultations to prevent influencing participant perceptions.
k. Samples should be collected before any study intervention administration. All reasonable attempts should be made to collect samples at the scheduled timepoints and record the actual dates and times of PK sample collections.

Table 2: SoA- Monotherapy Phase (ie, after Week 12)

Phase	Treatment										Early Term[c,e]	Safety Follow-Up[d,e]
Week	W14	W16	W18	W22	W24	W26	W30	W32	W34	W38		
Study Procedure[a,b]												

l. Mucosal biopsy samples will be collected from all participants during endoscopy for RNA expression analysis, histologic assessment, and single cell isolation.
m. Serum biomarkers and whole blood RNA and PBMCs will be collected from all participants to evaluate the molecular effects of each study intervention in UC.
n. Fecal biomarkers (including microbiome) and associated products analysis will be collected from all participants to evaluate the association between microbial activities, study intervention, and/or UC.
o. Certain laboratory abnormalities require re-testing and potential discontinuation of study intervention (See Sections 8.2.5 and 7.1, respectively).
p. An injection-site reaction is any adverse reaction at any SC study intervention injection site. Injection sites will be evaluated for reactions and any injection-site reaction should be recorded as an adverse event.
q. Whole blood (PBMC) samples are to be collected ideally within ±2 days of the endoscopy visit.

2. INTRODUCTION

Guselkumab (CNTO 1959 or TREMFYA®) is a fully human immunoglobulin G (IgG)1 lambda monoclonal antibody (mAb) that binds to the p19 subunit of human interleukin (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-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all *in vitro* assays examined.

Guselkumab is currently approved in the United States (US), European Union (EU), Canada, and several other countries for the treatment of moderate to severe plaque psoriasis. Clinical programs in non-plaque form psoriasis (generalized pustular psoriasis [GPP], erythrodermic psoriasis [EP], and palmoplantar pustulosis [PPP]) are being conducted in Japan only and Japan recently approved guselkumab for the treatment of patients with psoriasis, GPP, EP, and psoriatic arthritis (PsA). In addition, guselkumab is also being evaluated in PsA and Crohn's disease globally.

Golimumab (CNTO 148 or SIMPONI®) is a fully human anti-tumor necrosis factor alpha (TNFα) mAb that binds to TNFα with high affinity. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα. The overall anti-TNFα activity results in limited production or activity of inflammatory cytokines, thereby providing therapeutic benefit in various chronic inflammatory disorders, including ulcerative colitis (UC).

Golimumab has demonstrated an acceptable benefit/risk profile and is approved for treatment of moderately to severely active UC in over 90 countries worldwide. Additionally, golimumab is approved for 1 or more of the following indications around the world: rheumatoid arthritis (RA), PsA, ankylosing spondylitis (AS), nonradiographic axial spondyloarthritis (nr-Axial SpA), and polyarticular juvenile idiopathic arthritis (pJIA).

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

Note: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document. The term "study intervention" is used throughout this document in place of "study agent" or "study drug."

2.1. Study Rationale

Ulcerative colitis is an inflammatory disorder which involves the surface mucosa, the crypt epithelium, and submucosa of the colon.[57] Clinically, patients with UC suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, fever, and may also display prominent extraintestinal manifestations, commonly colitic arthritis, and AS.[57] The goals of UC treatment in general are the induction and maintenance of remission of symptoms to provide an improved quality of life, reduction in need for long-term corticosteroids, and minimization of cancer risk.[24] Biologic agents, most notably the anti-TNFα class, have revolutionized the clinical management

of inflammatory bowel disease (IBD [UC and Crohn's disease]), yet many patients either fail to respond or lose their initial response to treatment highlighting the significant unmet medical need for more effective therapies.[10,24,35] Biologic therapies used as monotherapies have short-term remission rates of <20%.[10,24,35] A therapeutic approach of targeting multiple pathogenic pathways may be required to achieve higher rates of clinical remission. Emerging evidence suggests that targeting both TNFα and IL-23 pathways may result in greater clinical efficacy (Section 2.1.2). Given the well-established scientific and clinical rationale for each monotherapy in IBD, the unmet medical need for more efficacious therapies in UC specifically, and the expected clinical benefit of combination therapy, this Phase 2a proof-of-concept (POC) clinical study will evaluate the efficacy and safety of short-term (ie, approximately 12 weeks) combination therapy with guselkumab and golimumab compared to either guselkumab or golimumab alone in the treatment of patients with moderately to severely active UC.

2.1.1. Rationale for Use of Guselkumab in Ulcerative Colitis

2.1.1.1. Nonclinical Evidence Implicating IL-23 as a Target in Ulcerative Colitis

The involvement of the IL-12/23 pathway in the pathogenesis of IBD is well established. Genome-wide association studies have implicated several genetic loci in the IL-12/23 pathway that are associated with susceptibility to UC and Crohn's disease, including the IL-23 receptor, the IL-12B subunit, Janus kinase (JAK) 2, and signal transducer and activator of transcription 3 genes.[4,9,12,28] Early nonclinical studies showed that treatment with an anti-IL-12/23p40 mAb abrogated or prevented disease in murine models of intestinal inflammation.[29,34] Subsequent studies dissecting the roles of IL-12p35, IL-12/23p40, and IL-23p19 demonstrated a key role for IL-23 in mediating local intestinal inflammation relative to systemic inflammation driven by IL-12.[18,65] The role of IL-23 in driving intestinal inflammation has been further evaluated in several murine colitis models. Mice treated with anti-IL-23p19 antibodies exhibit attenuated inflammation[31] and mice with a genetic deletion of the p19 subunit of IL-23 are protected in several models of intestinal inflammation.[26,69] These data suggest that the efficacy obtained with IL-12/23p40 blockade may be through the inhibition of IL-23 and provide a strong rationale for inhibiting only IL-23 in IBD.

2.1.1.2. Clinical Evidence Establishing Proof-of-Concept for IL-23 Targeted Therapy in Ulcerative Colitis

Clinical POC has been established for anti-IL-23 mAbs in both Crohn's disease and UC.[14,15,46,47,49] In a recently reported Phase 2 study, mirikizumab (anti-IL-23 mAb) demonstrated efficacy in the induction treatment for patients with moderately to severely active UC, as assessed by multiple measures including clinical response.[46] Overall AE frequencies were similar for mirikizumab and placebo-treated patients. There are several ongoing and planned studies in UC with anti-IL-12/23 and anti-IL-23 specific mAbs, including:

- ustekinumab (Phase 3, ClinicalTrials.gov Identifier: NCT02407236)
- mirikizumab (Phase 3, ClinicalTrials.gov Identifier: NCT03518086 and NCT03524092; Phase 2, ClinicalTrials.gov Identifier: NCT02589665)
- risankizumab (Phase 3, ClinicalTrials.gov Identifier: NCT03398148 and NCT03398135)

The therapeutic role of anti-IL-23 in Crohn's disease was first established by clinical studies of IL-12/23p40 antagonists (briakinumab[39] and ustekinumab[15]). Ustekinumab, an IL-12/23p40 antagonist, is approved for the treatment of moderate to severe Crohn's disease (STELARA United States Prescribing Information [USPI][56], Summary of Product Characteristics [SmPC][55]). While these programs demonstrated that blockade of both IL-12 and IL-23 is effective in treating Crohn's disease, they could not determine the relative contributions specific to the blockade of each of the 2 cytokines. Two other anti-IL-23 mAbs, risankizumab (BI 655066)[13,14,16] and brazikumab (MEDI2070, AMG-139)[49,50] have reported Phase 2 results demonstrating the efficacy of IL-23 blockade in subjects with moderate to severe Crohn's disease. Further, Phase 3 Crohn's disease programs are underway for risankizumab (ClinicalTrials.gov Identifier: NCT03105128) and guselkumab (Phase 2b/3, ClinicalTrials.gov Identifier: NCT03466411).

Given the similarities in the biology and treatment of Crohn's disease and UC, as well as the efficacy and safety of anti-IL-23 treatment demonstrated to date in both Crohn's disease and UC, there is strong rationale for the clinical development of guselkumab in UC.

2.1.2. Rationale for Combined Use of Guselkumab and Golimumab in Ulcerative Colitis

The purpose of this combination Phase 2a POC study is to provide critical data that will inform potential future studies for combination use of an anti-IL-23 intervention and an anti-TNFα intervention in UC.

As described in Section 2.1, there remains a high unmet need in the IBD patient population with many patients failing to achieve clinical response or clinical remission with current treatments. Addressing this unmet need may require targeting multiple pathogenic mechanisms through combination therapies. Combination therapy is already well accepted in the clinical management of IBD; studies show that patients treated with a combination of infliximab and azathioprine (AZA) are more likely to achieve corticosteroid-free remission than those treated with either monotherapy alone.[7,38] More recently, sponsors and independent investigators have initiated studies in IBD evaluating combinations of anti-TNFα agents with other biologic agents for periods up to 12 months.[6,25,58] Specifically, there is an ongoing open-label study to evaluate the efficacy and safety of combination therapy with vedolizumab, adalimumab, and methotrexate (MTX) for 26 weeks in subjects with Crohn's disease (ClinicalTrials.gov Identifier: NCT02764762).[58] There are also case series describing treatment successes of combination therapy with vedolizumab plus ustekinumab or various anti-TNFα agents in patients with UC and Crohn's disease for periods up to 12 months.[6,19,25]

Collectively, human genetics, nonclinical animal models and clinical data in IBD patients have validated the involvement of both TNFα and IL-23 signaling pathways in IBD pathogenesis and the role of monotherapies targeting these proteins in the treatment of IBD. However, as observed with anti-TNFα therapies, it is anticipated that a population of patients may not fully respond to anti-IL-23 therapy alone. In addition to addressing patients not fully responsive to monotherapy, there may be benefit to treating the patient population as a whole upfront with 2 agents versus monotherapy alone. Accordingly, this study will evaluate the effect of short-term treatment with both agents (ie, approximately 12 weeks), in a manner similar to ongoing evaluations in IBD.[58]

In support of this combination therapy approach, the sponsor has generated positive efficacy data from anti-TNFα/anti-IL-23 combination treatment in a nonclinical colitis model and evaluated the molecular impact of monotherapy versus combination therapy on the human disease using a network genomics approach (Section 2.2.1).

2.2. Background

2.2.1. Nonclinical Development

Full nonclinical development programs were conducted with guselkumab and golimumab in support of global submissions and approvals for both products. These included general toxicology and toxicokinetic (TK) 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 the guselkumab and golimumab nonclinical data is presented in the guselkumab IB and the golimumab IB, respectively.

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

2.2.1.1. Guselkumab

Pharmacology

Primary pharmacodynamic (PD) studies determined guselkumab target binding interactions, epitope mapping, *in vitro* mechanism of action, functional effects of neutralization, species cross-reactivity, and *in vivo* neutralization of human IL-23 in mice. Guselkumab was shown to bind and neutralize IL-23, and to be pharmacologically active in guinea pigs and the non-human primate. Guselkumab does not bind to or neutralize IL-23 in the rat or mouse. The cynomolgus monkey was selected to be the pharmacologically relevant toxicology species for guselkumab, and the guinea pig was selected as the species to assess fertility.

In accordance with the provisions of the International Conference on Harmonisation (ICH) S7A guidance document[22], safety pharmacology evaluations (cardiovascular [CV], respiratory, central nervous system) were incorporated into the design of the Good Laboratory Practice (GLP) repeat-dose toxicity study in cynomolgus monkeys. Additionally, a CV safety pharmacology study was conducted in cynomolgus monkeys.

Pharmacokinetics

The pharmacokinetic (PK) profile of guselkumab has been characterized in cynomolgus monkeys in (1) single-dose studies in which monkeys received a single intravenous (IV) and subcutaneous (SC) administration; (2) a 5-week/24-week study in which monkeys received repeated weekly IV and/or SC doses of guselkumab (followed by a 3-month recovery); and (3) an enhanced prenatal and postnatal developmental (ePPND) study in which pregnant females were administered repeated weekly SC doses of guselkumab. The PK profile was also characterized in guinea pigs that received repeated SC doses of guselkumab twice a week. The results showed that guselkumab behaves as a typical IgG-based therapeutic mAb. The TK results from all toxicology studies conducted in guinea pigs and monkeys demonstrated adequate and sustained drug exposure in the circulation to support the safety evaluation in animal species. In addition, the TK results also demonstrated cross-placenta distribution of circulating guselkumab to the fetus and no measurable excretion of guselkumab into milk. Only a small percentage (2.2%) of monkeys (2 of 90) were positive for anti-guselkumab antibodies and exhibited accelerated total systemic clearance of drug after IV administration or apparent total systemic clearance of drug after extravascular administration, and/or accelerated decrease in serum guselkumab concentrations. One of 24 (4.2%) infants from guselkumab-treated females in the ePPND study was also found to be positive for anti-guselkumab antibodies.

Toxicology

The guselkumab toxicology program evaluated the potential for sub-chronic and chronic toxicity, reproductive and developmental toxicity, tissue cross-reactivity (TCR), serum compatibility, and hemolytic potential using the cynomolgus monkey and guinea pig, the only pharmacologically relevant species. During the conduct of the initial non-GLP and GLP TCR assays, cytoplasmic binding of guselkumab to skeletal and cardiac myocytes was observed in both cynomolgus monkey and human tissues. As a result of the unusual binding, a CV safety pharmacology study with guselkumab was conducted in cynomolgus monkeys to evaluate any potential adverse effects of guselkumab on cardiac function. In the cynomolgus monkey, potential for toxicity was assessed in a GLP repeat-dose (5-week/24-week plus 3-month drug-free period) study conducted in 2 separate phases in different sets of animals. Developmental toxicity was evaluated in an ePPND toxicity study in cynomolgus monkeys. Effects of guselkumab on fertility and early embryonic development were evaluated in guinea pigs initially in non-GLP male and female fertility studies, and then in GLP male and female fertility studies. No adverse effects of guselkumab were observed in nonclinical toxicology studies. The guselkumab CV safety pharmacology and sub-chronic and chronic toxicity studies demonstrated that the No Observed Adverse Effect Level (NOAEL) for guselkumab in cynomolgus monkeys was at least 50 mg/kg/week. In the ePPND study, the NOAEL for both maternal and developmental outcomes in cynomolgus monkeys was also 50 mg/kg/week. In guinea pig fertility studies, the NOAEL was 100 mg/kg (administered twice-weekly). In all cases, doses were the highest administered in the respective test systems.

2.2.1.2. Golimumab

Pharmacology

In accordance with the provisions of the ICH S7A guidance document[22], safety pharmacology evaluations (CV, respiratory, central nervous system) were incorporated into the design of the GLP repeat-dose toxicity study in cynomolgus monkeys. No adverse effects were observed following single or repeated IV or SC dosing up to 50 mg/kg twice-weekly or in 6-month old cynomolgus monkey infants exposed to golimumab during a GLP pre- and postnatal development study.

Pharmacokinetics

The cynomolgus monkey was chosen as it was the only pharmacologically relevant species for golimumab PK and toxicology studies.

The PK profile of golimumab displayed dose-proportional PK with respect to maximum observed concentration and area under the serum concentration versus time curve. Following SC administration, maximum observed concentration was observed 1 to 3 days after administration with an absolute bioavailability of 77% or higher. Terminal elimination half-life ($t_{1/2}$) was similar following IV and SC administration and ranged from 0.39 to 8.84 days. As with other IgG1s, golimumab can be transported through the placental barrier and expose the fetus when golimumab is administered to pregnant cynomolgus monkeys. An embryo-fetal development study in cynomolgus monkeys demonstrated a substantial exposure to golimumab in both maternal and fetal circulation in response to twice-weekly SC administration of golimumab at doses of 25 mg/kg or 50 mg/kg. By the end of the second trimester (gestation day 100) the maternal serum concentration ranged from 1 to 99 times that of fetal serum concentration. Development of antibodies to golimumab was frequently observed in monkeys, especially following limited dosing at ≤10 mg/kg. Animals with shorter serum $t_{1/2}$ of golimumab produced antibodies to golimumab earlier than animals with longer $t_{1/2}$ values. It was expected that antibody to golimumab induction was less likely in human subjects because golimumab is a human IgG and thus should be less immunogenic to humans than to monkeys.

Toxicology

Nonclinical IV and SC toxicology studies were conducted in cynomolgus monkeys up to 6 months in duration. In addition, an embryo-fetal development study evaluating the maternal and fetal effects following maternal treatment during the period of organogenesis, a prenatal and postnatal development study evaluating the maternal and neonatal effects following maternal treatment during the fetal and lactation periods, and a study in young cynomolgus monkeys to provide safety information to support use in pediatric subjects was conducted. Chronic toxicity and reproductive and developmental toxicity of an anti-mouse TNFα mAb (cV1q) were also assessed to provide additional supportive data for the development of anti TNFα mAb therapies. An *in vitro* human TCR study was also conducted. No signs of toxicity considered golimumab-related were observed in any of these studies, except in 1 animal treated with golimumab at the lowest dose of 25 mg/kg IV that developed a disseminated histoplasmosis infection. This finding may have been due to a reactivation of a latent infection and was not unexpected based upon an

increased incidence of opportunistic infections (including histoplasmosis) in patients treated with anti-TNFα agents.

2.2.1.3. Combination of Guselkumab and Golimumab

While the sponsor has not performed combination toxicology studies, anti-TNFα and anti-IL-23 antibodies have been administered concomitantly to mice in a nonclinical model of colitis to evaluate the efficacy and molecular impact of the combination therapy on intestinal inflammation. Multiple dose combinations of anti-TNFα and anti-IL-23 antibodies have been tested in the agonist anti-CD40 murine model of innate colitis. In this acute model of intestinal inflammation mice received a single dose of antibodies (day -1) and were sacrificed 7 days after the induction of inflammation (day 0). Mice were weighed daily to monitor disease-associated wasting and colon tissue collected to assess intestinal inflammation. In the highest dose combination of 500 µg anti-TNFα and 500 µg anti-IL-23, no animals died and all animals showed improvement in weight and histological inflammation scores compared to diseased control-treated (phosphate buffered saline or isotype injected) animals.

In summary, combination of anti-TNFα and anti-IL-23 antibodies administered to mice in a nonclinical model of colitis showed improvement in weight and histological inflammation scores in the absence of any acute toxicity. Neither guselkumab nor golimumab presented any apparent overlapping toxicities detectable in nonclinical toxicology studies that could be expected to be potentiated when administered in combination, and the probability of PK or PD interaction in the combination is considered low.

2.2.2. Clinical Development

2.2.2.1. Current Status of Guselkumab Development

Guselkumab is a human mAb directed against the p19 subunit of IL-23 and thus specifically targets IL-23. A growing body of literature suggests that the IL-23 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases,[37,59] including psoriasis, PsA, and IBD. Susceptibility to psoriasis, PsA, and IBD has been shown to be associated with genetic polymorphisms in IL-23/IL-23 receptor components.[5,12,30,33,36]

The clinical development program for guselkumab includes studies in patients with psoriasis (including plaque psoriasis, GPP, EP, PPP), PsA, and RA. Clinical data from these studies indicate that guselkumab administered IV or SC was generally well tolerated. Additional information on these studies is provided in the guselkumab IB.

To date, guselkumab has been approved in the US, EU, Canada, and several other countries for the treatment of moderate to severe plaque psoriasis (TREMFYA USPI[63], SmPC[62]).

While this is the first clinical study conducted with guselkumab in UC to date, other anti-IL-23 mAbs have been studied in UC and Crohn's disease by other sponsors (Section 2.1.1.2), and the sponsor is also conducting a guselkumab Phase 2b/3 program in Crohn's disease (ClinicalTrials.gov Identifier: NCT03466411).

2.2.2.2. Current Status of Golimumab Development

Golimumab is a human anti-TNFα mAb and is being, or has been studied, in the treatment of the following clinical indications: RA, PsA, AS, nr-Axial SpA, sarcoidosis, uveitis, and asthma in adults; UC and type 1 diabetes in adults and children; and pJIA in children. Additional information on these studies is provided in the golimumab IB.

To date, golimumab is approved for the treatment of moderately to severely active UC in adult patients in over 90 countries worldwide. Golimumab is also approved for at least 1 of the following indications in adults: RA, PsA, AS, and nr-Axial SpA. In addition, golimumab is also approved for use in children with pJIA in over 30 countries including the EU.

The golimumab development program in adult UC consisted of 1 IV induction study (C0524T16)[42], 1 SC induction study (C0524T17)[44], and 1 SC maintenance study (C0524T18)[45]. C0524T16 and C0524T17 were both 6-week induction studies with identical study designs; the primary differences were the dose regimens and routes of administration. More information on these studies can be found in the golimumab IB.

2.3. Benefit/Risk Assessment

Given the well-established scientific and clinical rationale for each monotherapy in IBD (Section 2.1), the high unmet medical need in UC, and the expected clinical benefit of combination therapy, this Phase 2a POC clinical study will evaluate the efficacy and safety of short-term combination therapy with guselkumab and golimumab compared to guselkumab or golimumab alone in the treatment of patients with moderately to severely active UC. Importantly, all participants will have the benefit of receiving active treatment in this study as there is no placebo treatment arm. Although guselkumab is an experimental treatment in IBD, clinical POC has been established for anti-IL-23 mAbs in both UC and Crohn's disease.[14,15,46,47,49] In a recently reported Phase 2 study, mirikizumab (anti-IL-23 mAb) demonstrated efficacy in the induction treatment for patients with moderately to severely active UC, as assessed by multiple measures including clinical response.[46] Overall AE frequencies were similar for mirikizumab and placebo-treated patients.

The safety profiles of guselkumab and golimumab are well characterized due to large clinical programs leading to their respective approvals (guselkumab – psoriasis and golimumab – RA, PsA, AS, nr-Axial SpA, and UC). Based on the available data and the safety measures in this protocol, the overall benefit/risk assessment for using the selected dose regimens for combination therapy, guselkumab, and golimumab in this study is deemed acceptable based on the below considerations.

For guselkumab, the main risk, as described in Section 5 of the guselkumab IB, is infection. Other potential safety concerns, also described in greater detail in the guselkumab IB, are based on guselkumab being an immunomodulatory mAb and include malignancy and hypersensitivity. The approved dose regimen of guselkumab in psoriasis (100 mg SC at Week 0 and Week 4, and then every 8 weeks [q8w]) has been demonstrated to have a favorable safety profile, and dose regimens as high as 200 mg SC q8w have been shown to have favorable safety in a 6-month

Phase 2 trial in RA.[53] A higher guselkumab dose regimen was selected for this study compared to what is approved for psoriasis over the induction period (Week 0 to Week 12), because historically, doses during the induction period (up to 12 weeks) in IBD have been higher than those used in psoriasis for mAbs approved for both indications to achieve the desired efficacy in IBD (STELARA USPI[56], SmPC[55]; HUMIRA USPI[21], SmPC[20]). The proposed guselkumab dose for this protocol is the lowest of the 3 induction doses being evaluated in the ongoing guselkumab Phase2b/3 program in Crohn's disease (200 mg, 600 mg, 1200 mg IV). Additional details about the dose selection rationale for guselkumab are provided in Section 4.3.1.

The anti-TNF class of agents has been extensively studied and has a well-defined safety profile. Known risks for anti-TNF agents such as golimumab include infections, including serious infections, tuberculosis (TB), and opportunistic infections. Other known risks include, but are not limited to, lymphoma, leukemia, lupus-like syndrome, and demyelinating disorders (SIMPONI USPI[52], SmPC[51]). The dose regimen of golimumab in this protocol is consistent with the currently approved dose, and is consistent with the dose regimens evaluated in the golimumab Phase 3 clinical development program in UC that established the efficacy and safety of golimumab in patients with moderately to severely active UC.

Given the risk of serious infections associated with the anti-TNF class and combination biologic use, the eligibility criteria and screening assessments of this study are designed to exclude subjects with chronic/active infections or a predisposition to infections. Measures to ensure the early detection of TB, such as chest radiograph and QuantiFERON®-TB test, are outlined in Section 8.2.12 and participants with a history of latent or active TB are excluded from this study. Subjects older than 65 years of age are excluded from the study due to immunosenescence, which is defined as the state of dysregulated immune function that contributes to an increased susceptibility of the elderly to infection.[8,41] In contrast to the reported longer duration RA combination biologics studies (ie, up to 1 year),[17,67,68] the combination comparison phase of this study in UC is of relatively short duration (ie, approximately 12 weeks), meaning that participants randomized to the combination therapy intervention group will only receive 3 doses of guselkumab and 4 doses of golimumab that overlap. To reduce the risks associated with immunosuppression, immunomodulators (6-MP, AZA, and MTX) must be discontinued for at least 2 weeks before the first administration of study intervention. Additionally, participants taking more than 20 mg of prednisone or equivalent are excluded from the study, and there will be mandatory oral corticosteroid tapering beginning at Week 6. Participants will be closely monitored for signs and symptoms of infection during and after treatment. During the combination comparison phase, clinic visits are scheduled biweekly. Furthermore, safety will be monitored in the first 25 participants, randomized to any intervention group and treated on an ongoing basis, for any potential safety concerns that would result in a pause in dosing by an independent Data Monitoring Committee (DMC). Details about the evaluation of this initial cohort and subsequent DMC reviews are outlined in Section 9.5.1. Safety evaluations will include AEs, clinical laboratory tests (hematology and chemistry), vital signs and physical examinations, a screening electrocardiogram (ECG), hypersensitivity reactions, AEs temporally associated with infusion, injection-site reactions, and early detection of active TB. The safety follow-up period for this study is 16 weeks after the last dose of study intervention.

Based on the prospect of clinical efficacy with the study interventions being evaluated, the well characterized safety profiles of guselkumab and golimumab, and the safety measures in place, the overall benefit/risk of participation in this clinical study is deemed acceptable.

3. OBJECTIVES AND ENDPOINTS

This study will consist of 2 distinct phases: a 12-week combination comparison phase followed by a 26-week monotherapy phase.

3.1. Objectives

3.1.1. Primary Objectives

Combination Comparison Phase

- To evaluate the clinical efficacy of combination therapy with guselkumab and golimumab in participants with moderately to severely active UC.
- To evaluate the safety of combination therapy with guselkumab and golimumab in participants with moderately to severely active UC.

3.1.2. Secondary Objectives

Combination Comparison Phase

- To evaluate the effect of combination therapy with guselkumab and golimumab on endoscopic improvement.
- To evaluate the impact of combination therapy with guselkumab and golimumab on disease-specific health-related quality of life (HRQOL), including fatigue.
- To evaluate the efficacy of combination therapy with guselkumab and golimumab by negative response signature status at baseline.
- To evaluate the PK, immunogenicity, and PD of combination therapy with guselkumab and golimumab, including changes in C-reactive protein (CRP), fecal calprotectin, and other PD biomarkers.

Monotherapy Phase

- To evaluate the clinical efficacy of combination therapy followed by guselkumab monotherapy.
- To evaluate the safety of combination therapy followed by guselkumab monotherapy.
- To evaluate the effect of combination therapy followed by guselkumab monotherapy on endoscopic improvement.
- To evaluate the impact of combination therapy followed by guselkumab monotherapy on disease-specific HRQOL, including fatigue.

- To evaluate the efficacy of combination therapy followed by guselkumab monotherapy by negative response signature status at baseline.
- To evaluate the PK, immunogenicity, and PD of combination therapy followed by guselkumab monotherapy, including changes in CRP, fecal calprotectin, and other PD biomarkers.

3.1.3. Exploratory Objectives

- To explore the effect of combination therapy on patient-reported outcome (PRO) instruments (eg, Bristol Stool Form Scale [BSFS] and Patient's Global Impression of Change [PGIC] of Severity of UC).

3.2. Endpoints

3.2.1. Primary Endpoint

- Clinical response at Week 12, defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points with either a decrease in rectal bleeding subscore (RBS) ≥1 or a RBS of 0 or 1.

3.2.2. Major Secondary Endpoint

- Clinical remission at Week 12, defined as a Mayo score ≤ 2 with no individual subscore >1.

Note: Other remission definitions may be considered and will be fully described in the Statistical Analysis Plan (SAP).

3.2.3. Other Efficacy Endpoints

Combination Comparison Phase (ie, through Week 12)

- Endoscopic healing at Week 12 (Mayo endoscopic subscore of 0 or 1).
- Normalization of endoscopic appearance of the mucosa (Mayo endoscopic subscore of 0).
- Histologic healing at Week 12.
- Mucosal healing at Week 12 (Composite Mayo endoscopic healing and histologic healing).
- Change from baseline in the total score of the Inflammatory Bowel Disease Questionnaire (IBDQ) at Weeks 6 and 12.
- A >20-point improvement in the IBDQ score at Weeks 6 and 12.
- Change from baseline in the 7 domains and the abdominal pain numerical rating scale of Patient-Reported Outcomes Measurement Information System (PROMIS)-29 at Weeks 6 and 12.
- Fatigue response at Weeks 6 and 12 (based on the PROMIS Fatigue Short Form 7a; to be defined in the SAP).
- Clinical response, clinical remission, and endoscopic healing at Week 12 by negative response signature status at baseline.
- Change from baseline in the Mayo score at Week 12.

- Change from baseline in the partial Mayo score through Week 12.
- Change from baseline in CRP through Week 12.
- Change from baseline in fecal calprotectin concentration through Week 12.
- Normalization of CRP concentration at Week 12 among participants with abnormal CRP concentration at baseline.
- Normalization of fecal calprotectin concentration at Week 12 among participants with abnormal fecal calprotectin concentration at baseline.
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score at Weeks 0 and 12 by the level of Mayo endoscopy score at the corresponding visit.
- Change from baseline in the UCEIS score at Week 12.
- UCEIS score ≤4 at Week 12.
- UC-related emergency department visits, hospitalizations, and surgeries through Week 12.

Monotherapy Phase (ie, after Week 12)

- Clinical remission at Week 38.
- Clinical response at Week 38.
- Maintenance of clinical response at Week 38 among participants who achieved clinical response at Week 12.
- Endoscopic healing at Week 38.
- Normalization of endoscopic appearance of the mucosa at Week 38.
- Histologic healing at Week 38.
- Mucosal healing at Week 38.
- Clinical remission and not receiving concomitant corticosteroids at Week 38.
- Maintenance of clinical remission at Week 38 among participants who achieved clinical remission at Week 12.
- Change from baseline in the total score of the IBDQ at Weeks 24 and 38.
- A >20-point improvement in the IBDQ score at Weeks 24 and 38.
- Change from baseline in the 7 domains and the abdominal pain numerical rating scale of PROMIS-29 at Weeks 24 and 38.
- Fatigue response at Weeks 24 and 38.
- Clinical response, clinical remission, and endoscopic healing at Week 38 by negative response signature status at baseline.
- Change from baseline in the Mayo score at Week 38.
- Change from baseline in the partial Mayo score through Week 38.
- Change from baseline in CRP through Week 38.

- Change from baseline in fecal calprotectin concentration through Week 38.
- Normalization of CRP concentration at Week 38 among participants with abnormal CRP concentration at baseline.
- Normalization of fecal calprotectin concentration at Week 38 among participants with abnormal fecal calprotectin concentration at baseline.
- UCEIS score at Week 38 by the level of Mayo endoscopy score at Week 38.
- Change from baseline in the UCEIS score at Week 38.
- UCEIS score ≤4 at Week 38.
- UC-related emergency department visits, hospitalizations, and surgeries through Week 38.

3.2.4. Exploratory Endpoints

- BSFS score over time.
- The distribution of the PGIC of Severity of UC over time.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

3.3. Hypothesis

Combination therapy with guselkumab and golimumab will result in a rate of clinical response at Week 12 that is superior to both monotherapy arms.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, randomized, double-blind, active-controlled, parallel-group, multicenter, interventional POC clinical study designed to evaluate the efficacy and safety of combination therapy with guselkumab and golimumab in adults with moderately to severely active UC. The target population is men or women 18 to 65 years old with moderately to severely active UC, as defined by a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopy subscore ≥2 as obtained during the central review of the video endoscopy. Participants must be naïve to TNF antagonists and have failed or not tolerated conventional therapy with oral or IV corticosteroids or immunomodulators (6-mercaptopurine [6-MP] or AZA).

This study will consist of 2 distinct phases: a 12-week combination comparison phase followed by a 26-week monotherapy phase. At Week 0, a target of 210 participants will be randomized in a 1:1:1 ratio to either combination therapy with guselkumab and golimumab, guselkumab monotherapy, or golimumab monotherapy, stratified by the concomitant use of corticosteroids at baseline (Y/N). Participants randomized to combination therapy will receive guselkumab monotherapy after Week 12. Participants randomized to a monotherapy group will continue on their originally randomized monotherapy after Week 12. The combination therapy arm will employ the same dose regimens of guselkumab and golimumab being used in the respective monotherapy intervention groups to facilitate scientific interpretation of the results. The following is a description of the 3 intervention groups:

- **Combination therapy**: guselkumab 200 mg IV and golimumab 200 mg SC at Week 0; golimumab 100 mg SC at Weeks 2, 6, and 10; guselkumab 200 mg IV at Weeks 4 and 8 followed by guselkumab 100 mg SC q8w
- **Guselkumab monotherapy**: guselkumab 200 mg IV at Weeks 0, 4, and 8 followed by guselkumab 100 mg SC q8w
- **Golimumab monotherapy**: golimumab 200 mg SC injection at Week 0, followed by golimumab 100 mg at Week 2 and then golimumab 100 mg every 4 weeks (q4w)

In addition, placebo administrations (IV or SC) will be given, as appropriate, to maintain the blind throughout the duration of the study. Refer to Study Intervention (Section 6) for additional details.

Immunomodulators (6-MP, AZA, and MTX) must be discontinued for at least 2 weeks before the first dose of study intervention. For participants who are receiving oral corticosteroids at baseline, the investigator must begin tapering the daily dose of corticosteroids at Week 6. All participants will be evaluated for clinical worsening of UC throughout the study. The use of concomitant and prohibited therapies is described in Section 6.5. In general, doses of concomitant therapies for UC should remain stable through Week 38 (except for mandatory oral corticosteroid tapering beginning at Week 6), and concomitant therapies for UC should not be initiated unless considered medically necessary by the investigator. Initiation of prohibited therapies will result in discontinuation of study intervention.

Endoscopy with central read is planned for screening/baseline, Week 12, and Week 38. Consenting participants will have an additional endoscopy at Week 4, which will also be assessed by a central reader. Efficacy, PK and PD parameters, biomarkers, and safety will be assessed according to the Schedule of Activities (SoA) (Section 1.3). A pharmacogenomic blood sample will be collected from participants who consent to this component of the protocol (where local regulations permit). Participation in pharmacogenomic research is optional.

Overall participant duration will be up to 58 weeks total (screening: up to 8 weeks; treatment duration: 38 weeks [12 weeks for the combination comparison phase; 26 weeks for the monotherapy phase]; safety follow-up: approximately 16 weeks after the last administration of study intervention at Week 34). An interim analysis is planned to inform future clinical development (see details in Section 9.5). Database locks (DBLs) are planned at Weeks 12 and 38, and a final DBL is planned after all participants complete the safety follow-up visit. The end of the study will be defined as when the last participant completes his or her final safety follow-up visit.

An independent DMC will be commissioned for this study, refer to Section 9.5.1 for more details on the DMC.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

This type of parallel-group study design is consistent with the design of other combination therapy studies.[7,11,38,58] The combination therapy arm will employ the same dose regimens of guselkumab and golimumab that are being used in the respective monotherapy treatment arms which will allow the contribution of each monotherapy to the combination to be assessed relative to each monotherapy alone. The target population (ie, men or women 18 to 65 years old with moderately to severely active UC who are naïve to TNF antagonists and have failed or not tolerated conventional therapy) is considered appropriate given the study interventions being evaluated. For example, the inclusion of patients who previously failed TNF antagonists is not considered clinically appropriate for this study design since they could be randomized to the golimumab monotherapy treatment arm.

This study will consist of 2 distinct phases: a 12-week combination comparison phase followed by a 26-week monotherapy phase. The duration of the combination comparison phase (ie, approximately 12 weeks) is thought to provide sufficient time to evaluate the effect of combination therapy compared to monotherapy, while minimizing the potential risks associated with longer duration combination therapy. The 12-week duration of the combination comparison phase is important because if combination therapy merely shifted late responders to an earlier response, but did not increase the total fraction of responders, then combination therapy would provide limited benefit to patients with UC. Moreover, Week 12 efficacy endpoints are being used to evaluate other anti-IL-23 mAbs.[1,46] Participants randomized to a monotherapy group will continue in the monotherapy phase based on their original randomized treatment group, with participants in the combination therapy arm receiving guselkumab monotherapy after Week 12. The duration of 26 weeks for the monotherapy phase is thought to provide sufficient time to evaluate response in all 3 intervention groups.

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

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

4.2.2. DNA and Biomarker Collection

Biomarker samples will be collected to evaluate the cellular and molecular mechanism of action of guselkumab and golimumab, or help to explain interindividual variability in clinical outcomes, or may help to identify population subgroups that respond differently to either intervention. Serum, whole blood, and fecal samples will be collected from all participants to assess PD markers associated with the response to guselkumab and golimumab. Mucosal biopsies will also be obtained from all participants pre-treatment during screening and post-treatment at Weeks 12 and 38 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 guselkumab and

golimumab combination treatment or monotherapy with either agent in UC, and to aid in evaluating the intervention-clinical response relationship.

Two optional sub-studies are planned:

- **Optional Week 4 endoscopy and biopsy sub-study:** Only those participants who consent to participate in the optional sub-study will undergo Week 4 endoscopy assessment and biopsy collection. Exploratory analyses of intestinal mucosal tissue obtained by biopsy at Week 4 will be performed to delineate the mechanisms of action of guselkumab and/or golimumab by establishing a sequence of molecular and cellular effects beginning at an early time point. Whole blood (PBMCs) will also be collected. In addition, data collected at Week 4 will be explored for correlation with clinical efficacy observations at later time points.
- **Optional pharmacogenomic sub-study**: It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes, identify markers associated with disease susceptibility and prognosis, and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow for the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of guselkumab and/or golimumab and to identify genetic factors associated with UC or the response to guselkumab and/or golimumab treatment.

4.2.3. Patient-Reported Outcomes on Health-Related Quality of Life

Patient-reported outcome (PRO) evaluations (ie, IBDQ, PROMIS-29, PROMIS Fatigue 7-item Short Form, and PGIC of Severity of UC) will be used to assess the benefits of guselkumab and golimumab treatment on disease-specific and general HRQOL. Patient-reported outcomes will only be collected in countries where translations of the evaluations are available. See Section 8.1 for more details.

4.2.4. Medical Resource Utilization Collection

Medical resource utilization evaluations, including but not limited to UC-related emergency department visits, hospitalizations, and surgeries, will be collected for future evaluation of the health economics of guselkumab and golimumab treatment.

4.2.5. Study-Specific Ethical Design Considerations

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

The total blood volume to be collected from each participant in this study (maximum of approximately 350 mL over approximately 58 weeks) is far less than the American Red Cross standard limit for whole blood donation (approximately 475 mL q8w) and is, therefore, considered an acceptable amount of blood to be collected over this time. For more details regarding blood collection, see Blood Sample Collection in Section 8.

4.3. Justification for Dose

4.3.1. Guselkumab

The planned guselkumab dose is 200 mg IV at Weeks 0, 4, and 8 followed by 100 mg SC q8w. The approved psoriasis dose of guselkumab is 100 mg administered by SC injection at Week 0, Week 4, and q8w thereafter and dose regimens as high as 200 mg SC q8w have been shown to have favorable safety in a 6-month Phase 2 trial in RA. The sponsor selected a higher dose of guselkumab for this Phase 2a POC study in UC compared to what is approved for psoriasis over the induction period of Week 0 to Week 12 because, historically, doses in IBD have been higher than those in psoriasis for mAbs approved for both indications (STELARA USPI[56], SmPC[55]; HUMIRA USPI[21], SmPC[20]).

Regarding the safety of this higher IV guselkumab dose, single doses of guselkumab as high as 10 mg/kg, with the highest single dose tested being 987 mg, have been previously studied in a Phase 1 plaque psoriasis study in a limited number of participants. Additionally, guselkumab IV doses of up to 50 mg/kg weekly for 5 weeks and guselkumab SC doses of up to 50 mg/kg weekly for 24 weeks were well tolerated in cynomolgus monkeys, and did not result in any clinical or anatomic findings (Section 2.2.1.1). These data suggest an acceptable exposure margin between the predicted guselkumab exposures at the proposed dose regimen compared to those observed in toxicology studies; the estimated safety margin is approximately 19- to 26-fold for the 200 mg IV dosing.

This guselkumab dose regimen was further chosen to align with the dose regimens being tested in the guselkumab Phase 2b/3 Crohn's disease program while minimizing the potential safety risk in the combination setting (see Section 4.3.3). This is deemed to be a reasonable selection given the shared biology and the similar response to treatments between Crohn's disease and UC. Specifically, this guselkumab dose regimen corresponds to the lowest dose regimen planned to be evaluated in the dose-ranging portion of the Phase 2b/3 Crohn's disease program. Dose selection for the latter program was based on several considerations, including dose-response data from studies of guselkumab in plaque psoriasis, and published information on risankizumab (another anti-IL-23 mAb) in plaque psoriasis and Crohn's disease, and on the relative dosing requirements for anti-IL-23 mAbs in plaque psoriasis versus Crohn's disease. Specifically, in Crohn's disease, the 200 mg IV induction dose of risankizumab achieved clinical response and remission rates of 32% and 17% respectively at Week 8, approximating rates observed with STELARA at the approved dose in comparable patient populations.[14] A maintenance regimen of 100 mg SC q8W anchored at the approved psoriasis dose will be studied following the 200 mg IV induction therapy. The posology of other biologics in Crohn's disease suggests that once the

disease inflammatory burden is reduced, the drug exposures required to maintain efficacy may be lower than the exposures attained with initial induction doses.

4.3.2. Golimumab

The planned golimumab dose is the approved dose for UC (SIMPONI USPI[52], SmPC[51]). It is the highest approved golimumab dose across indications and the safety profile is well established:

- 200 mg initially administered by SC injection at Week 0, followed by 100 mg at Week 2 and then 100 mg q4w.

4.3.3. Guselkumab and Golimumab Combination

The objective of this Phase 2a study is to establish the POC for a combination treatment approach in UC by demonstrating clinically relevant benefit of guselkumab combined with golimumab as compared to monotherapy alone with either treatment. To achieve this objective, over the first 12 weeks, the combination therapy arm will employ the same dose regimens of guselkumab and golimumab that are being used in the respective monotherapy intervention groups which allows the contribution of each monotherapy to the combination to be assessed relative to each monotherapy alone. From Week 12, the same dose regimen of guselkumab that is being used in the monotherapy intervention group will be followed to see how well it performs as a maintenance therapy following combination induction treatment.

In nonclinical toxicology studies, neither guselkumab or golimumab present any apparent overlapping toxicities that could be expected to be potentiated when administered in combination. Moreover, the probability of PK or PD interaction in the combination is considered low. Guselkumab is a human IgG1λ mAb that binds IL-23 p19 while golimumab is a human IgG1κ mAb that binds to soluble and transmembrane bioactive forms of TNFα. Both are likely degraded into small peptides and amino acids via catabolic pathways typically associated with endogenous IgG metabolism, which has large capacity. Given the acceptable nonclinical and clinical safety profiles for guselkumab and golimumab and the short duration in the combination comparison phase (approximately 12 weeks), potential safety risk in the combination setting is considered to be manageable with careful monitoring and early intervention (including pre-defined stopping rule Section 2.3 and Section 7).

4.4. End of Study Definition

The study is considered completed when the last participant completes the last scheduled study assessment shown in the SoA (Section 1.3) 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.

5. STUDY POPULATION

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

The inclusion and exclusion criteria for enrolling participants in 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.

5.1. Inclusion Criteria

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

1. Male or female, 18 to 65 years old (inclusive).

2. Has a confirmed clinical diagnosis of UC at least 3 months before screening.

3. Has moderately to severely active UC, defined as a baseline (Week 0) Mayo score of 6 to 12, inclusive, using the Mayo endoscopy subscore obtained during the central review of the video endoscopy.

4. Has a screening endoscopy with ≥2 endoscopy subscore of the Mayo score as obtained during the central review of the video endoscopy.

Concomitant or previous medical therapies received

5. Must be naïve to TNF antagonists and have a prior or current UC medication history that includes at least 1 of the following:

    a. Inadequate response to or failure to tolerate current treatment with oral corticosteroids or immunomodulators (6-MP or AZA) as defined in Appendix 2 (Section 10.2).

    OR

    b. History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA) as defined in Appendix 2 (Section 10.2).

    OR

    c. 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).

6. Before the first administration of study intervention, the following conditions must be met:

    a. If receiving oral 5-aminosalicylic acid (5-ASA) compounds, the dose must have been stable for at least 2 weeks.

    b. 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.

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

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

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

a. Immunomodulators (6-MP, AZA, or MTX) for at least 2 weeks.

b. Vedolizumab for at least 18 weeks.

c. Tofacitinib and other inhibitors of JAKs for at least 4 weeks or 5 half-lives, whichever is longer.

d. Cyclosporine, mycophenolate mofetil, tacrolimus, or sirolimus for at least 4 weeks.

e. 6-thioguanine must have been discontinued for at least 4 weeks.

f. Rectal corticosteroids (ie, corticosteroids administered to the rectum or sigmoid colon via foam or enema or suppository) for at least 2 weeks.

g. Rectal 5-ASA compounds (ie, 5-ASAs administered to the rectum or sigmoid colon via foam or enema or suppository) for at least 2 weeks.

h. Parenteral corticosteroids for at least 2 weeks.

i. Total parenteral nutrition or enteral nutrition for at least 2 weeks.

j. Antibiotics for the primary treatment of UC (eg, ciprofloxacin, metronidazole, or rifaximin) for at least 2 weeks.

8. 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 administration 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 administration of study intervention.

9. A participant who has 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 administration of study intervention or a full colonoscopy to assess for the presence of malignancy at the screening visit.

Screening laboratory tests

10. Has screening laboratory test results within the following parameters:

a. Hemoglobin ≥8.0 g/dL (International System of Units [SI]: ≥80.0 g/L)

b. White blood cell count (WBC) ≥3 × 10^3/μL (SI: ≥3.0 × 10^9/L)

c. Neutrophils ≥1.5 × 10^3/μL (SI: ≥1.5 × 10^9/L)

d. Platelets ≥100 × 10^3/μL (SI: ≥100 × 10^9/L)

e. Serum creatinine ≤1.5 mg/dL (SI: ≤133 µmol/L)

f. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations must be within 2 times the upper limit of the normal range (ULN) for the laboratory conducting the test.

Tuberculosis

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

a. Has no history of latent or active TB before screening.

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

c. Has had no recent close contact with a person with active TB.

d. Criterion modified per Amendment 2.

d.1. Within 8 weeks prior to the first administration of study intervention, has a negative QuantiFERON®-TB test result. For a participant with an indeterminate QuantiFERON®-TB test, the test may be repeated once. If the result is indeterminate on repeat testing, the participant is considered a screen failure as outlined in Section 8.2.12.1.

Note: A negative tuberculin skin test result (see Appendix 3 [Section 10.3]) is required if the QuantiFERON®-TB test is not approved/registered in the country in which this protocol is being conducted. In Ukraine, while the QuantiFERON®-TB test is not approved/registered, it is accepted and a tuberculin skin test is not required.

e. Has a chest radiograph (both posterior-anterior and lateral views, or per country regulations where applicable), taken within 12 weeks before the first administration of study intervention and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

Contraception

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

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

12. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin) pregnancy test result at screening and a negative urine pregnancy test result at Week 0.

13. Before randomization, a woman must be (as defined in Appendix 4 [Section 10.4], Contraceptive and Barrier Guidance and Collection of Pregnancy Information):

a. Not of childbearing potential

OR

b. Of childbearing potential and:

- If heterosexually active, practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 6 months after last dose (ie, the end of relevant systemic exposure). Examples of highly effective methods of contraception are located in Appendix 4 (Section 10.4), Contraceptive and Barrier Guidance and Collection of Pregnancy Information; however, the method selected must meet local/regional regulations/guidelines for highly effective contraception.

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

14. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 6 months after the last study intervention.

15. 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.

16. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after receiving the last dose of study intervention.

General

17. Criterion modified per Amendment 2.

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

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

19. Each participant must sign a separate ICF if he or she agrees to provide optional DNA samples for research where local regulations permit. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by

both the participant and his or her legally acceptable representative. Refusal to give consent for the optional DNA samples does not exclude a participant from participation in the study.

20. Each participant must sign a separate ICF if he or she agrees to participate in the optional Week 4 endoscopy and biopsy sub-study. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the participant and his or her legally acceptable representative. Refusal to give consent for the optional Week 4 endoscopy and biopsy sub-study does not exclude a participant from participation in the study

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Has severe extensive colitis as evidenced by:

    a. Current hospitalization for the treatment of UC.

    OR

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

    OR

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

        1) Diarrhea with ≥6 bowel movements/day with macroscopic blood in stool
        2) Focal severe or rebound abdominal tenderness
        3) Persistent fever (≥37.5°C)
        4) Tachycardia (>100 beats/minute)
        5) Anemia (hemoglobin <8.5 g/dL)

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

3. Presence of a stoma.

4. Presence or history of a fistula.

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

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

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

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

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

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

11. Criterion modified per Amendment 2.

    11.1. Has a stool culture or other examination positive for an enteric pathogen, including *Clostridium difficile* toxin, within 4 months before the first administration of study intervention, unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen.

Concomitant or previous medical therapies received

12. Has received the following prescribed medications or therapies:

    a. A biologic therapy targeted at IL-12 and/or IL-23 (eg, ustekinumab, briakinumab, guselkumab, mirikizumab, tildrakizumab, brazikumab, or risankizumab).
    b. A biologic therapy targeted at TNF (eg, golimumab, infliximab, etanercept, adalimumab, or certolizumab pegol).
    c. Natalizumab within 12 months of first study intervention administration.
    d. Agents that deplete B or T cells (eg, rituximab, alemtuzumab) within 12 months of first study intervention administration, or continue to manifest depletion of B or T cells more than 12 months after completion of therapy with lymphocyte-depleting agents.
    e. Any investigational drug within 4 weeks before first administration of study intervention or within 5 half-lives of the investigational agent, whichever is longer.
    f. Apheresis (eg, Adacolumn or Cellsorba apheresis) within 2 weeks before the first administration of study intervention.

Infections or predisposition to infections

13. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Inclusion Criterion 11 for information regarding eligibility with a history of latent TB.

14. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis, recurrent cystitis), an open, draining, or infected skin wound, or an ulcer.

15. Has a chest radiograph within 3 months before the first administration of study intervention that shows an abnormality suggestive of a malignancy or current active infection, including TB.

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

17. Is seropositive for antibodies to hepatitis C virus (HCV) without a history of successful treatment, defined as being negative for HCV ribonucleic acid (RNA) at least 24 weeks after completing antiviral treatment.

18. Tests positive for hepatitis B virus (HBV) infection (see Appendix 5 [Section 10.5], Hepatitis B Virus Screening with HBV DNA Testing).

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

19. Has had a Bacille Calmette-Guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks before baseline.

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

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

22. Has current signs or symptoms of a clinically significant infection. Ongoing 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).

23. Has evidence of a herpes zoster infection ≤8 weeks before baseline.

Malignancy or increased potential for malignancy

24. Has any known malignancy or has a history of malignancy (with the exception of basal cell carcinoma; squamous cell carcinoma in situ of the skin; or cervical carcinoma in situ that has been treated with no evidence of recurrence; or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years before screening).

25. Presence or history of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (eg, nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or periaortic areas), or clinically significant hepatomegaly or splenomegaly, or monoclonal gammopathy of undetermined significance.

Coexisting medical conditions or past medical history

26. Has known allergies, hypersensitivity, or intolerance to guselkumab or golimumab or their excipients (refer to the respective guselkumab and golimumab IBs).

27. Has severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease, or signs or symptoms thereof.

28. Has a history of, or concurrent congestive heart failure including medically controlled, asymptomatic congestive heart failure.

29. Has a history of a demyelinating disorder such as multiple sclerosis or optic neuritis.

30. Has a transplanted organ (with the exception of a corneal transplant performed >12 weeks before screening).

31. Criterion deleted per Amendment 2.

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

33. Has unstable suicidal ideation or suicidal behavior in the last 6 months that may be defined as a Columbia-Suicide Severity Rating Scale (C-SSRS) rating at screening of: Suicidal Ideation with Intention to Act (“Ideation level 4”), Suicidal Ideation with Specific Plan and Intent (“Ideation level 5”), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt), and is considered to be at risk by the investigator based on an evaluation by a mental health professional. In addition, participants with C-SSRS

ratings of Wish to be Dead ("Ideation level 1"), Non-Specific Active Suicidal Thoughts ("Ideation level 2"), Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act ("Ideation level 3"), or non-suicidal self-injurious behavior who are determined to be at risk by the investigator may not be randomized.

34. Has poor tolerability of venipuncture or lacks adequate venous access for required blood sample collections during the study period.

35. Is a woman who is pregnant, or breast-feeding, or planning to become pregnant, or is a man who plans to father a child while enrolled in this study or within 6 months after the last dose of study intervention.

General

36. Is currently participating or intends to participate in any other study using an investigational agent or procedure during participation in this study.

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

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

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 6 [Section 10.6], Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.5, 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, contraceptive requirements).

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

intervention for other live vaccines.

4. Must not receive guselkumab or golimumab outside of this protocol or participate in any other clinical study with an investigational agent while in this study, and must terminate study participation if they do. A participant who intends to participate in any other clinical study with an investigational agent should complete the Week 12 visit or early termination visit as described in Section 1.3 before he or she terminates study participation.

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

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

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

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

Retesting

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

Rescreening

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

6. STUDY INTERVENTION

6.1. Study Interventions Administered

- All participants will receive an IV infusion of either guselkumab or placebo at Weeks 0, 4, and 8.
- All participants will receive 1 SC injection of either guselkumab or placebo at Weeks 16, 24, and 32.
- All participants will receive 2 SC injections of either golimumab or placebo at Week 0, and 1 SC injection of either golimumab or placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34.

For the baseline (W0) visit, the IV study intervention should be administered first. The SC study intervention should be administered approximately 30 minutes after the IV study intervention infusion is complete. If multiple SC injections are administered within the administration visit, each injection of study intervention should be given at a different location of the body.

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Guselkumab and golimumab and the corresponding placebo for each intervention will be manufactured and provided under the responsibility of the sponsor. Refer to the respective IBs for a list of excipients. Detailed instructions on the administration of study intervention will be provided in the site Investigational Product Procedures Manual (IPPM) and Investigation Product Preparation Instructions (IPPI).

Guselkumab

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

Golimumab

Golimumab for SC injection will be supplied as a 100 mg/mL sterile liquid in a single-use PFS. Placebo for golimumab for SC injection will be supplied as a 1 mL sterile liquid in a single-use PFS.

6.2. Preparation/Handling/Storage/Accountability

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

Guselkumab should be clear and colorless to light yellow solution that may contain small translucent particles. Do not use guselkumab if the liquid is cloudy or discolored, or has large

particles. Golimumab should be clear to slightly opalescent and colorless to light yellow. Do not use golimumab if the solution is discolored or cloudy, or if foreign particles are present. 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.

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

6.2.1. Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions.

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

Potentially hazardous materials such as used ampules, needles, syringes, and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

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.

6.3. Measures to Minimize Bias: Randomization and Blinding

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

Intervention Allocation

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 3 intervention groups (1:1:1 ratio), based on a computer-generated randomization

schedule prepared before the studies by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by concomitant use of corticosteroids at baseline (Y/N). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study intervention kit(s) for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then be given the relevant participant details to uniquely identify the participant.

Blinding

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

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

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

The post-baseline results of CRP and fecal calprotectin tests performed by the central laboratory will be blinded to the study sites. If a study site requests these data, it will be provided to them after the final safety analyses have been completed.

Treatment assignment blinding will be maintained for study sites, site monitors, and participants until the final safety DBL and analyses are completed.

In this study, the full sponsor unblinding will occur after the Week 38 DBL. However, a planned interim analysis will occur after the first 30% to 60% of randomized participants have either completed the Week 12 visit or have terminated study participation before Week 12. At the time of this interim analysis, a limited number of sponsor personnel (except for site monitors, who have interactions with the investigative sites) will become unblinded to only those first 30% to 60% of randomized participants. The purpose and analytical details for this interim analysis are provided in Section 9.5. After all 210 randomized participants have either completed the Week 12 visit or have terminated study participation before Week 12, the Week 12 DBL will occur and the data for participants will be unblinded and released for analysis to a limited number of sponsor personnel (except for site monitors, who have interactions with the investigative sites). A subsequent Week 38 DBL will occur when all 210 randomized participants have either completed the Week 38 visit or have terminated study participant before Week 38. Following the Week 38 DBL, the treatment assignment information will be unblinded to the sponsor for all participants and released to the sponsor for analysis. The final safety DBL

will occur when all randomized participants have either completed the final safety visit or have terminated study participation. Additional DBLs may occur as needed.

Identification of sponsor personnel who will have access to the unblinded participant-level data at the time of each DBL will be documented before unblinding.

Under normal circumstances, the investigator blind should not be broken unless specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant. In such cases, the investigator may in an emergency determine the identity of the treatment via the IWRS. It is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. If the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

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

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

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

6.4. Study Intervention Compliance

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

Compliance with the treatment schedule is strongly encouraged. 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.

6.5. Concomitant Therapy

Prestudy therapies administered up to 30 days before the first administration of study intervention must be recorded on the eCRF. Concomitant therapies must be recorded throughout the study, from signing of the informed consent to the last study visit.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the type of therapy, treatment period, dosage, route of administration, and indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

6.5.1. Concomitant Medications

Immunomodulators (6-MP, AZA, and MTX) must be discontinued 2 weeks prior to the first dose of study intervention, as defined in the Inclusion Criteria (Section 5.1). Participants who are receiving oral 5-ASA compounds or oral corticosteroids for the treatment of UC at baseline should maintain a stable dose for the specified period before baseline, as defined in the Inclusion Criteria (Section 5.1). In general, participants who are receiving these medications for UC at baseline (ie, Week 0) should maintain a stable dose through Week 38, with the exception of oral corticosteroids. Therapies can only be discontinued or reduced in dose after Week 0 if investigator judgment requires it because of toxicity or other medical necessity; even if the toxicity resolves, the therapy should not be restarted. Oral corticosteroids must be maintained at baseline doses through Week 6, and all participants must begin tapering oral corticosteroids at Week 6, unless medically not feasible (see further details in Section 6.5.1.1, Oral Corticosteroids Tapering).

Enrolled participants **should not initiate** any of the following concomitant UC-specific medical therapies:

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

If the above medical therapies are initiated or medication doses are changed based on medical necessity as assessed by the investigator, participants should continue to attend all study visits and have all assessments. While this does not represent a deviation from the study protocol and the participants may remain on their assigned therapy, it may be considered a treatment failure. Treatment failures due to UC medication changes will be defined in the SAP.

6.5.1.1. Oral Corticosteroids Tapering

At Week 6, all participants who were taking oral corticosteroids at Week 0 must begin tapering corticosteroids. This tapering is mandatory, unless not medically feasible, and should follow the

recommended schedule shown in Table 3. If participants experience worsening of their disease activity while tapering corticosteroids, further dose decreases may be suspended, and/or their oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator. The oral corticosteroid dose, however, may not be increased above the Week 0 dose unless due to medical necessity. 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).

Table 3: Recommended Tapering Schedule for Oral Corticosteroids

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

6.5.2. Prohibited Concomitant Medications

Participants who initiate the following treatments during study participation will have their study intervention discontinued:

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

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

As protection of human research participants is paramount, it is recognized that initiating such therapies may rarely be required due to medical necessity. However, initiation of these prohibited medications should be documented as a deviation from the study protocol, and participants will be discontinued from receiving further study intervention (Section 7).

Participants who discontinue study intervention administration should complete the appropriate visit(s) as described in Section 1.3.

Note: Participants must not receive guselkumab or golimumab 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 the appropriate visit(s) as described in Section 1.3.

6.6. Dose Modification

No dose adjustment of study intervention will be permitted during the study.

6.7. Intervention After the End of the Study

This protocol is designed to provide participants with up to approximately 38 weeks of treatment.

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.

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 under the following conditions:

1. The participant initiates treatment with prohibited concomitant medication(s) (Section 6.5.2).
2. The participant has a colectomy.
3. The participant becomes pregnant or plans a pregnancy within the study period. Refer to Appendix 4 (Section 10.4), Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
4. The participant (or the participant's legally acceptable representative) withdraws consent for administration of study intervention.
5. The participant develops an opportunistic infection.

6. The participant is deemed ineligible according to the following TB screening criteria:

   – A diagnosis of active TB is made.

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

     A participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive or indeterminate QuantiFERON®-TB test result (and/or a positive tuberculin skin test result in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities).

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

7. Criterion modified per Amendment 2.

   7.1. The participant has a serious adverse reaction that is related to an injection or an infusion, including an injection-site or infusion reaction, 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.

8. 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, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

9. The participant has severe hepatic function abnormalities, as described in Section 8.2.5 and Appendix 7 (Section 10.7).

10. The participant is diagnosed with a malignancy including squamous cell skin cancer. Consideration may be given to allowing participants who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study intervention.

11. The participant develops congestive heart failure.

12. The participant is diagnosed with a demyelinating disorder.

13. The participant develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA.

14. The investigator believes that for safety or tolerability reasons, it is in the best interest of the participant to discontinue study intervention.

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

1. Persistent inadequate response or worsening of UC based on signs, symptoms, and/or laboratory values. If the participant experiences AEs consistent with clinically significant worsening of UC at any time during the study, these events should be evaluated by the investigator and the study medical monitor to decide on discontinuation of study

intervention. Discontinuation of study intervention should be considered in participants with clinically significant worsening of UC where continuation of the study intervention is not in the best interest of the participant.

2. Criterion modified per Amendment 2.

   2.1. The participant develops a serious infection, including but not limited to sepsis or pneumonia.

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

3. The participant reports suicidal ideation with intention to act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), or any suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline C-SSRS assessment. If a participant can be adequately treated with psychotherapy and/or pharmacotherapy based on an evaluation by a mental health professional, then the participant, at the discretion of the investigator, may be continued with treatment if agreed to by the medical monitor or designee. Discussion of such participants with the medical monitor or designee is required (see Section 8.2.6).

4. Criterion deleted per Amendment 2.

5. The participant has hematology abnormalities as described below:

   - Two sequential absolute neutrophil counts $<0.75 \times 10^3/\mu L$ (SI: $<0.75 \times 10^9/L$)
   - Two sequential absolute lymphocyte counts $<0.5 \times 10^3/\mu L$ (SI: $<0.5 \times 10^9/L$)
   - Two sequential hemoglobin values <8.0 g/dL (SI: <80.0g/L) or a decrease of >30% from baseline
   - Two sequential platelet counts $<75 \times 10^3/\mu L$ (SI: $<75 \times 10^9/L$)

   Note: These laboratory abnormalities should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

6. The participant develops a severe injection-site or infusion reaction.

If a participant discontinues study intervention for any reason before the end of the treatment period, assessments should be obtained as specified in the SoA (Section 1.3). If the reason for withdrawal from the study is withdrawal of consent, every effort should be made to conduct the early termination assessments, as indicated in the SoA, prior to terminating study participation. After termination of study participation, no additional assessments are allowed.

7.2. Participant Discontinuation/Withdrawal From the Study

Participant discontinuation/withdrawal from the study is defined as no longer following up for study visits. It is different from discontinuation from study intervention, as described in Section 7.1.

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

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

Participants who terminate study participation will not be required to return for any follow-up assessments; however, these participants should complete the safety and efficacy evaluations specified in the SoA (Section 1.3) at the time they terminate study participation. No additional evaluations are performed after a participant's withdrawal from the study.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study intervention assigned to the withdrawn participant may not be assigned to another participant. Additional participants will not be entered.

7.2.1. Withdrawal From the Use of Research Samples

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

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

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

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

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 6 [Section 10.6], 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

If a participant is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the participant and determine the reason for discontinuation/withdrawal.

Such efforts should include repeated telephone calls, certified letters, and email requests. The measures taken to follow up must be documented. Refer to Section 7.2, Participant Discontinuation/Withdrawal From the Study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker (PD), pharmacogenomic, medical resource utilization, and safety measurements applicable to this study.

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

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

For women of childbearing potential only, additional serum or 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.

Medical resource utilization data will be collected. Refer to Section 8.9, Medical Resource Utilization for details.

At their last study visit, each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share his/her experience as a volunteer in this study. The responses will be collected by an external party and provided anonymously to the sponsor.

Screening Phase

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

Diaries will be provided to each participant to record concomitant medications, stool production, and episodes of rectal bleeding. A Mayo diary will be completed from recall at screening and will be used to calculate a partial Mayo score (Section 8.1.1) to assess the participant's eligibility for further screening and to train the participant on the use of the diary. Participants with a partial Mayo score ≥3 can proceed with endoscopy. Participants will be instructed to complete a daily Mayo diary for 7 days immediately before each visit and bring them to every visit for data collection and review by the investigator/study coordinator.

Bristol Stool Form Scale diaries will also be provided to participants to classify the form (or consistency) of their stools during the combination comparison phase of the study (Section 8.1.8). Participants will complete the BSFS as a daily diary entry from Week 0 through Week 12.

The screening endoscopy must be performed within 2 weeks (and at least 4 days) before the baseline (Week 0) visit. Participants who are identified as being at increased risk for colon cancer (Section 5.1, Inclusion Criterion #9) or for adenomatous polyps (Section 5.1, Inclusion Criterion #8) 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 must elapse between a colonoscopy with polypectomy and the Week 0 visit. Histology results from the polypectomy must be available to confirm absence of colonic mucosal dysplasia before first administration of study intervention (Section 5.2, Exclusion Criterion #8).

Women of childbearing potential must have a negative serum pregnancy test result at screening and a negative urine pregnancy test result at the Week 0 visit. Participants must be reminded that they are required to use a highly effective method of contraception during the study (as described in Section 5.1, Inclusion Criterion 13) and must continue taking such precautions for 6 months after receiving the last administration of study intervention. The method(s) of contraception used by each participant must be documented.

Participants must undergo testing for TB (Section 8.2.12) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. A participant's eligibility according to TB screening criteria is described in Section 5.1, Inclusion Criterion 11.

Blood Sample Collection

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

The maximum total blood volume to be collected from each participant in the study will be approximately 350 mL over approximately 58 weeks. This total may vary due to:

- whether or not the participant consents to take part in the optional pharmacogenomic sub-study (5 mL).

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

Sample Collection and Handling

The actual dates and times of sample collection must be recorded on the 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.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IBs)
- IPPM
- IPPI
- Laboratory Manual
- eCRF completion instructions
- Patient recruitment materials
- Sample ICFs
- IWRS Manual
- Biopsy Manual
- ePRO equipment
- Endoscopy kit
- Imaging Manual
- Lab kits

8.1. Efficacy Assessments

Efficacy evaluations will include the following:

- Mayo score and Partial Mayo score
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS)
- Inflammatory PD markers including CRP and fecal calprotectin
- Patient-reported outcome measures to assess HRQOL outcomes and fatigue (ie, IBDQ, PROMIS-29, and PROMIS Fatigue 7-item Short Form [7a])
- Exploratory patient-reported symptom measures including BSFS and PGIC of Severity of UC

The SoA summarizes the frequency and timing of efficacy measurements applicable to this study (Section 1.3).

8.1.1. Mayo Score and Partial Mayo Score

The **Mayo score** (see Appendix 8 [Section 10.8]) was developed from the criteria of Truelove and Witts[64] for mild, moderate, and severe UC and from the criteria of Baron et al[3] for grading endoscopic appearance. The Mayo score is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, physician's global assessment, and endoscopy findings) each with a score range of 0 (normal activity) to 3 (severe activity) and a total score range of 0 to 12 points. A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severely active disease. The endoscopic findings will be assessed by the investigator (ie, local endoscopist) during the endoscopy procedure and by the central reader reviewing a video of the endoscopy. Participant eligibility at baseline will be based on the final reported endoscopic subscore as determined by the following process:

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

Specific details will be provided in the imaging charter.

Mayo scores are calculated using the following:

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

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

If 1 or more of the 4 Mayo subscores is missing at a specific visit, but not all 4 subscores are missing, the last available Mayo subscore will be carried forward to compute a full Mayo score and a partial Mayo score at that visit. If all 4 subscores are missing at a specific visit, the Mayo score and partial Mayo score will be considered missing at that visit.

8.1.2. Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

The **UCEIS** is an index that provides an overall assessment of endoscopic severity of UC, based on mucosal vascular pattern, bleeding, and ulceration.[61] The score ranges from 3 to 11, with a higher score indicating more severe disease by endoscopy. The UCEIS score will be assessed only by the central video readers for all endoscopies.

8.1.3. C-Reactive Protein

C-reactive protein has been demonstrated to be useful as a marker of inflammation in subjects with IBD. In subjects with UC, elevated CRP has been associated with severe clinical activity, an elevated sedimentation rate, and active disease as detected by colonoscopy.[54,66] 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 intestinal inflammation and response to treatment in participants with IBD, especially in UC.[2] 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 concentration will be performed by the central laboratory using a validated method. Additional tests may also be performed on the stool samples for additional markers that are related to intestinal inflammation and treatment response such as the microbiome.

8.1.5. Inflammatory Bowel Disease Questionnaire

The **IBDQ**[23] is a validated, 32-item, self-reported questionnaire for participants with IBD that will be used to evaluate the disease-specific HRQOL across 4 dimensional scores: bowel symptoms (loose stools, abdominal pain), systemic functions (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). Scores range from 32 to 224, with higher scores indicating better outcomes.

8.1.6. PROMIS-29

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

symptom-oriented domains of PROMIS-29 (anxiety, depression, fatigue, pain interference, and sleep disturbance), higher scores represent worse symptomatology. On the function-oriented domains (physical functioning and social role), higher scores represent better functioning.

8.1.7. PROMIS Fatigue 7-items Short Form

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

8.1.8. Bristol Stool Form Scale

The **BSFS** is a medical aid to classify the form (or consistency) of human feces into 7 categories.[27] It has been used as a research tool to evaluate the effectiveness of treatments for various diseases of the bowel (eg, irritable bowel syndrome). Participants will complete the BSFS as a daily diary entry from Week 0 through Week 12.

8.1.9. Patient's Global Impression of Change (PGIC) of Severity of Ulcerative Colitis

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

8.2. Safety Assessments

Details regarding the independent DMC are provided in Section 9.5.1.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Appendix 9 (Section 10.9), Adverse Events: 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 endpoint is reached.

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

8.2.1. Physical Examination

Physical examinations 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.

Total body skin examination will be performed to evaluate for any suspected malignant skin lesions including basal cell carcinoma, squamous cell carcinoma, and melanoma.

8.2.2. Height and Weight

Height and weight will be measured as specified in the SoA. Participants will be instructed to remove shoes and outdoor apparel and gear prior to these measurements.

8.2.3. Vital Signs

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

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

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

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

8.2.4. Electrocardiogram

A 12-lead ECG will be performed at screening.

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

8.2.5. Clinical Safety Laboratory Assessments

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

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

- **Hematology assessments** will include but are not limited to the following: hemoglobin, hematocrit, platelet count, total and differential WBC count.

  Mandatory Re-Testing

  The following hematology abnormalities require monitoring and re-testing (ideally within 3-5 days):

- Absolute neutrophil count <1.2 × 10^3/μL (SI: <1.2 × 10^9/L)
- Absolute lymphocyte count <0.5 × 10^3/μL (SI: <0.5 × 10^9/L)
- Any single hemoglobin value <8.0 g/dL (SI: <80.0 g/L), or any decrease in hemoglobin >2.0 g/dL (SI: >20.0 g/L) from baseline
- Platelet count <100 × 10^3/μL (SI: <100 × 10^9/L)

The medical monitor or designee and the clinical site will be notified if these abnormal laboratory values are identified in any participant during the conduct of the study.

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

  A medical monitor or designee and the clinical site will be notified if pre-specified abnormal laboratory values defined in the Laboratory Manual are identified in any participant during the conduct of the study.
- **Serology**: HIV antibody, HBV antibodies and surface antigen, and HCV antibody.
- **Abnormal liver function tests:** If laboratory testing for a participant who is enrolled in the study and receiving study intervention reveals an increase of serum aminotransferases (ALT or AST) to >3 x ULN and an increase of bilirubin to >2 x ULN, study intervention should be suspended immediately. In addition, laboratory tests for ALT, AST, alkaline phosphatase, and total bilirubin should be confirmed by a retest within 24 hours if possible, but no later than 72 hours following notification of test results. See Appendix 7 (Section 10.7; Liver Safety: Suggested Actions and Follow-up Assessments) for additional information on monitoring and assessment of abnormal liver function tests.
- **Pregnancy testing:** Female participants of childbearing potential will undergo a serum β-human chorionic gonadotropin pregnancy test at screening, and a urine pregnancy test before each study intervention administration, at the early termination visit, and the safety follow-up visit.

8.2.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS defines 5 subtypes of suicidal ideation and 4 possible suicidal behaviors, as well as non-suicidal self-injurious behavior and completed suicide. It will be used as a screening tool to prospectively evaluate suicidal ideation and behavior in this study, as part of a comprehensive evaluation of safety. The C-SSRS is an investigator-administered questionnaire.[32,40] Two versions of it will be used in this study: the 'Baseline/Screening' version of the C-SSRS will be conducted during the screening visit and the 'Since Last Visit' version of the C-SSRS will be completed at all other visits through the end of the study.

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

At screening, the C-SSRS will be the first assessment performed after signing informed consent, before any other study procedure. At all subsequent visits, the C-SSRS will be performed

according to the assessment schedule and should be performed after other PROs but before any other study procedures. Participants will be interviewed by the investigator or trained study-site personnel in a private, quiet place.

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

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

Participants with C-SSRS ratings of Wish to be Dead ("Ideation level 1"), Non-Specific Active Suicidal Thoughts ("Ideation level 2"), Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act ("Ideation level 3") or non-suicidal self-injurious behavior must be determined not to be at risk by the investigator in order to be randomized in the study. Any questions regarding eligibility of such participants should be discussed with the medical monitor or designee.

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

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

Interruption or the discontinuation of study treatment should be considered for any participant who reports Suicidal Ideation with Intention to Act ("Ideation level 4"), Suicidal Ideation with Specific Plan and Intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline C-SSRS assessment and who is deemed to be at risk by the investigator based upon evaluation by a mental health professional. If a participant can be adequately treated with psychotherapy and/or pharmacotherapy then the participant, at the discretion of the investigator, may be continued with treatment if agreed to by the medical monitor or designee. Discussion of such participants with the medical monitor or designee is required (see Section 7.1, Discontinuation of Study Intervention).

Any C-SSRS finding, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (see Appendix 9 [Section 10.9], Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

8.2.7. Concomitant Medication Review

Concomitant medications will be reviewed 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.

8.2.9. Hypersensitivity Reactions

Before any SC injection or IV infusion of study intervention, appropriately trained personnel and medications 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).

In the case of anaphylaxis, injectable epinephrine (intramuscular), respiratory assistance, and other proper resuscitative measures are essential and must be available at the study site where the injections or infusions are being administered.

Participants who experience serious adverse reactions related to an injection or infusion must strongly be considered to be discontinued from further study intervention administrations.

Participants who experience reactions following an injection or infusion that result in bronchospasm with wheezing and/or dyspnea that requires ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm Hg or blood pressure <90/60 mm Hg must be discontinued from additional study intervention administration (see Section 7).

Participants who experience reactions suggestive of serum sickness (resulting in symptoms such as myalgia and/or arthralgia with fever and/or rash that are not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after administration of study intervention, must be discontinued from further study intervention administration. Note that these signs and symptoms may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

8.2.10. Adverse Events Temporally Associated With Infusion

Any AE (except laboratory abnormalities) that occurs during or within 1 hour after the IV infusion of study intervention will be carefully evaluated. Minor infusion-related AEs may be managed by slowing the rate of the IV infusion and/or treating with antihistamines and/or acetaminophen (paracetamol) as clinically indicated. If an IV infusion of study intervention is

interrupted because of an AE that, in the opinion of the investigator, is not severe or does not result in a serious adverse event (SAE), the infusion may be restarted with caution.

8.2.11. Infections

Study intervention should not be administered to a participant with a clinically significant, active infection. Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits (see SoA, Section 1.3). If a participant develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study intervention must be strongly considered.

8.2.12. Tuberculosis Evaluations

8.2.12.1. Initial Tuberculosis Evaluation

Participants must undergo testing for TB and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. Investigators have the option to use both the QuantiFERON®-TB test and the tuberculin skin test (refer to Appendix 3 [Section 10.3]) to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated in order to evaluate a participant who has high risk of having latent TB. If either the QuantiFERON®-TB test or the tuberculin skin test is positive, the participant is considered to have latent TB infection and is excluded from the study.

Participants with a negative QuantiFERON®-TB test result (and a negative tuberculin skin test result in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin is mandated by local health authorities) are eligible to continue with pre-randomization procedures. Participants with a newly identified positive QuantiFERON®-TB (or tuberculin skin) test result are excluded from the study and must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed. For a participant with an indeterminate QuantiFERON®-TB test, the test may be repeated once. If the result is indeterminate on repeat testing, the participant is considered a screen failure.

8.2.12.2. Ongoing Tuberculosis Evaluation

Early Detection of Active Tuberculosis

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

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

  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"

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

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

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

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment is warranted. Study intervention administration should be interrupted during the investigation. A positive QuantiFERON®-TB test or tuberculin skin test result should be considered detection of latent TB. Participants with a positive or indeterminate QuantiFERON®-TB test or positive tuberculin skin test must immediately discontinue further administration of study intervention and be encouraged to return for scheduled study visits according to the SoA (Section 1.3).

8.3. Adverse Events and Serious Adverse Events

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

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

Anticipated events will be recorded and reported as described in Appendix 10 (Section 10.10).

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 9 (Section 10.9), Adverse Events: 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, including those spontaneously reported to the investigator within 16 weeks after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

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

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 9 (Section 10.9), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

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

8.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention (see Section 7).

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required (see Appendix 4 [Section 10.4], Contraceptive and Barrier Guidance and Collection of Pregnancy Information and Appendix 9 [Section 10.9], Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting).

8.3.5. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first study intervention administration(s) in subjects participating in this clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the event, according to the procedures in Appendix 9 (Section 10.9), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting for SAEs. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Treatment of Overdose

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

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

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

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

8.5. Pharmacokinetics and Immunogenicity

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

8.5.1. Evaluations

At visits where only serum concentration of guselkumab and golimumab will be evaluated (ie, no antibodies to guselkumab and golimumab 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 serum concentration of golimumab, and a back-up.

At visits where serum concentration of guselkumab and golimumab and antibodies to guselkumab and golimumab will be evaluated, 1 venous blood sample of sufficient volume should be collected. Each serum sample will be divided into 5 aliquots: 1 for serum concentration of guselkumab, 1 for serum concentration of golimumab, 1 for antibodies to guselkumab, 1 for antibodies to golimumab, 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.

8.5.2. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of guselkumab and golimumab using respective 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.

Immunogenicity

The detection and characterization of anti-guselkumab and anti-golimumab antibodies will be performed using respective validated assay methods by or under the supervision of the sponsor. All samples collected for detection of anti-guselkumab and anti-golimumab antibodies will also be evaluated for guselkumab and golimumab serum concentrations to enable interpretation of the antibody data.

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

Serum samples will be used to evaluate various guselkumab and golimumab PK parameters based on blood drawn from all participants according to the SoA (Section 1.3). A population PK analysis approach may also be used to derive PK parameters when appropriate.

Pharmacokinetic/Pharmacodynamic Evaluations

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

8.5.4. Immunogenicity Assessments

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

8.6. Pharmacodynamics

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

8.7. Genetics

Genetic variation may be important contributory factors to interindividual differences in drug disposition, response, and clinical outcomes. Genetic (DNA) factors may also serve as markers for disease susceptibility and prognosis and may identify population subgroups that respond differently to a drug. DNA samples will be analyzed for identification of genetic factors to better understand the molecular effects of guselkumab and/or golimumab treatment and/or UC, and to evaluate markers that can predict clinical response. Genetic (DNA) research may consist of the analysis of 1 or more candidate genes or analysis of the entire genome (as appropriate) in relation to treatment(s) and/or UC.

A pharmacogenomic whole blood sample of approximately 5 mL will be collected (where local regulations permit) for genetic analyses as specified in the SoA (Section 1.3). Only participants who sign the consent form to participate in the genetic assessment will have whole blood DNA samples collected. Participation in the pharmacogenomic sub-study is optional.

8.8. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab and/or golimumab in the treatment of UC. Combination TNFα and IL-23 blockade will be compared to the selective inhibition of TNFα or IL-23. Assessments will include the evaluation of relevant biomarkers in serum, whole blood, stool, and mucosal biopsy samples collected as specified in the SoA (Section 1.3). 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 and golimumab combination treatment or monotherapy of either agent.
2. To understand UC pathogenesis.
3. To understand why an individual participant may respond differently to guselkumab or golimumab.
4. To develop tests for guselkumab, golimumab and/or UC.

Instructions for the collection and shipment of biomarker samples will be found in the Laboratory Manual.

8.8.1. Serum

Serum samples for biomarker analyses will be obtained from all participants as specified in the SoA. Analysis of serum samples for biomarkers 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.

8.8.2. Whole Blood (RNA)

Whole blood samples will be collected from all participants as specified in the SoA. Total RNA will be isolated and used for differential gene expression analyses to identify mRNA or microRNA expression patterns that are relevant to guselkumab, golimumab, and/or UC. Analysis will also be conducted to identify markers that can predict clinical response.

8.8.3. Fecal

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

8.8.4. Mucosal Biopsy (RNA, Histology, and Single Cell Isolation)

Mucosal biopsy samples will be collected from all participants during endoscopy at the times specified in the SoA for RNA expression analysis, histologic assessment, and single cell isolation. Total RNA will be isolated and used for differential gene expression analyses to identify mRNA or microRNA expression patterns that are relevant to guselkumab or golimumab treatment and/or UC, and to evaluate markers that can predict therapeutic response. The biopsy samples collected will also be used for the histologic and immunohistochemical assessment of disease and healing. Protein and gene expression will be measured at higher resolution in various immune cell populations isolated from these biopsy samples.

8.8.4.1. Optional Week 4 Endoscopy and Biopsy Sub-study

Mucosal biopsies will be obtained at Week 4 only from participants who agree to participate in the optional sub-study. This optional sub-study is included to investigate early onset of action at Week 4 and to assess whether data collected at Week 4 correlate with clinical efficacy at later time points. The endoscopic assessment will also be conducted for this time point. The endoscopy subscores will be used to calculate full Mayo scores for this timepoint (see Section 8.1.1).

8.8.5. Whole Blood (PBMCs)

Whole blood samples will be collected from all participants as specified in the SoA. Peripheral blood mononuclear cells (PBMCs) will be isolated and used for single cell isolation. Protein and gene expression that are relevant to study intervention and/or UC will be measured at higher resolution in PBMCs isolated from whole blood. To match with single cell analysis in colonic biopsies, whole blood samples will also be obtained at Week 4 from participants who agree to participate in the optional endoscopy and biopsy sub-study.

8.8.6. Negative Response Signature

The negative response signature is a predictive gene expression signature, initially discovered from colon biopsies collected at baseline from a subset of participants in the ACT 1 infliximab UC study[43], refined in the PURSUIT golimumab UC study[44], and prospectively evaluated for prediction of mucosal healing in an open-label study of 103 UC subjects treated with golimumab

(PROgECT).[60] Using machine learning approaches, it was found that this length-13 gene signature predicted anti-TNFα nonresponse by mucosal healing with good accuracy, identifying 63% of mucosal healing nonresponders with a negative predictive value of 0.87. The signature had similar negative predictive value in a Phase 2a study of a JAK inhibitor in UC suggesting that it may be mechanism agnostic.[48] Efficacy of guselkumab and golimumab combination treatment or monotherapy treatment will be evaluated by negative response signature status at baseline (see Sections 3.1.2 and Section 3.2.3).

8.9. Medical Resource Utilization

Medical resource utilization, including but not limited to UC-related emergency department visits, hospitalizations, and surgeries, will be collected 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. Specific details will be provided in the SAP.

Descriptive statistics (eg, mean, median, standard deviation [SD], interquartile 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, Cochran-Mantel-Haenszel [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 will be compared using an analysis of variance (ANOVA) or analysis of covariance (ANCOVA), unless otherwise specified. If the normality assumption is in question, an ANOVA or ANCOVA on the van der Waerden normal scores will be used.

Unless otherwise specified, the analysis of endpoints related to the endoscopy subscore, including the Mayo score, will be based on the final reported endoscopic subscore as defined in Section 8.1.1.

All statistical testing will be performed at a significance level of 0.1 (1-sided) unless otherwise specified. Nominal p-values will be displayed for all treatment comparisons.

9.1. Statistical Hypotheses

The primary hypothesis is that guselkumab and golimumab combination therapy is superior to both monotherapy arms as assessed by the proportion of participants achieving clinical response at Week 12.

9.2. Sample Size Determination

A sample size of 210 participants (70 per intervention group) was determined by the power to detect a significant difference in the proportion of participants in clinical response at Week 12 (primary endpoint) between the combination therapy and both monotherapies using a 1-sided chi-square test with 0.1 significance level for each comparison. The study is sized such that the combination therapy has approximately 80% power (based on simulations) to achieve both comparisons to monotherapy for the primary endpoint.

The assumptions for the sample size calculations were based on data from the past golimumab programs conducted by the sponsor in participants with UC who were naïve to biologic therapy. The proportion of participants in clinical response at Week 12 is expected to be 55% for golimumab compared to 51% observed at Week 6 in study C0524T17 (PURSUIT), as the PURSUIT program suggested that the response rate might increase slightly with further treatment. This was also confirmed in study CNTO148UCO2001 (PROgECT).[60] The tested dose of guselkumab is assumed to have the same clinical response rate as golimumab at Week 12. The proportion of participants in clinical response at Week 12 is assumed to be 75% for the combination therapy, which is based on the additive effect from both monotherapies (20% improvement from each monotherapy relative to a historical placebo response of 35%). The different combinations of clinical response rate assumptions and associated power are displayed in Table 4.

Table 4: Power to Detect a Treatment Effect of the Combination Therapy Versus Both Guselkumab Monotherapy and Golimumab Monotherapy Based on the Proportion of Participants Achieving Clinical Response at Week 12

Golimumab (n=70)	Guselkumab (n=70)	Combination Therapy (n=70)	Power
50%	50%	70%	79%
50%	55%	70%	66%
55%	60%	75%	69%
55%	**55%**	**75%**	**81%**
55%	60%	80%	90%
60%	60%	80%	85%

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Randomized Analysis Set	All participants who are randomized
Full Analysis Set	All randomized participants who receive at least 1 dose of study intervention
Safety Analysis Set	All randomized participants who receive at least 1 dose of study intervention
PK Analysis Set	All randomized participants who receive at least 1 dose of study intervention and have at least 1 valid blood sample drawn for PK analysis

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Population for Efficacy Analysis

Unless otherwise noted, efficacy analyses will be based on the Full Analysis Set, which is defined as all randomized participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment they received.

9.4.1.2. Primary Endpoint Analyses

The primary endpoint is clinical response at Week 12 defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points with either a decrease in RBS ≥1 or a RBS of 0 or 1. The endoscopy subscore will be based on the final reported endoscopy subscore.

Participants who have a colectomy or ostomy, or have protocol-prohibited medication changes (to be detailed in the SAP), or who have discontinued study intervention due to unsatisfactory therapeutic effect or an AE of worsening UC, before the Week 12 visit will be considered not to be in clinical response at Week 12, regardless of the actual Mayo score.

Participants with a missing Mayo score (ie, all 4 Mayo subscores are missing) or who do not return for evaluation at Week 12 will be considered not to be in clinical response at Week 12.

For testing of the primary endpoint, the efficacy of combination therapy versus each monotherapy will be compared. For both statistical comparisons of the primary endpoint, a CMH chi-square test stratified by concomitant use of corticosteroids at baseline (Y/N) will be used. The testing will be done simultaneously at the 1-sided 0.1 level of significance for each comparison.

The study will be considered positive if the combination therapy group is significantly different from both monotherapy groups for the primary endpoint.

To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint will be conducted using different missing data approaches; these analyses will be described in the SAP.

Subgroup analyses of the primary endpoint will be performed based on demographic and baseline disease characteristics, and baseline concomitant UC medication use and history of UC-related medications. Additional subgroup analyses of other endpoints (eg, clinical remission) may be considered and will be described in the SAP.

9.4.1.3. Major Secondary Endpoint Analyses

The major secondary endpoint is clinical remission at Week 12 defined as Mayo score ≤ 2 with no individual subscore >1. Note: Other remission definitions may be considered and will be fully described in the SAP.

Participants who meet 1 or more treatment failure rules (as specified for the primary endpoint) before Week 12 will be considered not to be in clinical remission at Week 12.

Participants with a missing Mayo score (ie, all 4 Mayo subscores are missing) or who do not return for evaluation at Week 12 will be considered not to be in clinical remission at Week 12.

If both tests of the primary endpoint are positive, a CMH chi-square test (1-sided) stratified by concomitant use of corticosteroids at baseline (Y/N) will be used to compare the efficacy of the combination therapy to each monotherapy for the major secondary endpoint. The testing will be done simultaneously at the 1-sided 0.1 level of significance for each comparison.

9.4.1.4. Other Efficacy Endpoint Analyses

Pairwise comparisons of the combination therapy with each monotherapy will be made for the endpoints specified in Section 3.2.3 with details that are to be specified in the SAP.

All statistical testing will be performed at the 1-sided 0.1 significance level. No adjustments for multiple comparisons will be made for these other efficacy endpoints and nominal p-values will be presented.

9.4.1.5. Exploratory Endpoint Analyses

Exploratory analyses will be conducted for BSFS scores over time and the distribution of PGIC of UC severity over time (details will be provided in the SAP).

9.4.2. Safety Analyses

Safety data, including but not limited to, AEs, SAEs, infections, serious infections, changes in laboratory assessments will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Details will be specified in the SAP.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the MedDRA. Treatment-emergent AEs are AEs with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs which are treatment-emergent will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

The following analyses of AEs will be used to assess the safety of participants:

- Frequency and type of AEs.
- Frequency and type of SAEs.
- Frequency and type of reasonably related AEs as assessed by the investigator.
- Frequency and type of AEs leading to discontinuation of study intervention.

- Frequency and type of infections, including serious infections and infections requiring oral or parenteral antimicrobial treatment.
- Frequency and type of AEs temporally associated with infusion.
- Frequency and type of injection-site reactions.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, or who experience a severe or a serious AE.

Clinical Laboratory Tests

The following summaries of clinical laboratory tests will be used to assess participant safety:

- Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry).
- Summary of maximum NCI-CTCAE toxicity grade for post-baseline laboratory values (hematology and chemistry).

Listings of participants with any abnormal post-baseline laboratory values of NCI-CTCAE grade ≥2 will also be provided.

Suicidal Ideation and Behavior

Suicidal ideation and behavior based on the C-SSRS and AEs will be summarized descriptively.

9.4.3. Other Analyses

Pharmacokinetic Analyses

Serum guselkumab and golimumab concentrations over time will be summarized for the PK Analysis Set. Descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each nominal sampling timepoint. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database or data presentations. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing time of study intervention administration). Detailed rules for the analysis will be specified in the SAP.

Population PK modeling may be conducted when appropriate. If these population PK analyses are conducted, the results of these analyses will be presented in a separate report.

Immunogenicity Analyses

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

A listing of participants who are positive for antibodies to guselkumab and to golimumab will be provided, respectively. The maximum titers of antibodies to guselkumab and to golimumab will be summarized for participants who are positive for antibodies to guselkumab and to golimumab, respectively.

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

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum concentrations of guselkumab and golimumab and the efficacy measures and/or relevant biomarker(s) may be explored graphically when appropriate. Additional analysis may be conducted if deemed necessary.

Biomarkers Analyses

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. Any biomarker samples received by the contract vendor or sponsor after the cutoff date will not be analyzed, and therefore, will be excluded from the biomarker analysis.

Changes in serum protein analytes, fecal biomarkers, and biopsy and whole blood RNA obtained over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and response to treatment will be explored. Biomarker analyses will be summarized in a separate technical report.

The biomarker analyses will characterize the effects of guselkumab and/or golimumab to identify biomarkers relevant to treatment, and to determine if these biomarkers can predict response to guselkumab or golimumab. Results of serum, stool, whole blood, and mucosal biopsy analyses will be reported in separate technical reports.

Pharmacogenomic Analyses

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

Medical Resource Utilization Analyses

Medical resource utilization data will be descriptively summarized by intervention group.

9.5. Interim Analysis

For the purpose of future clinical development planning, there will be 1 interim analysis for this study. Depending on the enrollment rate, the sponsor anticipates that the interim analysis will take place when 30% to 60% of randomized participants have either completed their Week 12 visit or have terminated their study participation before Week 12. No database locks are planned for interim analyses unless otherwise stated.

A limited number of sponsor personnel will review the interim data. As this interim analysis does not affect the conduct or completion of the study, it will not require multiplicity adjustment for the final analysis.

9.5.1. Data Monitoring Committee

An external independent DMC will be established and will meet periodically to review interim unblinded safety data to ensure the continuing safety of the participants enrolled in the study. The DMC will consist of 2 physicians and a statistician. The DMC responsibilities, authorities, and procedures will be documented in a separate DMC charter.

The DMC's initial responsibility will be careful review of the safety data from the first 25 participants randomized to any intervention group and treated. Similar to conduct of a Phase 1 study, the safety of these first 25 participants will be monitored on an ongoing basis for any potential safety concerns that would result in a pause in dosing. Detailed guidance for the DMC regarding these reviews will be provided in the DMC charter. Once the 25th participant is randomized, the DMC will perform a review of unblinded safety tables. If no new safety concerns are identified during this initial review period, then the subsequent DMC reviews will include monthly reports of all SAEs in enrolled participants as well as review of unblinded safety tables at least every 3 months. After each safety review, the DMC will make recommendations regarding the continuation of the study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARC	Anticipated Event Review Committee
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AZA	azathioprine
BCG	Bacille Calmette-Guérin
BSFS	Bristol Stool Form Scale
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
CV	cardiovascular
DBL	database lock
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EP	erythrodermic psoriasis
ePPND	enhanced prenatal and postnatal development
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPP	generalized pustular psoriasis
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL	interleukin
IPPI	Investigation Product Preparation Instructions
IPPM	Investigational Product Procedures Manual
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
JAK	Janus kinase
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No Observed Adverse Effect Level
nr-Axial SpA	nonradiographic axial spondyloarthritis
PBMC	peripheral blood mononuclear cell

PD	pharmacodynamic
PFS	prefilled syringe
PFS-U	PFS assembled in an UltraSafe Plus™ Passive Needle Guard
PGIC	Patient's Global Impression of Change (of Severity of Ulcerative Colitis)
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic
POC	proof-of-concept
PPP	palmoplantar pustulosis
PQC	product quality complaint
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PsA	psoriatic arthritis
q4w	every 4 weeks
q8w	every 8 weeks
RA	rheumatoid arthritis
RBS	rectal bleeding subscore
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TB	tuberculosis
TCR	tissue cross-reactivity
TK	toxicokinetic
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	white blood cell

Definitions of Terms

Data collection system (DCS)	Includes data collected via electronic case report forms (eCRFs) and ancillary systems such as the Interactive Web Response System (IWRS), patient-reported outcome (PRO) tablets, laboratory database and imaging database.
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.

10.2. Appendix 2: Definition of Inadequate Response to or Intolerance of Corticosteroids or AZA/6 MP and Corticosteroid Dependence

CORTICOSTEROIDS

Subjects 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.

Subjects 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.

Subjects are corticosteroid dependent if they have failed to successfully taper their corticosteroid (ie, had a flare of disease) within 3 months of starting therapy, or if a relapse occurs within 3 months after stopping corticosteroids or if they are unable to discontinue these agents without flare within 3 months after starting them.

6-MERCAPTOPURINE (6-MP) OR AZATHIOPRINE (AZA):

Subjects have failed to respond to 6-MP or AZA if they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving:

- At least 3 months of therapy with 1 mg/kg/day of 6-MP or 2 mg/kg/day of AZA.

  OR

- A lower dosage of 6-MP or AZA when country or local guidelines specify a different treatment regimen. (In such an event, the country 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 subject 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.

Subjects 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: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Participants should never be allowed to read their own tuberculin skin test results. If a participant fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a participant who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the participants may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). *Tuberculosis, a comprehensive international approach*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

10.4. Appendix 4: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy and Appendix 10.9 Adverse Events: 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**

  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

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.

As noted in Inclusion Criterion 13, study participants who are women of childbearing potential must be practicing a highly effective method of contraception and remain on a highly effective method while receiving study intervention and until 6 months after last dose. Examples of highly effective methods of contraception are provided below; however, the method selected must meet local/regional regulations/guidelines for highly effective contraception.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(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 should 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 should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy during the study

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

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.5. 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 total):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA test is **negative**, the participant ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this protocol.

These eligibility criteria based on HBV test results are also represented in Table 1 below.

Table 1: Eligibility based on hepatitis B virus test results

HEPATITIS B TEST RESULT			STATUS
Hepatitis B surface antigen (HBsAg)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	
negative	negative	negative	**Eligible**
negative	(+)	negative	
negative	(+)	(+)	
(+)	negative *or* (+)	negative *or* (+)	**Not eligible**
negative	negative	(+)	**(Require testing for presence of HBV DNA*)**

* If HBV DNA is detectable, the participant is not eligible for this protocol. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, the participant is not eligible for the protocol.

For participants who **are not eligible for this protocol due to HBV test results**, consultation with a physician with expertise in the treatment of HBV infection is recommended.

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

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), the latest version of the Declaration of Helsinki, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the Data Collection System (DCS) 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, 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 Food and Drug Administration [FDA] 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the 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 adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site

- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country 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 4.2.5, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.5.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

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

INFORMED CONSENT PROCESS

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may

entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

A participant may be rescreened 1 time. Participants who are rescreened are required to sign a new ICF.

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

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes 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. This consent also addresses the 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. 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.

Exploratory DNA, 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.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. The start of the storage period is defined as last participant last visit. Samples will only be used to understand guselkumab and golimumab, to understand UC, to understand differential intervention responders, and to develop tests/assays related to guselkumab and golimumab 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 Research Samples).

COMMITTEES STRUCTURE

Data Monitoring Committee

Details regarding the DMC are presented in Section 9.5.1.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding guselkumab and golimumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of guselkumab and golimumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Data for each study participant will be collected in the eCRF or ancillary data collection systems such as the IWRS, PRO tablets, laboratory database, and imaging database. Case report forms are prepared and provided by the sponsor for each participant in electronic format. Collectively, all data collection via eCRFs and ancillary systems will comprise what is referred to in this protocol as the DCS.

All DCS 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 eCRF are accurate and correct.

Study data will be transcribed by study-site personnel from source documentation to an eCRF or the appropriate ancillary DCS, as applicable. Study-specific data from each source will be transmitted in a secure manner to the sponsor.

Worksheets may be used as source documentation to capture data and facilitate completion of the eCRF or entry of data into the applicable ancillary data system. Data must be entered into the DCS in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

Necessary eCRF or ancillary data modifications can only be made by the investigator or appropriate site personnel using eCRF system functionality and/or ancillary data revision procedures. All data changes will be recorded in an audit trail.

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 should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source (eSource) system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

MONITORING

The sponsor will use a combination of monitoring techniques (central, remote, and on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site, as allowed by local regulation. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the applicable DCS component (as defined in the monitoring guidelines) with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source

documents will be identified to ensure that all sources of original data required to complete the applicable DCS component are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be

retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE CLOSURE

Study Termination

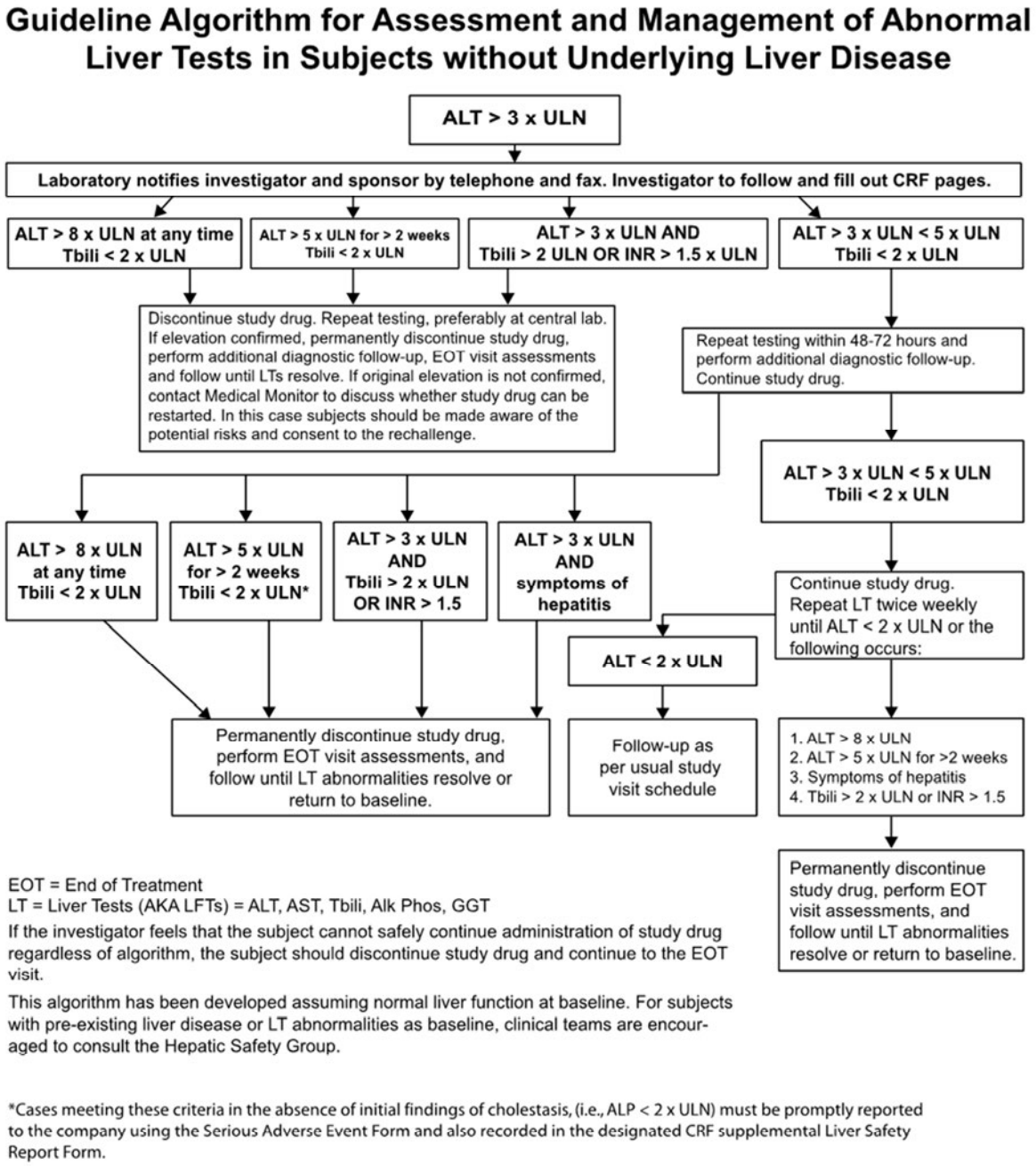
The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.7. Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments



*Cases meeting these criteria in the absence of initial findings of cholestasis, (i.e., ALP < 2 x ULN) must be promptly reported to the company using the Serious Adverse Event Form and also recorded in the designated CRF supplemental Liver Safety Report Form.

Abbreviations

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRF=case report form; EOT=end of treatment (end of intervention); GGT=gamma-glutamyltransferase; INR=international normalized ratio; LT/LFT=liver tests/liver function tests; Tbili=total bilirubin; ULN=upper limit of normal.

10.8. Appendix 8: Mayo Score

Mayo scoring system for assessment of ulcerative colitis activity

Stool frequency[a]
0 = Normal number of stools for this patient
1 = 1-2 stools more than normal
2 = 3-4 stools more than normal
3 = 5 or more stools more than normal

Rectal bleeding[b]
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passed

Findings of endoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment[c]
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

[a] At the screening visit, each person indicates the number of stools he/she passed in a 24-hour period when in remission or before his/her UC diagnosis, thereby serving as his/her own control to establish the degree of abnormality of stool frequency.
[b] The daily bleeding score represents the most severe bleeding of the day.
[c] The physician's global assessment acknowledges the 3 other criteria, the patient's recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

10.9. Appendix 9: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference 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 adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab and golimumab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB for guselkumab or for golimumab, respectively.

Adverse Event Associated With the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An adverse event that is not related to the use of the intervention.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant treatment(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the intervention. An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant treatment(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

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

SPECIAL REPORTING SITUATIONS

Special reporting situations must be reported by the investigator or site staff personnel to the sponsor or designee within 24 hours after being made aware of the event. Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study intervention, eg, name confusion)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number

- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a participant in a study within 16 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.10. Appendix 10: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

Adverse Events Associated with the Study Population

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

Reporting of Anticipated Events

All adverse events will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described under All Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described under Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study intervention, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

10.11. Appendix 11: Protocol Amendment History

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

Amendment 1 - 24 Sep 2018

Overall Rationale for the Amendment: The overall reason for the amendment is to incorporate health authority feedback on additional safety precautions. In addition, revisions were made to improve clarity and consistency in the protocol.

Section number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; 4.2.5 Study-Specific Ethical Design Considerations; 8 Study Assessments and Procedures	The protocol was revised to collect hematology and chemistry (including liver biochemistry) laboratory test results from every 4 weeks to every 2 weeks (Weeks 0, 2, 4, 6, 8, 10, and 12) during the combination comparison phase and from every 8 weeks to every visit (Weeks 14, 16, 18, 22, 24, 26, 30, 32, 34, and 38) during the monotherapy phase. The maximum total blood volume to be collected from each participant in the study was revised from approximately 265 mL to approximately 310 mL.	Hematology and chemistry (including liver biochemistry) tests will be collected more frequently to enhance safety monitoring.
8.2.5 Clinical Safety Laboratory Assessments	The following criteria for retesting were added under Hematology assessments in Section 8.2.5: Mandatory Re-testing The following hematology abnormalities require monitoring and re-testing (ideally within 3-5 days): - Absolute neutrophil count $<1.2 \times 10^3$ cells/µL (SI: $<1.2 \times 10^9$ cells/L) - Absolute lymphocyte count $<0.5 \times 10^3$ cells/µL (SI: $<0.5 \times 10^9$ cells/L) - Any single hemoglobin value <8.0 g/dL (SI: <80.0 g/L), or any decrease in hemoglobin >2.0 g/dL (SI: >20.0 g/L) from baseline - Platelet count $<100 \times 10^3$ cells/µL (SI: $<100 \times 10^9$ cells/L) The medical monitor or designee and the clinical site will be notified if these abnormal laboratory values are identified in any participant during the conduct of the study.	Monitoring and retesting for certain laboratory abnormalities were added to the protocol as a safety precaution.
7.1 Discontinuation of Study Intervention	The following criteria and note were added to the list of conditions for which discontinuation of a participants' study intervention must be <u>strongly considered</u>: 5. The participant has hematology abnormalities as described below: - Two sequential absolute neutrophil counts $<0.75 \times 10^3$ cells/µL (SI: $<0.75 \times 10^9$ cells/L) - Two sequential absolute lymphocyte counts	Discontinuation criteria for cytopenia (including lymphopenia and neutropenia) were added as a safety precaution.

Section number and Name	Description of Change	Brief Rationale
	$<0.5 \times 10^3$ cells/μL (SI: $<0.5 \times 10^9$ cells/L) - Two sequential hemoglobin values <8.0 g/dL (SI: <80.0g/L) or a decrease of >30% from baseline - Two sequential platelet counts $<75 \times 10^3$ cells/μL (SI: $<75 \times 10^9$ cells/L) Note: These laboratory abnormalities should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.	
1.3 Schedule of Activities	The following footnote was added to Hematology and chemistry on Table 1 and Table 2 of the Schedule of Activities: Certain laboratory abnormalities require re-testing and potential discontinuation of study intervention (See Sections 8.2.5 and 7.1, respectively).	Footnote was added to direct investigators to Sections 8.2.5 and 7.1 for laboratory values that may require retesting or potential discontinuation of study intervention, respectively.
7.1 Discontinuation of Study Intervention	The description of the first criterion under discontinuation of a participant's study intervention must be strongly considered under the following conditions was revised to say: 1. Persistent inadequate response or worsening of UC based on signs, symptoms, and/or laboratory values.	The description was clarified for investigators to strongly consider discontinuation based on signs, symptoms, and/or laboratory values for persistent inadequate response or worsening of UC.
1.3 Schedule of Activities; 6.1 Study Interventions Administered	The following was added as a footnote to Week 0, Administer study intervention on Table 1 of the Schedule of Activities and to Section 6.1: For the baseline (W0) visit, the IV study intervention should be administered first. The SC study intervention should be administered approximately 30 minutes after the IV study intervention infusion is complete.	Clarify when the IV and SC study interventions should be administered at Week 0.
5.1 Inclusion Criteria	Inclusion criterion #7b was revised to discontinue vedolizumab from at least 8 weeks to at least 18 weeks before the first administration of study intervention: 7 b. Vedolizumab for at least 18 weeks.	The washout period for vedolizumab was revised to 18 weeks to be consistent with the serum half-life of vedolizumab.
5.1 Inclusion Criteria; 5.2 Exclusion Criteria; 8 Study Assessments; 10.3 Appendix 3: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	For the following inclusion criteria, the time frame for precautions for reproduction was revised from 16 weeks to 6 months: 13 b. 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 6 months after last dose (ie, the end of relevant systemic exposure). 14. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 6 months after the last study intervention. 16. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after receiving the last dose of study intervention.	The time frame for participants to use a highly effective method of contraception and to continue taking precautions after receiving the last administration of study intervention was revised from 16 weeks to 6 months to align with the longest duration defined for SIMPONI.

Section number and Name	Description of Change	Brief Rationale
	The following exclusion criterion revised the timeframe for precautions for reproduction from 16 weeks to 6 months: 35. Is a woman who is pregnant, or breast-feeding, or planning to become pregnant, or is a man who plans to father a child while enrolled in this study or within 6 months after the last dose of study intervention.	
5.2 Exclusion Criteria	Exclusion criterion #1c.4) was revised from >90 beats/minute to >100 beats/minute: 1 c. 4) Tachycardia (>100 beats/minute)	The exclusion criterion for tachycardia was increased to >100 beats/minute since the normal adult heart rate has been considered historically to range from 60 to 100 beats per minute, with sinus tachycardia being defined as a sinus rhythm with a rate exceeding 100 beats per minute.
5.2 Exclusion Criteria	Exclusion criteria #12c and #12d were modified to include a time frame: 12 c. Natalizumab within 12 months of first study intervention administration. 12 d. Agents that deplete B or T cells (eg, rituximab, alemtuzumab) within 12 months of first study intervention administration, or continue to manifest depletion of B or T cells more than 12 months after completion of therapy with lymphocyte-depleting agents.	A time frame of 12 months was specified for patients who previously received natalizumab or agents that deplete B or T cells.
6.5.1 Concomitant Medications	Conventional immunomodulators (ie, 6-MP, AZA, or MTX) were removed from the list of concomitant UC-specific medical therapies that enrolled participants should not initiate.	Conventional immunomodulators are listed under prohibited concomitant medications; therefore, participants who initiate 6-MP, AZA, or MTX during the study will have their study intervention discontinued.
7.1 Discontinuation of Study Intervention	The following criterion was added to the list of conditions for which a participant's study treatment intervention must be discontinued: 13. The participant develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA.	This criterion was added as a safety precaution.
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: _____

_____

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_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Yasmine Wasfi, MD, PhD

Institution: Janssen Research & Development

Signature: PPD Date: PPD
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 7 March 2019