Janssen Research & Development*

Clinical Protocol

Protocol Title

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

GALAXI

Short Title

A Study of the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Crohn's Disease

Protocol CNTO1959CRD3001; Phase 2/3
AMENDMENT 5

CNTO 1959 (guselkumab)

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

EudraCT NUMBER: 2017-002195-13

Status: Approved
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Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-136754231, 7.0

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 5	12 July 2022
Amendment 4	21 July 2021
Amendment 3	20 October 2020
Amendment 2	13 November 2019
Amendment 1	10 December 2018
Original Protocol	06 December 2017

Amendment 5 (12 July 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Minor changes, such as those made for editorial purposes, or to correct grammatical or typographical errors, are not described.

Overall Rationale for the Amendment:

After review of the Phase 2 (GALAXI 1) Week 48 database lock (DBL) results, the Sponsor engaged in negotiations with Health Authorities regarding the Phase 3 study endpoints and analyses. Following negotiations with health authorities, the co-primary endpoints in the original GALAXI Phase 3 studies were modified for the United States (US) and other countries/territories throughout the world as applicable, creating Global co-primary endpoints. As other health authorities preferred the Week 12 co-primary endpoints be retained, these endpoints are now labeled as Regional co-primary endpoints.

Protocol Amendment 5 now contains two modules within the Endpoints and Hypothesis Section 3.2.2 for the Phase 3 studies (GALAXI 2 and GALAXI 3). The first module refers to the Global Endpoints and Hypotheses where the co-primary endpoints have been modified to composite endpoints that reflect short-term and long-term efficacy of guselkumab versus placebo. These co-primary endpoints are also consistent with the recent STRIDE guidelines that support a treatment goal of early clinical response prior to achievement of clinical and endoscopic long-term goals (Turner 2021). The major secondary endpoints have also been adjusted to incorporate evaluation of long-term efficacy of guselkumab versus placebo as well as ustekinumab.

The second module in the Endpoints and Hypothesis Section 3.2.2 refers to Regional Endpoints and Hypotheses where the original co-primary endpoints have been retained for the Phase 3 studies. The original major secondary endpoints, including those to assess long-term efficacy, have also been retained. Consistent with the Global approach, corticosteroid-free clinical remission at Week 48 and endoscopic response at Week 48 have been added to the Regional major secondary endpoints to evaluate the long-term efficacy of guselkumab vs. placebo. Finally, a composite endpoint of clinical remission at Week 48 and endoscopic response at Week 48 in the same

participant has been added to the Global and Regional major secondary endpoints. This composite endpoint is also consistent with the STRIDE guidelines where improvement in both clinical and endoscopic long-term outcomes should be targeted in the same participant (Turner 2021).

In addition, the sample size required to appropriately power the Global co-primary endpoints and the Regional co-primary endpoints, as well as key Regional major secondary endpoints to demonstrate the long-term efficacy of guselkumab versus placebo, was reassessed based on the Week 48 DBL results from the Phase 2 (GALAXI 1) study and was reduced from the original size. Based on this assessment, a total Phase 3 sample size of approximately 980 participants (approximately 490 participants in each Phase 3 study) will provide adequate power and an adequate number of participants to assess the safety of guselkumab in Crohn's disease. The reduced sample size provides the opportunity to obtain appropriate scientific data while reducing the number of participants exposed to placebo. Of note, the decision to reduce the sample size was not based on knowledge of any data from the Phase 3 GALAXI studies, as these studies are still blinded and will remain blinded to the Sponsor until the Week 48 database lock.

The changes made to the clinical protocol CNTO1959CRD3001 as part of Protocol Amendment 5 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.15, Appendix 15: Protocol Amendment History.

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

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Section Number and Name	Description of Change	Brief Rationale
	[redacted]	
[redacted]	[redacted]	[redacted] ed.
1.3. SoA; Table 3	Updated footnote h and i.	To allow study evaluations through telehealth visit; to clarify that CDAI assessments may be done at on-site study visit.
2. Introduction	Removed text regarding regulatory status of guselkumab which is found in the Investigator Brochure.	To streamline the protocol.
4.1. Overall Design; 10.14. Appendix 14	Added guidance on study conduct during major disruption.	To provide guidance on study conduct during major disruption.
4.1.3.4. Endpoints and Evaluations	Removed LTE Database lock at Week 144 and Week 192.	To update the LTE database lock plan.
5.1. Inclusion Criteria #4	Added a note to clarify guidance for handling polyps identified during ileocolonoscopy.	Clarification
5.1. Inclusion Criteria; 5.2. Exclusion Criteria; 10.4. Appendix 4	• Removed "limited" from Inclusion Criterion #5 and Exclusion Criterion #7. • Added review by medical monitor/sponsor of ustekinumab exposed participants in specific circumstances.	Feedback from sites suggests that ustekinumab exposed participants (those who do not have inadequate response) often are treated beyond a single induction dose and a single maintenance dose
5.1. Inclusion Criteria #8; 8.2.6. Tuberculosis Evaluations	Updated handling of potential false positive results in the initial TB evaluations.	To be consistent with current guidance on TB evaluations.
5.2. Exclusion Criteria #20	Added a note pertaining to premalignant conditions.	Clarification
5.2. Exclusion Criteria #31	Added "or sponsor" to "investigator".	Clarification
6.5.2. Prohibited Concomitant Medications	Added IL-23 antagonists to list of prohibited concomitant medications.	Updated based on approved medication availability for Crohn's disease
9. Statistical Considerations	Added SAP to cover LTE.	Clarification on SAPs covering the core and LTE study periods.
9.1.2. Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)	Removed text for the co-primary and major secondary hypotheses and referred to Section 3.2.3.	To minimize redundancy, some sections were removed and cross-referenced appropriately.
10.2. Appendix 2	Removed "within the past 5 years" from the sentence below: • 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, AZA, or MTX to treat Crohn's disease ~~within the past 5 years~~.	Clarification on timing of documentation of intolerance.

Section Number and Name	Description of Change	Brief Rationale
10.3. Appendix 3	The paragraph after item 1.b.6 was moved to follow item 2.d.2 and modified slightly.	To clarify that the paragraph applies to both primary non-responders and to secondary non-responders.
10.12. Appendix 12	Updated guidelines on anticipated events.	To align with current protocol guidelines.
Throughout the protocol	Minor grammatical, formatting, or spelling errors and inconsistency were corrected.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Protocol number: CNTO1959CRD3001

EudraCT Number: 2017-002195-13

OVERVIEW OF PROTOCOL

The clinical development program for guselkumab in Crohn's disease is designed to evaluate the safety and efficacy of guselkumab compared with placebo and an active control (ustekinumab) and will be conducted under this single protocol: a Phase 2/3, randomized, double-blind, placebo- and active-controlled (ustekinumab), parallel-group, multicenter protocol to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active Crohn's disease who have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy.

Under this protocol, there are 3 separate studies: a 48-week Phase 2 dose-ranging study (ie, GALAXI 1) and 2 identical 48-week Phase 3 confirmatory studies (ie, GALAXI 2 and GALAXI 3). Participants who complete the 48-week Phase 2 or Phase 3 studies may be eligible to enter the long-term extension (LTE [Week 48 to Week 252]) and receive approximately 4 additional years of treatment. The overall Phase 2/3 development program will enroll approximately 1,340 participants with a total duration for each participant of up to approximately 5 years.

OBJECTIVES AND HYPOTHESES

Phase 2 Dose-Ranging Study (GALAXI 1)

Objectives

- Primary Objectives
  - To evaluate the clinical efficacy of guselkumab in participants with Crohn's disease
  - To evaluate the safety of guselkumab
- Secondary Objectives
  - To evaluate the dose-response of guselkumab to inform dose selection for the Phase 3 portion of this protocol
  - To evaluate the efficacy of guselkumab on endoscopic improvement
  - To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of guselkumab therapy, including changes in C-reactive protein (CRP) and fecal calprotectin
- Other Objectives
  - To evaluate the impact of guselkumab on health-related quality of life (HRQOL) and health economics outcome measures
  - To evaluate the efficacy of guselkumab on histologic improvement
  - To evaluate the impact of treatment with guselkumab on intestinal mucosal gene expression profiles and cellular composition associated with Crohn's disease

Hypothesis

The primary hypothesis for GALAXI 1 is that guselkumab is superior to placebo in inducing a reduction from baseline in the Crohn's Disease Activity Index (CDAI) score in participants with moderately to severely active Crohn's disease.

Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)

GALAXI 2 and GALAXI 3 are identical studies and have the same objectives and hypotheses, as described below.

Objectives

- Primary Objectives
  - To evaluate the clinical and endoscopic efficacy of guselkumab in participants with Crohn's disease
  - To evaluate the safety of guselkumab
- Secondary Objectives
  - To evaluate the impact of guselkumab on HRQOL
  - To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin
- Other Objectives
  - To evaluate the impact of guselkumab on health economics outcome measures
  - To evaluate the efficacy of guselkumab on histologic improvement
  - To evaluate the impact of treatment with guselkumab on intestinal mucosal gene expression profiles and cellular composition associated with Crohn's disease

Hypothesis

The protocol will contain two modules for co-primary and major secondary endpoints. The first module will be referred to as Global and will apply to the US and other countries/territories around the world where the co-primary endpoints have been modified as below. The second module will be referred to as Regional and will apply to those countries/territories who will retain the original protocol Week 12 co-primary endpoints.

Global Hypotheses

The co-primary hypotheses will be tested within each of GALAXI 2 and GALAXI 3 separately.

The co-primary hypotheses are that guselkumab is superior to placebo in achieving:

- clinical response at Week 12 and clinical remission at Week 48
- clinical response at Week 12 and endoscopic response at Week 48

Regional Hypotheses

The co-primary hypotheses will be tested within each of GALAXI 2 and GALAXI 3 separately.

The co-primary hypotheses are that guselkumab is superior to placebo in achieving:

- clinical remission at Week 12
- endoscopic response at Week 12

OVERALL DESIGN

Under this protocol, there are 3 separate studies: a 48-week Phase 2 dose-ranging study (ie, GALAXI 1) and 2 identical 48-week Phase 3 confirmatory studies (ie, GALAXI 2 and GALAXI 3). All 3 studies will be conducted using a treat-through study design, ie, participants are randomized to treatment regimens at Week 0 and will remain on that treatment regimen through at least Week 48 of each study, unless otherwise indicated.

In the Phase 2 dose-ranging study (ie, GALAXI 1), the safety and efficacy of guselkumab dose regimens spanning a wide induction and maintenance dose range will be evaluated to support the selection of induction and maintenance dose regimens for confirmatory evaluation in Phase 3. It is estimated that 250 to 500 participants may be required to select the dose regimens that will be evaluated in Phase 3. Therefore, the first 250 participants in GALAXI 1 will be enrolled into an Initial Dose Decision Cohort. Since data from more participants may be required to inform the dose decision, the sponsor may elect to continue enrollment and newly enrolled participants (ie, starting from participant #251) will be randomized into a Transition Cohort while the data from the Initial Dose Decision Cohort are being collected and analyzed. If the decision is made to proceed with enrollment into the Transition Cohort, it is anticipated that a maximum of approximately 250 additional participants will be enrolled into GALAXI 1 (ie, 250 in the Initial Dose Decision Cohort and up to 250 in the Transition Cohort) prior to the dose decision. If a dose decision for Phase 3 is not made by the time the 500th patient is randomized, enrollment will be paused until a decision for Phase 3 dosing, or a decision to terminate the development program, is made.

This is an operationally seamless protocol in countries where the local health authorities have approved a seamless transition. In the countries that have approved a seamless transition, there will be no break in enrollment between the Phase 2 and Phase 3 studies if enrollment continues into the Transition Cohort and a dose decision can be made before 500 patients are randomized. Transition from the Phase 2 portion to the Phase 3 portion of the protocol will occur once the dose decision for Phase 3 has been made and implemented. In countries where the local health authority requires additional regulatory approval prior to initiating the Phase 3 studies, enrollment will pause until approval is received. In all countries, all participants randomized after the dose decision has been implemented will be part of the Phase 3 studies.

In the Phase 3 dose-confirming studies (ie, GALAXI 2 and GALAXI 3), the safety and efficacy of the selected guselkumab dose regimens will be evaluated. GALAXI 2 and GALAXI 3 are identical from a study design perspective. The goal of conducting two replicate studies is to achieve independent confirmation of clinical efficacy in two independent samples of patients, which is required by some health authorities. A target of approximately 490 participants will be enrolled in each of the Phase 3 studies, for a total target sample size of approximately 980 participants in the Phase 3 portion of the protocol.

Participants who complete the 48-week Phase 2 or Phase 3 studies may be eligible to enter the LTE to receive approximately 4 additional years of treatment.

Target Population

The target population in all 3 studies under this protocol will consist of participants ≥18 years of age at the time of informed consent with moderately to severely active Crohn's disease (of at least 3 months' duration). Participants must have colitis, ileitis, or ileocolitis previously confirmed by radiography, histology, and/or endoscopy.

Active Disease Criteria

At baseline, participants must have active Crohn's disease, defined as follows:

1. Clinically active Crohn's disease
2. Endoscopic evidence of ileocolonic Crohn's disease

Medication History Criteria

In addition, a broad participant population eligible for systemic therapy will be evaluated in this protocol and will include participants who have demonstrated an inadequate response or failed to tolerate previous conventional therapy or biologic therapy.

Note that participants with prior exposure to interleukin (IL)-12/23 or IL-23 agents are ineligible for entry into this protocol, with the exception of participants who have had exposure to and who have not demonstrated failure or intolerance to ustekinumab.

Evaluations

Throughout the 3 studies, efficacy, PK, biomarkers, and safety will be assessed at time points indicated in the appropriate Schedule of Activities.

An external Independent Data Monitoring Committee (DMC), with defined roles and responsibilities as governed by a DMC charter, will assess the safety of participants across the 3 studies. The DMC's initial responsibility will be careful review of the safety data from the first 25 participants randomized and treated in GALAXI 1. After that, ongoing safety data reviews will continue as specified in the DMC charter. After each review, the DMC will make recommendations to the sponsor about the continuation of the studies.

End of study

For each of the 3 studies conducted under this protocol, the studies are considered completed when the last participant completes the last scheduled study assessment or if a decision has been made by the sponsor not to pursue an indication in Crohn's disease and appropriate follow-up has been completed. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

NUMBER OF PARTICIPANTS

The overall GALAXI Phase 2/3 protocol will enroll a total of approximately 1,340 participants with a total duration for each participant of up to approximately 5 years.

INTERVENTION GROUPS AND DURATION

Phase 2 Dose-Ranging Study (GALAXI 1)

All participants in the Phase 2 study will be randomized to 1 of 5 treatment groups as described below. Participants will remain on their assigned treatment regimens through the end of the 48-week study, unless otherwise specified.

Group 1: Guselkumab Regimen 1 CCI [redacted]

Participants will receive guselkumab CCI [redacted] from Week 0 through Week 8 (ie, total of 3 C [redacted] doses). At Week 12, participants will continue treatment with guselkumab CCI [redacted] through Week 44.

Group 2: Guselkumab Regimen 2 CCI [redacted]

Participants will receive guselkumab CCI [redacted] from Week 0 through Week 8 (ie, total of 3 C [redacted] doses). At Week 12, participants will continue treatment with guselkumab CCI [redacted] through Week 44.

Group 3: Guselkumab Regimen 3 [redacted]

Participants will receive guselkumab [redacted] from Week 0 through Week 8 (ie, total of 3 [redacted] doses). At Week 16, participants will continue treatment with guselkumab [redacted] through Week 40.

Group 4: Active Control, Ustekinumab [redacted]

Participants will receive a single ustekinumab [redacted] induction dose at Week 0 (weight-based [redacted] doses approximating [redacted] as outlined below). At Week 8, participants will receive ustekinumab [redacted] maintenance [redacted] through Week 40.

- Ustekinumab [redacted] (weight ≤55 kg)
- Ustekinumab [redacted] (weight >55 kg and ≤85 kg)
- Ustekinumab [redacted] (weight >85 kg)

Group 5: Placebo → Placebo or Ustekinumab Crossover

Participants will receive placebo [redacted] from Week 0 through Week 8 (ie, total of [redacted] doses). At Week 12, participants will continue treatment based on their clinical response status as follows:

- **Placebo responders:** Continue placebo treatment [redacted] from Week 12 through Week 44.
- **Placebo nonresponders:** Receive a single ustekinumab [redacted] induction dose at Week 12 (weight-based [redacted] doses approximating [redacted] as outlined above). At Week 20, participants will receive ustekinumab [redacted] maintenance [redacted] through Week 44.

Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)

Based on the Phase 2 data, 2 guselkumab dose regimens (ie, [redacted] induction → [redacted] maintenance) were selected for confirmatory evaluation in Phase 3. Identical dose regimens are to be evaluated in both Phase 3 studies.

Group 1: Guselkumab Regimen 1 [redacted]

Participants will receive guselkumab [redacted] from Week 0 through Week 8 (ie, total of 3 [redacted] doses). At Week 12, participants will continue treatment with guselkumab [redacted] through Week 44.

Group 2: Guselkumab Regimen 2 [redacted]

Participants will receive guselkumab [redacted] from Week 0 through Week 8 (ie, total of 3 [redacted] doses). At Week 16, participants will continue treatment with guselkumab [redacted] through Week 40.

Group 3: Active Control – Ustekinumab [redacted]

(Same as in GALAXI 1 above)

Group 4: Placebo → Placebo or Ustekinumab Crossover

(Same as in GALAXI 1 above)

EFFICACY EVALUATIONS AND ENDPOINTS

Efficacy evaluations will include the following:

- Crohn's Disease Activity Index (CDAI)
- PRO-2 (the unweighted CDAI components of the total number of liquid or very soft stools and the abdominal pain score)
- Endoscopic assessments based on the presence and absence of mucosal ulcerations and the Simple Endoscopic Score for Crohn's Disease (SES-CD)
- Histologic assessments based on the Global Histology Activity Score
- Inflammatory PD markers including CRP and fecal calprotectin
- Fistula assessment
- HRQOL outcome measures including Inflammatory Bowel Disease Questionnaire, Patient-Reported Outcomes Measurement Information System (PROMIS)-29, PROMIS Fatigue Short Form 7a, and 5-level EuroQol five dimensions instrument
- Health economics outcome measures including the Work Productivity and Activity Impairment Questionnaire in Crohn's disease
- Exploratory patient-reported symptom measures including Bristol Stool Form Scale, Abdominal Pain – Numerical Rating Scale, Patient's Global Impression of Severity of Crohn's Disease, and Patient's Global Impression of Change of Severity of Crohn's Disease

Endpoints in the Phase 2 Study (GALAXI 1)

The primary endpoint and major secondary endpoints evaluate the short-term efficacy of guselkumab versus placebo. These endpoints are described below.

- Primary Endpoint
  - Change from baseline in the CDAI score at Week 12.
- Major Secondary Endpoints
  - Clinical remission at Week 12 (defined as CDAI score <150).
  - Clinical response at Week 12 (defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150).
  - PRO-2 remission at Week 12 (defined as an abdominal pain [AP] mean daily score at or below 1 [ie, AP≤1] AND a stool frequency [SF] mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline).
  - Clinical-biomarker response at Week 12 (clinical response based on CDAI score and ≥50% reduction from baseline in CRP or fecal calprotectin).
  - Endoscopic response at Week 12 (defined as at least 50% improvement from baseline in the SES-CD score or SES-CD score ≤2).

Endpoints in the Phase 3 Studies (GALAXI 2 and GALAXI 3)

GALAXI 2 and GALAXI 3 have the same primary and major secondary endpoints, whether Global or Regional.

Global Co-primary Endpoints

The Global co-primary endpoints are:
- clinical response at Week 12 and clinical remission at Week 48
- clinical response at Week 12 and endoscopic response at Week 48

For these endpoints, comparisons will be made within each study between each guselkumab dose (guselkumab CCI [redacted] and placebo.

Global Major Secondary Endpoints

The Global major secondary endpoints are grouped into 3 categories based on timepoint and comparator; note that these are grouped for the purpose of categorization but are not presented in the order of testing in the multiplicity-controlled testing procedure (the specific order for the testing procedure will be provided in the statistical analysis plan).

The following Global major secondary endpoints evaluate the short-term efficacy of guselkumab versus placebo in each study:

- Clinical response at Week 4
- Clinical remission at Week 12
- Endoscopic response at Week 12
- Fatigue response at Week 12
- Clinical remission at Week 12 and endoscopic response at Week 12
- Endoscopic remission (Global definition) at Week 12

The following long-term endpoints evaluate guselkumab versus placebo in each study:

- Clinical response at Week 12 and corticosteroid-free clinical remission at Week 48
- Clinical response at Week 12 and endoscopic remission (Global definition) at Week 48

The following long-term endpoints evaluate guselkumab versus ustekinumab:

- Clinical remission at Week 48
- Endoscopic response at Week 48
- Clinical remission at Week 48 and endoscopic response at Week 48
- Endoscopic remission (Global definition) at Week 48
- Deep remission (Global definition) at Week 48

Regional Co-primary Endpoints

The Regional co-primary endpoints are:

- clinical remission at Week 12
- endoscopic response at Week 12

For these endpoints, comparisons will be made within each study between the combined guselkumab induction dose group and placebo.

Regional Major Secondary Endpoints

The Regional major secondary endpoints are grouped into 3 categories based on timepoint and comparator; note that these are grouped for the purpose of categorization but are not presented in the order of testing in the multiplicity-controlled testing procedure (the specific order for the testing procedure will be provided in the statistical analysis plan).

The following Regional major secondary endpoints evaluate the short-term efficacy of guselkumab versus placebo:

- PRO-2 remission at Week 12
- Fatigue response at Week 12
- Endoscopic remission (Regional definition) at Week 12

The following long-term endpoints evaluate guselkumab versus placebo:

- Corticosteroid-free clinical remission at Week 48
- Endoscopic response at Week 48

The following long-term endpoints evaluate guselkumab versus ustekinumab:

- Endoscopic remission (Regional definition) at Week 48
- Clinical remission at Week 48
- Endoscopic response at Week 48
- Durable clinical remission at Week 48
- PRO-2 remission at Week 48
- Clinical remission at Week 48 and endoscopic response at Week 48
- Corticosteroid-free remission at Week 48

PHARMACOKINETIC EVALUATIONS

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

IMMUNOGENICITY EVALUATIONS

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

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Inflammatory PD markers (CRP and fecal calprotectin) will be evaluated. Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab or ustekinumab treatment and/or Crohn's disease. Assessments will include the evaluation of relevant biomarkers in serum, whole blood, stool, and ileocolonic biopsy samples.

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample will be collected from participants who consent to this component of the protocol to allow for pharmacogenomic research as necessary where local regulations permit. Participation in pharmacogenomic research is optional. Deoxyribonucleic acid (DNA) samples will be analyzed for identification of genetic factors that may be associated with clinical response.

MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS EVALUATIONS

Medical resource utilization, including but not limited to Crohn's disease-related hospitalizations and surgeries, will be collected in the studies. The Work Productivity and Activity Impairment Questionnaire in Crohn's Disease will also be utilized to evaluate work productivity.

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 evaluation and other infection assessment, clinical laboratory blood tests (complete blood count and serum chemistries), vital signs (as defined in the Schedule of Activities), suicidality assessment, concomitant medication review, and observations for injection-site reactions, reactions temporally associated with an infusion, and/or allergic reactions.

STATISTICAL METHODS

Sample Size Calculation

Taking into account a mixed biologic therapy failure or intolerance (BIO-Failure)/conventional therapy failure or intolerance (CON-Failure) population in this program, sample size assumptions for the overall

randomized population were based on the ratio of an approximate 25% to 50% of participants in the CON-Failure patient population.

Phase 2 Dose-Ranging Study (GALAXI 1)

The sample size is based on statistical power considerations (for both the Initial Dose Decision Cohort and the Total Phase 2 Population) and the objective of selecting induction and maintenance dose regimens for confirmatory evaluation in Phase 3.

Assuming the mean CDAI reductions from baseline at Week 12 of approximately 105 to 115 in the guselkumab high [redacted] induction dose group versus approximately 45 to 50 in the placebo group with a common standard deviation of 100, for the Initial Dose Decision Cohort, 50 participants per treatment group (with 250 participants in total) will provide greater than 80% power to detect a treatment difference between guselkumab high [redacted] induction dose group and placebo using a 2-sample t-test at the α=0.05 (2-sided) level. For the Total Phase 2 Population, based on the minimum number of participants (70 per treatment group and 350 in total), the power is greater than 90% for the change from baseline in the CDAI score at Week 12, and greater than 85% for clinical remission at Week 12 assuming clinical remission rates of approximately 12% to 15% for placebo and approximately 35% to 40% for the guselkumab high [redacted] induction dose at Week 12.

Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)

GALAXI 2 and GALAXI 3 are separate studies and will have separate type I error control at the 2-sided 0.05 significance level.

The power for the key endpoints in these Phase 3 studies (ie, Global co-primary endpoints, Regional co-primary endpoints, Regional endpoints of corticosteroid-free clinical remission at Week 48 and endoscopic response at Week 48 [which are meant to demonstrate the long-term efficacy of guselkumab versus placebo]), as well as the adequate number of participants needed to assess the safety of guselkumab in Crohn's disease, were considered in determining the appropriate sample size for these Phase 3 studies. Based on this, a total sample size of approximately 980 participants (approximately 490 participants per study, consisting of 140 participants in each of the two guselkumab treatment groups, 70 participants in the placebo treatment group, and 140 participants in the ustekinumab group) will provide at least 90% power for these key endpoints in each study.

Global Co-primary Endpoints:

For the co-primary endpoint of clinical response at Week 12 and clinical remission at Week 48: In each of the Phase 3 studies, assuming a rate of 8% to 10% for placebo and a minimum of a 40% difference between guselkumab and placebo based on Phase 2 (GALAXI 1) results, 140 participants in each guselkumab dose group and 70 participants in the placebo group will provide >99% power for this endpoint at the 0.05 (2-sided) alpha level.

For the co-primary endpoint of clinical response at Week 12 and endoscopic response at Week 48: In each of the Phase 3 studies, assuming a rate of approximately 2% to 5% for placebo and a minimum of a 30% difference between guselkumab and placebo based on Phase 2 (GALAXI 1) results, 140 participants in each guselkumab dose group and 70 participants in the placebo group will provide >99% power for this endpoint at the 0.05 (2-sided) alpha level.

Regional Co-primary Endpoints:

For the co-primary endpoint of clinical remission at Week 12: In each of the Phase 3 studies, assuming a clinical remission at Week 12 rate of approximately 10% to 15% for placebo and a 35-40% difference between guselkumab and placebo based on Phase 2 (GALAXI 1) results, 280 participants in the combined guselkumab induction dose group and 70 participants in the placebo group, respectively, will provide greater than 99% power for clinical remission at Week 12 at an overall Type 1 error rate controlled at 0.05 (2-sided).

For the co-primary endpoint of endoscopic response at Week 12: In each of the Phase 3 studies, assuming an endoscopic response at Week 12 rate of approximately 10% to 13% for placebo and a 20% to 25% difference between guselkumab and placebo based on Phase 2 (GALAXI 1) results, 280 participants in the combined guselkumab induction dose group and 70 participants in the placebo group, respectively, will provide approximately 95% power for endoscopic response at Week 12 at an overall Type 1 error rate controlled at 0.05 (2-sided).

Statistical Analyses for Phase 2 Dose-Ranging Study (GALAXI 1)

Primary Efficacy Analysis

The primary efficacy analysis is based on the Full Analysis Set, defined as all participants who are randomized and who have received at least 1 dose of study intervention in GALAXI 1. The primary endpoint of the change from baseline in the CDAI score at Week 12 will be analyzed using a Mixed Model for Repeated Measures (MMRM) approach.

Major Secondary Efficacy Analyses

The major secondary endpoints of clinical remission (either based on CDAI or on PRO-2), clinical response, and clinical-biomarker response at Week 12 will be compared between each guselkumab dose group and the placebo group using the Cochran-Mantel-Haenszel (CMH) test (2-sided) stratified by baseline CDAI score (≤300 or >300) and BIO-Failure status (Yes/No), at a significance level of 0.05. Endoscopic response at Week 12 will be compared between each guselkumab dose group and the placebo group using the CMH test (2-sided) stratified by SES-CD score (≤12 or >12) and BIO-Failure status (Yes/No), at a significance level of 0.05.

A multiple testing procedure to control the Type 1 error at α=0.05 (2-sided) over the primary and major secondary endpoints will be prespecified in the Phase 2 SAP.

Statistical Analyses for Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)

GALAXI 2 and GALAXI 3 have identical study designs, objectives, and endpoints. Efficacy analyses within each study will be based on the Primary Analysis Set for that study, which includes all randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).

Primary Efficacy Analysis

Global Primary Analysis

For testing of the *Global co-primary endpoints*, the efficacy of each dose of guselkumab versus placebo will be compared. A CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) will be used.

To control the Type I error at the 2-sided 0.05 significance level, a fixed sequence testing approach will be used for the co-primary endpoints in each study separately. Specifically, the sequential testing will begin with the guselkumab CCI [redacted] CCI group with the following 2 co-primary endpoints tested sequentially:

- clinical response at Week 12 and clinical remission at Week 48
- clinical response at Week 12 and endoscopic response at Week 48

followed by the guselkumab CCI [redacted] group with the same co-primary endpoints tested sequentially:

- clinical response at Week 12 and clinical remission at Week 48
- clinical response at Week 12 and endoscopic response at Week 48

Each study will be considered positive if the CCI [redacted] guselkumab group is significantly different from the placebo group for both of the co-primary endpoints.

Regional Primary Analysis

For testing of the *Regional co-primary endpoints*, the efficacy of the induction dose of guselkumab versus placebo will be compared. As such, within each study, the two guselkumab groups that are randomized to receive identical guselkumab induction treatment through Week 12 will be combined for these comparisons. To control the Type I error at the 2-sided 0.05 significance level, a fixed sequence testing approach will be used with the following 2 co-primary endpoints tested sequentially:

- clinical remission at Week 12
- endoscopic response at Week 12

A CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) will be used.

Major Secondary Efficacy Analyses

Within each study, the major secondary endpoints will be compared between the combined guselkumab induction dose group and the placebo group (for short-term endpoints) or between each guselkumab dose group and the placebo group (or ustekinumab group) for long-term endpoints. For all 3 types of comparisons, the CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) will be used.

A testing procedure to control the Type-I error at the 2-sided 0.05 significance level for the co-primary endpoints and the major secondary endpoints will be performed for each study separately. Furthermore, there will be separate testing procedures for the Global and Regional endpoints. Each study will be tested with a separate testing procedure. Within each study's Global testing procedure, some tests of each guselkumab group vs. ustekinumab may be based on data pooled across studies.

Other Planned Analyses

Pharmacokinetic Analyses

Serum guselkumab and ustekinumab concentrations will be summarized for each guselkumab/ustekinumab treatment group over time using descriptive statistics. A population PK analysis using a nonlinear mixed-effects model will be used to characterize the PK of guselkumab. The influence of important covariates on the population PK parameter estimates may be evaluated. Details will be provided in a population PK analysis plan, and results of the population PK analysis will be presented in a separate technical report.

Immunogenicity Analyses

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

Biomarker Analyses

Changes in serum protein analytes and whole blood ribonucleic acid (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. RNA analyses will be summarized in a separate technical report.

Pharmacokinetic/Pharmacodynamic Analyses

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

Medical Resource Utilization and Health Economics Analyses

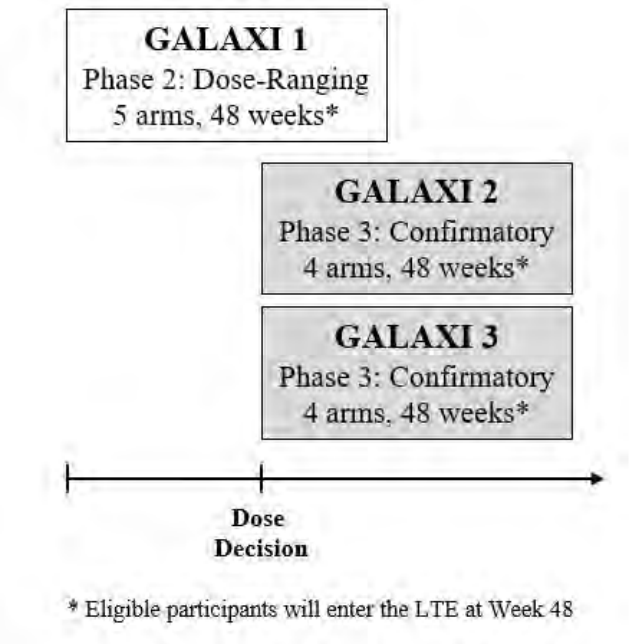
Medical resource utilization and health economics, including work productivity, will be summarized by treatment group.

Safety Analyses

Safety analyses will include summaries of AEs and laboratory parameters. These summaries will be based on participants who received at least 1 dose of study intervention in each respective study.

1.2. Schema

Figure 1: Overview of the GALAXI Phase 2/3 Protocol



1.3. Schedule of Activities (SoA)

Table 1: SoA – Screening Activities of GALAXI 1, GALAXI 2, and GALAXI 3

Study Procedures	SCR (-5 wks)	Notes
Administrative		
Informed consent	X	
Inclusion/exclusion criteria	X	
Medical history and demographics	X	
ECG	X	
Chest radiograph	X	Chest radiograph (posterior-anterior and lateral views) must be obtained within 12 weeks before the Week 0 visit.
QuantiFERON®-TB In-Tube Test (or T-SPOT® Test for sites in Japan)	X	All participants will undergo QuantiFERON-TB testing (or T-SPOT test for sites in Japan where local regulations permit). A tuberculin skin test is additionally required if the QuantiFERON-TB test is not approved/registered in the country in which this protocol is being conducted. The QuantiFERON-TB and the tuberculin skin tests are not required at screening for participants with a history of latent TB, if active TB has been ruled out, and if appropriate treatment has been initiated/completed (as described in Inclusion Criterion 8).
Stool studies to evaluate for enteric pathogens	X	Stool studies for enteric pathogens may be performed at screening at either the central or a local laboratory and must include a stool culture and *Clostridioides difficile* (formerly known as *Clostridium difficile)* toxin assay. Although stool studies may be processed at either the central or local laboratory, the central laboratory is preferred when available. Stool studies must have been performed within 4 months before Week 0. Additional testing, such as ova and parasites or *Escherichia coli* O157:H7 assessment, may be performed at the investigator's clinical discretion.
HBV and HCV testing	X	
HIV test	X	
Provide participant diary (CDAI, BSFS, AP-NRS) and training	X	Provide participants with the take-home diary and provide training on diary completion. A minimum of 7 days of CDAI data during the screening period is required to calculate the CDAI score at baseline (Week 0).
Schedule video ileocolonoscopy	X	During the initial screening visit the video ileocolonoscopy should be scheduled, if feasible.
Safety Assessments		
Physical examination	X	
Weight	X	
Height	X	
Vital signs	X	Temperature, pulse/heart rate, respiratory rate, and blood pressure
Urine pregnancy test	X	
C-SSRS	X	At the screening visit, the C-SSRS should be completed as the first assessment after signing informed consent and before any other tests, procedures, or other consultations to prevent influencing participant perceptions.
Efficacy Assessments		
Fistula assessment	X	
Video ileocolonoscopy	X	To prevent interfering with the collection of CDAI data for the Week 0 visit, the screening endoscopy will be performed at least 8 days before but no more than approximately 3 weeks before the Week 0 visit.
Stool sample (fecal calprotectin)	X	If stool samples are collected around the time of the screening ileocolonoscopy, they must be collected before the start of the bowel preparation.
CRP	X	

Table 1: SoA – Screening Activities of GALAXI 1, GALAXI 2, and GALAXI 3

Study Procedures	SCR (-5 wks)	Notes
Clinical Laboratory Assessments		
Hematology and Chemistry	X	
Serum Biologic Levels	(X)	Testing is optional. See Exclusion Criteria #6 for washout requirements and serum biologic level testing. Serum levels obtained as part of standard of care practice prior to the screening period can be submitted as source documentation as long as the participant did not receive the biologic after the serum level was obtained.
Pharmacodynamics and Biomarkers		
Ileocolonoscopy biopsy sample collections for histology	X	
Ileocolonoscopy biopsy sample collections for exploratory RNA and protein assessments (where local regulations permit).	X	
Stool sample (fecal biomarkers and microbiome; where local regulations permit)	X	
Ongoing Participant Review		
Concomitant therapy	X	Concomitant therapies should be documented after signing informed consent and should continue for the duration of the screening period.
Adverse events	X	The reporting of adverse events should begin after the informed consent is signed and should continue for the duration of the screening period.
Abbreviations: AP-NRS=abdominal pain – numerical rating scale; BSFS=Bristol Stool Form Scale; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; RNA=ribonucleic acid; SCR=screening; TB=tuberculosis; wks=weeks.		

Table 2: SoA – Week 0 to Week 48 of GALAXI 1, GALAXI 2, and GALAXI 3

Week:	0	4	8	12 [a]	16	20	24	28	32	36	40	44	48 [b,c]	Notes
Study Procedures [d,e]														
Administrative														
Inclusion/exclusion criteria	X													
Study Intervention Administration														
Review medical history	X													
Randomization	X													Randomization should be performed approximately 5 weeks after screening/informed consent signing.
Administer study intervention	X	X	X	X	X	X	X	X[f]	X	X[f]	X	X[f]		All assessments described in this table are to be completed prior to study intervention administration, unless otherwise specified. PRO assessments should be completed first, followed by the C-SSRS, and then any other clinical procedures, tests, or consultations.
Safety Assessments														
Vital signs	X	X	X	X	X	X	X	X[f]	X	X[f]	X	X[f]		Includes temperature, pulse/heart rate, respiratory rate, and blood pressure. Must be obtained: • before each C infusion, approximately every 30 minutes during the infusion, and for 1 hour at approximately 30-minute intervals after completion of the final infusion • prior to and approximately 30 minutes after the final C injection
Urine pregnancy test	X	X	X	X	X	X	X	X[f]	X	X[f]	X	X[f]	X	Must be performed before every study intervention administration in female participants of childbearing potential.
TB evaluation / other infection assessment	X	X	X	X	X	X	X	X[f]	X	X[f]	X	X[f]	X	If TB is suspected at any time during the study, a chest radiograph and QuantiFERON-TB test (or T-SPOT test for sites in Japan where local regulations permit) should be performed. A tuberculin skin test is additionally required if the QuantiFERON-TB test is not approved/registered in the country in which this protocol is being conducted.
Injection-site evaluation			X	X	X	X	X	X[f]	X	X[f]	X	X[f]		An injection-site reaction is any adverse reaction at an C study intervention injection site. Injection sites will be evaluated for reactions and any injection-site reaction will be recorded as an AE.
C-SSRS	X	X	X	X	X	X	X	X[f]	X	X[f]	X	X[f]	X	For visits between Week 0 and Week 48, the C-SSRS should be completed after all PROs and before any other tests, procedures, or other consultations to prevent influencing participant perceptions.

Table 2: SoA – Week 0 to Week 48 of GALAXI 1, GALAXI 2, and GALAXI 3

Week:	0	4	8	12 [a]	16	20	24	28	32	36	40	44	48 [b,c]	Notes
Study Procedures [d,e]														
Efficacy Assessments														
Collect and review participant diary (CDAI, BSFS, AP-NRS)	X	X	X	X	X	X	X	X[f]	X	X[f]	X	X[f]	X	Diary information should be completed daily and participants should bring their diaries to each visit. The daily diary includes patient-reported data for the CDAI (includes PRO-2 components), BSFS, and AP-NRS. Collection for BSFS and AP-NRS will conclude at Week 48. CDAI: The most recent hematocrit value obtained during the screening window will be used to calculate CDAI at Week 0. For all other visits, the most recent hematocrit value obtained will be used to calculate the CDAI.
Weight	X	X	X	X	X	X	X	X[f]	X	X[f]	X	X[f]	X	Weight measurement is used to support CDAI assessments, PK modeling, and safety.
Fistula assessment	X	X	X	X	X	X	X	X[f]	X	X[f]	X	X[f]	X	
Video ileocolonoscopy		(X)		X									X	To prevent interfering with the collection of CDAI data, the video ileocolonoscopy must be performed at least 8 days before or at the designated visit (ie, Week 4, Week 12, and Week 48). If performed on the day of the designated visit, the 7 days before the initiation of the colonoscopy preparation should be utilized to calculate CDAI scores for these visits. (Optional Week 4: Only those participants who consent to participate in the optional substudy will undergo Week 4 video ileocolonoscopy and biopsy collection. Participation in the optional Week 4 substudy will target approximately 200 study participants.)
Stool sample (fecal calprotectin)	X	X	X	X			X						X	Week 0: Not required if sample already collected within 2 weeks of the Week 0 visit. Week 4, Week 12, Week 48: Stool samples required for this visit must be obtained before the start of the bowel preparation for the video ileocolonoscopy that is also scheduled for the visit.

Table 2: SoA – Week 0 to Week 48 of GALAXI 1, GALAXI 2, and GALAXI 3

Week:	0	4	8	12 [a]	16	20	24	28	32	36	40	44	48 [b,c]	Notes
Study Procedures [d,e]														
CRP	X	X	X	X	X	X	X		X		X		X	Week 0: Not required if sample already collected within 2 weeks of the Week 0 visit.
Patient-Reported Outcomes (PROs)														PRO assessments for efficacy (PGIC, PGIS, IBDQ, PROMIS-29, PROMIS Fatigue Short Form 7a, and EQ-5D-5L) and health economics (WPAI-CD) should be administered before the C-SSRS and before any clinical procedures or tests are performed.
PGIS	X		X	X			X						X	
PGIC			X	X			X						X	
IBDQ	X		X	X			X						X	
PROMIS-29	X		X	X			X						X	
PROMIS Fatigue Short Form 7a	X		X	X			X						X	
EQ-5D-5L	X			X			X						X	
Health Economics														
WPAI-CD	X			X			X						X	
Clinical Laboratory Assessments														
Hematology and chemistry	X	X	X	X	X	X	X		X		X		X	Week 0: laboratory tests are not required if screening laboratory tests were performed within 2 weeks of the Week 0 visit.
Pharmacokinetics and Immunogenicity														
Study intervention serum concentration	X	X	X	X	X	X	X		X		X		X	Blood samples should be collected before the administration of study intervention. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of PK sample collections. Week 0, Week 4, Week 8, Week 12: At these study visits with C dosing, blood samples for PK analysis should be collected before the start of and approximately 60 minutes after completion of the final infusion.
Assessment for antibody to study intervention	X	X	X	X			X		X		X		X	Blood samples should be collected before the administration of study intervention. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of sample collections.
Pharmacodynamics and Biomarkers														
Whole blood sample collection for RNA analysis (where local regulations permit)	X	X		X			X						X	Whole blood for RNA analysis will be collected from all participants in the study to assess the RNA transcriptome related to both Crohn's disease and response to guselkumab and ustekinumab.

Table 2: SoA – Week 0 to Week 48 of GALAXI 1, GALAXI 2, and GALAXI 3

Week:	0	4	8	12 [a]	16	20	24	28	32	36	40	44	48 [b,c]	Notes
Study Procedures [d,e]														
Serum biomarkers (where local regulations permit)	X	X		X			X						X	Serum biomarkers will be collected from all participants in the study to assess peripheral proteins related to both Crohn's disease and response to guselkumab and ustekinumab, including (but not limited to) IL-17A and IL-22.
Ileocolonoscopy biopsy sample collections for histology		(X)		X									X	(Optional Week 4: Only those participants who consent to participate in the optional substudy will undergo Week 4 video ileocolonoscopy and biopsy collection. Participation in the optional Week 4 substudy will target approximately 200 study participants.)
Ileocolonoscopy biopsy sample collections for exploratory RNA and protein assessments (where local regulations permit).		(X)		X									X	
Stool sample (fecal biomarkers and microbiome; where local regulations permit)	X	X	X	X			X						X	
Pharmacogenomics (DNA)														
Genetic (DNA) evaluations	X													Whole blood will be collected only from participants who consent to participate in the optional DNA analysis.
Ongoing Participant Review														
Concomitant therapy	X	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	X	
Crohn's disease-related hospitalizations and surgeries	X	X	X	X	X	X	X	X	X	X	X	X	X	Hospitalization for the Week 4 (optional), Week 12, and Week 48 ileocolonoscopy is not included in this category.

Table 2: SoA – Week 0 to Week 48 of GALAXI 1, GALAXI 2, and GALAXI 3

Week:	0	4	8	12 [a]	16	20	24	28	32	36	40	44	48 [b,c]	Notes
Study Procedures [d,e]														

Abbreviations: AE=adverse event; AP-NRS=abdominal pain – numerical rating scale; BSFS=Bristol Stool Form Scale; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; DNA=deoxyribonucleic acid; EQ-5D-5L=5-level EuroQol five dimensions instrument (includes the EQ-5D descriptive system [EQ-5D] and the EQ visual analog scale [EQ-VAS]); DNA=deoxyribonucleic acid; IBDQ=Inflammatory Bowel Disease Questionnaire; IL=interleukin; CCI [redacted]; PK=pharmacokinetic(s); PGIC=Patient's Global Impression of Change (of Severity of Crohn's Disease); PGIS=Patient's Global Impression of Severity (of Crohn's Disease); PRO=patient-reported outcome; PROMIS=Patient-Reported Outcomes Measurement Information System; CCI [redacted] RNA=ribonucleic acid; CC [redacted]; TB=tuberculosis; WPAI-CD=Work Productivity and Activity Impairment–Crohn's Disease.

Footnotes:

a. If a participant discontinues study intervention prior to the Week 12 visit, the participant should complete the evaluations as detailed under the Study Intervention Discontinuation (SID) visit at the time of SID. In addition, the participant should return for the Week 12 visit and complete all evaluations specified at Week 12 (except the ileocolonoscopy if already completed at the SID visit) and have a final efficacy and safety (FES) visit approximately 16 weeks after their last study intervention administration. See Table 4 for additional details.

b. If a participant discontinues study intervention prior to the Week 48 visit, the participant should complete the evaluations as detailed under the SID visit at the time of SID. In addition, the participant should return for a FES visit approximately 16 weeks after their last study intervention administration. See Table 4 for additional details.

c. Participants who are entering the long-term extension (LTE) at Week 48 should complete the Week 48 activities in this table (Table 2) and then refer to Table 3 for Week 48 study intervention administration activities. Participants who do not enter the LTE at Week 48 should complete a FES visit approximately 16 weeks after their last study intervention administration. See Table 4 for additional details.

d. Visit window should be ±4 days for each visit up to and including Week 12; after Week 12 to end of study, visit window should be ±7 days.

e. All assessments are to be completed before study intervention administration, unless otherwise specified. PRO assessments should be completed first, followed by the C-SSRS, and then any other clinical procedures, tests, or consultations.

f. The evaluations listed for these visits will be applicable in the Phase 3 portion of the protocol if both C [redacted] and C [redacted] maintenance dosing are evaluated.

Table 3: SoA – Week 48 to Week 240 (Long-Term Extension) for Eligible Participants Who Have Completed Week 48 of GALAXI 1, GALAXI 2, or GALAXI 3

CCI

[redacted]

Table 3: SoA – Week 48 to Week 240 (Long-Term Extension) for Eligible Participants Who Have Completed Week 48 of GALAXI 1, GALAXI 2, or GALAXI 3

CCI

[redacted]

Table 3: SoA – Week 48 to Week 240 (Long-Term Extension) for Eligible Participants Who Have Completed Week 48 of GALAXI 1, GALAXI 2, or GALAXI 3

CCI

Table 4: SoA – Study Intervention Discontinuation (SID) Visit and the Final Efficacy and Safety (FES) Follow-Up Visit for GALAXI 1, GALAXI 2, or GALAXI 3: (a) Participants to Complete SID and/or FES Visits, Plus Additional Study Visits

(a) Participants should complete the SID and/or the FES visits, and additional study visits, as outlined below

	SID [a]	FES [b]	Additional Visit Required	Notes
Participant terminates study participation at any time during the study	X			Evaluations for SID should be completed prior to participant terminating study participation.
Participant discontinues study intervention at or prior to the Week 12 visit	X	X	Week 12 (see Table 2)	Discontinuation prior to Week 12: A video ileocolonoscopy at Week 12 is not required if already completed at the SID visit prior to Week 12. Discontinuation at Week 12: A video ileocolonoscopy is required at Week 12 (or can be performed as part of the SID visit after Week 12).
Participant discontinues study intervention after Week 12 and up to the Week 48 visit	X	X		Discontinuation after Week 12 (visit and ileocolonoscopy) and before Week 44: A video ileocolonoscopy (with biopsy samples) is optional (or can be performed as part of the SID visit). Discontinuation at Week 44 or Week 48: A video ileocolonoscopy (with biopsy samples) is required (or can be performed as part of SID visit).
Participant completes the 48-week study but does not enter the LTE at Week 48		X	Week 48 (see Table 2)	

Table 4: SoA – Study Intervention Discontinuation (SID) Visit and the Final Efficacy and Safety (FES) Follow-Up Visit for GALAXI 1, GALAXI 2, or GALAXI 3: (a) Participants to Complete SID and/or FES Visits, Plus Additional Study Visits

Participant discontinues study intervention after Week 48 and up to Week 240	X	X		Discontinuation after Week 48 and before Week 96: The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 48, since these participants would have completed the procedure as part of the Week 48 visit. Discontinuation after Week 96 and before Week 144: The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 96, since these participants would have completed the procedure as part of the Week 96 visit. Discontinuation after Week 144 and before Week 192: The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 144, since these participants would have completed the procedure as part of the Week 144 visit. Discontinuation after Week 192 and before Week 240: The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 192, since these participants would have completed the procedure as part of the Week 192 visit.
Participant completes LTE participation at Week 240		X	Week 240 (see Table 3)	The FES should occur around Week 248 or 252 (ie, approximately 16 weeks after the last study intervention administration at Week 232 [for CC dosing] or Week 236 [for CC dosing]).

Abbreviations: FES=final efficacy and safety (follow-up visit); LTE=long-term extension; CCI SID=study intervention discontinuation (visit).
Footnotes:
a. The SID visit should be completed at the time of SID.
b. The FES visit should be completed approximately 16 weeks after the last study intervention administration.

Table 5: SoA – Study Intervention Discontinuation (SID) Visit and the Final Efficacy and Safety (FES) Follow-Up Visit for GALAXI 1, GALAXI 2, or GALAXI 3: (b) Evaluations to be Completed at the SID or FES Visits

(b) Evaluations to be completed at the SID or FES visits are outlined below

Period:	SID	FES	Notes
Study Procedures			
Safety Assessments			
Physical examination	X	X	
Vital signs	X	X	Include temperature, pulse/heart rate, respiratory rate, and blood pressure.
Urine pregnancy test	X	X	Must be performed in female participants of childbearing potential.
TB evaluation / other infection assessment	X	X	If TB is suspected at any time during the study, a chest radiograph and QuantiFERON-TB test (or T-SPOT test for sites in Japan where local regulations permit) should be performed. A tuberculin skin test is additionally required if the QuantiFERON-TB test is not approved/registered in the country in which this protocol is being conducted.
C-SSRS	X	X	The C-SSRS should be completed after all PROs and before any other tests, procedures, or other consultations to prevent influencing participant perceptions.
Efficacy Assessments			
Collect and review participant diary (CDAI, BSFS, AP-NRS)	X	X	For the FES, daily diary information should be collected for each of the 14 days before the visit. The daily diary includes patient-reported data for the CDAI (includes PRO-2 components), BSFS, and AP-NRS. Collection for BSFS and AP-NRS will conclude at Week 48. The most recent hematocrit value obtained will be used to calculate the CDAI.
Weight	X	X	Weight measurement is used to support CDAI assessments, PK modeling, and safety.
Fistula assessment	X		
Video ileocolonoscopy	X		To prevent interfering with the collection of CDAI data, the ileocolonoscopy must be performed at least 8 days before or at the designated visit. If performed on the day of the designated visit, the 7 days before the initiation of the colonoscopy preparation should be utilized to calculate CDAI scores. The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 48, since these participants would have completed the procedure as part of the Week 48 visit.
Stool sample (fecal calprotectin)	X		Stool samples required for this visit must be obtained before the start of the bowel preparation for the video ileocolonoscopy that is also scheduled for the visit.
CRP	X	X	
Patient-Reported Outcomes (PROs)			PRO assessments for efficacy (PGIC, PGIS, IBDQ, PROMIS-29, PROMIS Fatigue Short Form 7a, and EQ-5D-5L) and health economics (WPAI-CD) should be administered before the C-SSRS and before any clinical procedures or tests are performed. The IBDQ, PROMIS-29, and WPAI-CD assessments should be performed if a participant discontinues in the LTE.
PGIS	X		
PGIC	X		
IBDQ	X		
PROMIS-29	X		
PROMIS Fatigue Short Form 7a	X		
EQ-5D-5L	X		
Health Economics			
WPAI-CD	X		

Table 5: SoA – Study Intervention Discontinuation (SID) Visit and the Final Efficacy and Safety (FES) Follow-Up Visit for GALAXI 1, GALAXI 2, or GALAXI 3: (b) Evaluations to be Completed at the SID or FES Visits

(b) Evaluations to be completed at the SID or FES visits are outlined below

Period:	SID	FES	Notes
Clinical Laboratory Assessments			
Hematology and Chemistry	X	X	
Pharmacokinetics/ Immunogenicity			
Study intervention serum concentration	X	X	All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of PK sample collections.
Assessment for antibody to study intervention	X	X	All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of sample collections.
Pharmacodynamics and Biomarkers			
Whole blood sample collection for RNA analysis (where local regulations permit)	X		Whole blood for RNA analysis will be collected from all participants in the study to assess the RNA transcriptome related to both Crohn's disease and response to guselkumab and ustekinumab.
Serum biomarkers (where local regulations permit)	X		Serum biomarkers will be collected from all participants in the study to assess peripheral proteins related to both Crohn's disease and response to guselkumab and ustekinumab, including (but not limited to) IL-17A and IL-22.
Ileocolonoscopy biopsy sample collections for histology	X		
Ileocolonoscopy biopsy sample collections for exploratory RNA and protein assessments (where local regulations permit)	X		
Stool sample (microbiome; where local regulations permit)	X		
Ongoing Participant Review			
Concomitant therapy	X	X	
Adverse events	X	X	
Crohn's disease-related hospitalizations and surgeries	X	X	Hospitalization for ileocolonoscopy at the SID visit is not included in this category.

Abbreviations: AP-NRS=abdominal pain–numerical rating scale; BSFS=Bristol Stool Form Scale; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; EQ-5D-5L=5-level EuroQol five dimensions instrument (includes the EQ-5D descriptive system [EQ-5D] and the EQ visual analog scale [EQ-VAS]); FES=final efficacy and safety (follow-up visit); IBDQ=Inflammatory Bowel Disease Questionnaire; PGIC=Patient's Global Impression of Change (of Severity of Crohn's Disease); LTE=long-term extension; PGIS=Patient's Global Impression of Severity (of Crohn's Disease); PK=pharmacokinetic(s); PRO=patient-reported outcome; PROMIS=Patient-Reported Outcomes Measurement Information System; RNA=ribonucleic acid; SID=study intervention discontinuation; TB=tuberculosis; WPAI-CD=Work Productivity and Activity Impairment–Crohn's Disease.

2. INTRODUCTION

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. In this manner, guselkumab inhibits the biologic activity of IL-23 in all in vitro assays examined.

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to Section 2.2 in this protocol and the latest version of the guselkumab Investigator's Brochure (IB).

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

There is a high unmet need for new treatment options in Crohn's disease that are safe and effective, especially new therapies that can provide improved long-term efficacy (ie, sustained remission) over currently available therapies.

The clinical development program for guselkumab in Crohn's disease is designed to evaluate the safety and efficacy of guselkumab compared with placebo and an active control (ustekinumab) and will be conducted under this single protocol: a Phase 2/3, randomized, double-blind, placebo- and active-controlled (ustekinumab), parallel-group, multicenter protocol to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active Crohn's disease who have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy.

Under this protocol, there are 3 separate studies: a 48-week Phase 2 dose-finding study (ie, GALAXI 1) and 2 identical 48-week Phase 3 confirmatory studies (ie, GALAXI 2 and GALAXI 3). Participants who complete the 48-week Phase 2 or Phase 3 studies may be eligible to enter the long-term extension (LTE [Week 48 to Week 252]) and receive approximately 4 additional years of treatment. The overall Phase 2/3 development program will enroll approximately 1,340 participants with a total duration for each participant of up to approximately 5 years.

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

The clinical and scientific rationale in support of the overall development program is described in Section 2.1.

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

2.1.1. Unmet Need in Crohn's Disease

Currently, there are 3 classes of biologic agents approved for the treatment of moderately to severely active Crohn's disease: tumor necrosis factor (TNF) antagonist therapies (infliximab, adalimumab, certolizumab), integrin inhibitors (natalizumab and vedolizumab), and IL-12/23 inhibitors (ustekinumab). Although the introduction of biologic agents has significantly improved the clinical management of patients with moderately to severely active Crohn's disease, a sizable proportion of the target patient population is non-responsive or will lose response over time. A review of the available data for approved biologic agents highlighted the unmet need in achieving and maintaining long-term remission, especially among patients who have previously failed biologic treatments. In all-treated patients (ie, all patients who were randomized at Week 0 of the studies evaluated), the estimated rates of clinical remission at 1 year in the biologic therapy failure or intolerance (BIO-Failure) population is around 20%, and ranges from 20% to 50% in the conventional therapy failure or intolerance (CON-Failure) population.[13]

In summary, there remains considerable unmet medical need for new treatment options, especially therapies with novel mechanisms of action that have the potential to raise the efficacy bar and maximize the proportion of patients who achieve and maintain clinical remission.

2.1.2. Rationale for Targeting IL-23 in Crohn's Disease

2.1.2.1. Preclinical Evidence Implicating IL-23 as a Target in Crohn's Disease

Genetic and animal model studies have explored the contribution of IL-12 and IL-23 in driving the pathophysiology of Crohn's disease. The results indicate that IL-23 plays a predominant role in inflammatory bowel disease (IBD) and emerging evidence suggests that blocking IL-23 alone may be a more effective strategy than blocking both IL-12 and IL-23.

Initial observations from genetic and animal model data suggest that Crohn's disease is mediated by IL-12 and/or IL-23, potentially through the Th1 and Th17 pathways they induce, respectively.[16] However, increasing evidence suggests a predominant role for IL-23 in Crohn's disease. Genome-wide association studies identified polymorphisms in the interleukin-23 receptor gene that are associated with Crohn's disease.[1] The role of IL-23 in driving intestinal inflammation has been shown in several mouse models. Mice treated with anti-IL-23 antibodies exhibited attenuated inflammation,[16] and mice with a genetic deletion of the p19 subunit of IL-23 are protected in several models of intestinal inflammation.[11]

2.1.2.2. Clinical Evidence Establishing Proof of Concept for Targeting IL-23 in Crohn's Disease

The potential therapeutic role of IL-23 in Crohn's disease was first established by clinical studies of IL-12/23p40 antagonists (briakinumab[18] and ustekinumab[8]). Ustekinumab (STELARA®) was recently approved for the treatment of moderately to severely active Crohn's disease (STELARA Summary of Product Characteristics [SmPC][22]; STELARA US Prescribing Information[23]). While these programs demonstrated that blockade of both IL-12 and IL-23 is effective in treating Crohn's disease, they could not ascertain the relative contributions of the 2 cytokines.

More recent studies of 2 anti-IL-23 antagonists, risankizumab (previously BI-655066)[7,9] and brazikumab (formerly MEDI2070, AMG 139),[20] reported Phase 2 results demonstrating efficacy of IL-23 blockade in participants with moderately to severely active Crohn's disease. The magnitude of efficacy observed in each of these studies suggests the potential for improved efficacy compared with ustekinumab (anti-IL-12/23), recognizing the limitations of cross-study comparisons as well as the comparatively small size of the IL-23 Phase 2 studies.

2.1.2.2.1. Clinical Experience with IL-12/23-Targeted Therapy (Ustekinumab) in Crohn's Disease

The ustekinumab Phase 3 program in Crohn's disease included two 8-week studies evaluating the efficacy and safety of ustekinumab CCI induction, and one maintenance study evaluating the efficacy and safety of ustekinumab CCI maintenance, for a total duration of 52 weeks of treatment. Ustekinumab was evaluated in the full spectrum of biologic-eligible patients with Crohn's disease, ie, those who were conventional therapy failures and those who were biologic therapy failures. After a single ustekinumab CCI induction dose at Week 0, approximately 21% and 40% of BIO-Failure and CON-Failure participants, respectively (versus approximately 7% and 20% of placebo-treated participants, respectively), achieved clinical remission at Week 8 (as evaluated by the Crohn's Disease Activity Index [CDAI]).[8] Among participants who responded to ustekinumab C CI induction and were rerandomized to receive ustekinumab CC maintenance CCI, approximately 53% and 49% of participants were in clinical remission at Week 52, respectively, compared with 36% of participants who received placebo maintenance.[8]

2.1.2.2.2. Clinical Experience with IL-23-Targeted Therapy in Crohn's Disease

Recent Phase 2 studies of 2 IL-23 mAbs, risankizumab[7,9] and brazikumab,[20] demonstrated their efficacy in improving clinical signs and symptoms, reducing inflammatory biomarkers, and improving endoscopic findings in participants primarily with biologic-refractory Crohn's disease.

Cross-study comparisons of clinical remission rates with the IL-23 blockers suggest the potential for improved efficacy compared with ustekinumab. It is notable that the induction doses used in the studies of both risankizumab (200 and CCI at Weeks 0, 4, 8) and brazikumab CCI at Weeks 0, 4) were considerably higher than approved ustekinumab dosing CCI at Week 0). A cross-compound meta-analysis suggests that the risankizumab dosing, in particular, may be at the higher end of the dose-response curve (see Section 4.3, Justification for Dose). Furthermore, the Phase 2 study with risankizumab also suggested the potential that response rates may not reach maximum until after 6 months of treatment. With doses of CCI for up to 6 months, clinical remission rates of approximately 50% were observed in all-treated patients,[9] substantially higher than remission rates previously reported for other agents, including ustekinumab, in similar study populations at similar follow-up time points. Of those participants who were in remission at 6 months and who continued risankizumab maintenance treatment CCI approximately 70% were in remission at 1 year.[6]

2.1.3. Overall Rationale for Guselkumab in Crohn's Disease

In summary, the collective genetic and preclinical evidence implicates the prominent role of selectively targeting IL-23 in modulating the underlying pathophysiology of IBD. The available clinical experience of 2 IL-23 antagonists and the established evidence from an approved IL-12/23 antagonist (ustekinumab) have demonstrated proof of mechanism and proof of concept, respectively, for targeting IL-23 in the treatment of Crohn's disease. Together, the available evidence provide support for investigating guselkumab in the treatment of Crohn's disease.

2.2. Background

2.2.1. Guselkumab Clinical Experience

This protocol represents the first studies of guselkumab in patients with Crohn's disease.

This section provides a summary of the sponsor's assessment of how the overall clinical experience with guselkumab across various indications supports the investigation of guselkumab in Crohn's disease. Details about these guselkumab clinical development programs across various indications are provided in Section 4 of the latest version of the guselkumab IB.

Through the cutoff date of 30 June 2017, 2,805 subjects have been exposed to guselkumab across all indications in completed and ongoing studies, including 185 healthy subjects, 2,336 subjects with psoriasis, 129 subjects with psoriatic arthritis (PsA), and 155 subjects in other indications.

The largest clinical experience to date with guselkumab has been in plaque psoriasis, primarily based on dosing at CCI in the Phase 2 and Phase 3 clinical development program (n=1,748); but also at doses up to CCI in a small number of participants (n=10) during Phase 1 clinical development. The safety profile of guselkumab in participants with moderate to severe plaque psoriasis based on data from the Phase 2 study (CNTO1959PSO2001) and 3 Phase 3 studies (CNTO1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003) is described in Section 4.4 of the latest version of the guselkumab IB. Briefly, of the 1,748 guselkumab-treated participants in the Phase 2 and Phase 3 studies, 1,393 participants were exposed for at least 6 months and 728 participants were exposed for at least 1 year. The LTEs of the Phase 3 studies (CNTO1959PSO3001 and CNTO1959PSO3002) are ongoing and will evaluate the safety and efficacy of guselkumab through up to 5 years of follow-up.

The totality of the safety data available to date show that guselkumab, administered CCI at doses of CCI in participants with plaque psoriasis, is well-tolerated and has a safety profile comparable to placebo over 16 weeks, and safety remained favorable when referenced versus active comparator (adalimumab) over 1 year. Additional safety data in other indications (in participants who also receive concomitant immunomodulators as background therapy) at guselkumab doses as high as CCI (Phase 2 rheumatoid arthritis study; n=54) did not identify any clinically significant safety signals through 1 year. Finally, a limited number of healthy participants (n=30) received single doses of CCI guselkumab between CCI and up to CCI. Of the 6 participants in the CCI dose group, the highest dose received was CCI in 1 participant. No clinically significant safety signals were identified.

Since the initiation of the GALAXI protocol, higher doses of guselkumab (up to CCI CC I have been administered in two clinical studies (a Phase 1 pharmacokinetic [PK] study in healthy Japanese participants and a Phase 2 study in participants with hidradenitis suppurativa).

2.2.2. Guselkumab Nonclinical Studies

A comprehensive overview of the nonclinical development program for guselkumab is available in Section 3 of the latest version of the guselkumab IB.

This section provides a summary of the sponsor's assessment of how the overall nonclinical data support the safety of the proposed dosing for guselkumab in this Phase 2/3 program in Crohn's disease. Details regarding the proposed dose regimen and dose rationale are described in Section 4.3.1 of this protocol.

To place the proposed clinical dosing for guselkumab in Crohn's disease patients into perspective relative to the existing preclinical data, the predicted cumulative 12-week human exposures during the induction phase (based on the highest induction dose tested in this protocol, ie, CCI given at Weeks 0, 4, 8) were compared with the exposure at the no-observed-adverse-effect level (NOAEL) in cynomolgus monkeys following weekly C CI administration in the 5-week arm of the subchronic toxicology study. In addition, predicted cumulative 12-week human exposures during the induction phase were compared with the exposure at the NOAEL in cynomolgus monkeys following weekly CC I administration in the 24-week arm of the subchronic toxicology study. Thereafter, the predicted human exposure at steady-state (based on the highest maintenance dose tested in this protocol, ie, CCI was compared with the exposure at the NOAEL in cynomolgus monkeys following weekly CC I administration in the 24-week arm of the subchronic toxicology study. These data are presented in Table 6.

Table 6: Guselkumab Predicted Exposure Margins During the Induction and Maintenance Phases of Treatment

Parameters	Mean C_{max} (µg/mL)	Mean AUC (µg.day/mL)
(a) CCI Induction Dosing		
Cynomolgus Monkey Exposure at the NOAEL (CCI week) Following 4 Weekly C Doses	1432[a]	4817[b]
Cynomolgus Monkey Exposure at the NOAEL (CCI week) Following 24 Weekly C Doses	993[a]	5412[b]
Human Predicted C Exposure	326[c]	1491[d]
Predicted Exposure Margin (Cyno C vs Human C [e]	***4.4***	***3.2***
Predicted Exposure Margin (Cyno C vs Human C [e]	***3.0***	***3.6***
(b) CCI Maintenance Dosing		
Cynomolgus Monkey Exposure at the NOAEL (CCI week) Following 24 Weekly C Doses	993[a]	5412[b]
Human Predicted C Exposure	30[c]	134[d]
Predicted Exposure Margin (Cyno C vs Human CC [e]	33.1	40.4

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

AUC=area under the serum concentration versus time curve; Cmax=maximum concentration; NOAEL= no-observed-adverse-effect level; CCI

From a nonclinical perspective, the risk to Crohn's disease patients is considered low when guselkumab is administered C once CCI at doses up to CCI (approximately CCI in humans) followed by the proposed maintenance doses of up to CCI, based on no adverse findings observed in cynomolgus monkeys following 5 weeks of once-weekly subchronic C dosing at CCI and 24 weeks of chronic once-weekly CC dosing. As summarized above, the actual exposure data (area under the serum concentration versus time curve [AUC]) achieved in monkeys relative to the predicted Week 8 to Week 12 C clinical induction dosing interval AUC, or steady-state CC maintenance interval AUC (both normalized to weekly dosing to compare with the monkey dosing interval) provide ample exposure margins for the proposed clinical doses. This is further supported by the fact that guselkumab is a late-stage biotherapeutic with a good clinical safety profile in participants with plaque psoriasis, with data generated primarily at CCI CCI but also at doses up to CCI and CCI C in a limited number of patients with plaque psoriasis and in healthy normal volunteers, respectively, during Phase 1 of clinical development. Additionally, since the initiation of the GALAXI protocol, higher doses of guselkumab (up to CCI CC have been administered in two clinical studies (a Phase 1 PK study in healthy Japanese participants and a Phase 2 study in participants with hidradenitis suppurativa). Lastly, risankizumab (an IL-23 inhibitor with clinical potency comparable to guselkumab) has been

studied in patients with Crohn's disease at up to [redacted] for 6 months and was reported to be well-tolerated.

2.3. Benefit-Risk Assessment

Based on the available data and the proposed safety measures discussed below, the sponsor contends that the benefit-risk of the selected dose regimens of guselkumab to be investigated in this protocol is acceptable. Additionally, the dose regimens of ustekinumab that have been included in this protocol are consistent with the approved dose regimens of ustekinumab for which a favorable benefit-risk has already been established in Phase 3 pivotal studies.

2.3.1. Guselkumab

Guselkumab has undergone extensive nonclinical and clinical development as summarized in the latest version of the IB and described briefly in Section 2.2. The collective efficacy and safety results of the Phase 1, Phase 2, and Phase 3 clinical studies in healthy volunteers and patients with plaque psoriasis and the regulatory approval for the plaque psoriasis indication established a favorable benefit-risk profile for guselkumab in the treatment of plaque psoriasis. This clinical experience provided support to the development of guselkumab in other inflammatory diseases such as PsA, generalized pustular psoriasis, erythrodermic psoriasis, and palmoplantar pustulosis.

Available animal and human data support the critical role of IL-23 in the pathogenesis of Crohn's disease, and studies with other anti-IL-23 mAbs suggest that selective targeting of IL-23 may achieve higher levels of efficacy than that observed with other mechanisms of action, including ustekinumab, in patients with moderately to severely active Crohn's disease (Section 2.1.2.2).

Clinical data with ustekinumab and other anti-IL-23 mAbs suggest that maximum efficacy in Crohn's disease may require higher doses and exposures than those used in psoriasis. For example, initial dosing of ustekinumab in Crohn's disease [redacted] in a 70 kg patient) is approximately 4-fold higher than in psoriasis ([redacted] at Week 0 and Week 4). Therefore, induction doses up to [redacted] given [redacted] for 3 doses and maintenance doses up to [redacted] will be studied in the Phase 2 portion of this trial to evaluate whether higher doses and exposures of guselkumab are needed for maximum efficacy in Crohn's disease. Data from non-clinical toxicology studies (Section 2.2.2) provide adequate exposure margins for the proposed clinical doses in this protocol. As discussed in Section 2.2.1 and Section 2.2.2, since the initiation of the GALAXI protocol, higher doses of guselkumab (up to [redacted] have been administered in two clinical studies (a Phase 1 PK study in healthy Japanese participants and a Phase 2 study in participants with hidradenitis suppurativa). In addition, comparable doses/exposures have been previously evaluated in the Phase 2 studies of 2 other anti-IL-23 mAbs, and no significant safety concerns have been reported after treatment through 1 year.

The approved dose regimen of guselkumab in psoriasis ([redacted] at Week 0 and Week 4, and then [redacted] has been demonstrated to have a favorable safety profile, and dose regimens as high as [redacted] have been shown to have favorable safety in a Phase 2 trial in rheumatoid arthritis. The main risk, as described in detail 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, as well as liver injury, based on an event of potential drug-induced liver injury (DILI) that occurred in a single participant at the highest Phase 2 induction dose administered. Since there is limited clinical information available for the higher dose regimens of guselkumab (as proposed in this protocol), safety will be evaluated in an initial cohort of 25 patients by an independent Data Monitoring Committee (DMC). Details about the evaluation of this initial cohort and the decision to continue or modify the protocol are outlined in Section 9.5.2 and in the DMC charter. The early safety evaluation of the initial cohort will ensure acceptable safety for continued study of the proposed Phase 2 and Phase 3 dose regimens in larger numbers of patients, and the ongoing unblinded safety assessments by the DMC throughout the Phase 2 and 3 studies will ensure patient safety in the overall development program. Since the initiation of the GALAXI protocol, higher doses of guselkumab (up to CCI [redacted] have been administered in two clinical studies (a Phase 1 PK study in healthy Japanese participants and a Phase 2 study in participants with hidradenitis suppurativa).

2.3.2. Active Comparator: Ustekinumab

Ustekinumab (STELARA) is the active comparator in this protocol. Ustekinumab is a human IgG1 kappa mAb that binds with high affinity and specificity to the p40 subunit common to both human IL-12 and human IL-23.

Ustekinumab is an approved treatment for moderately to severely active Crohn's disease in adult patients in several countries including the US, Canada, and the EU; submissions for regulatory approval of the Crohn's disease indication are currently under review in a number of countries globally.

The proposed induction and maintenance dosing of ustekinumab in this protocol is consistent with the currently approved country labels globally and is consistent with the dose regimens evaluated in the ustekinumab Phase 3 clinical development program in Crohn's disease that established the efficacy and safety of ustekinumab in patients with moderately to severely active Crohn's disease. Additional details about the dose selection rationale for ustekinumab are provided in Section 4.3.2.

The general benefits and risks of ustekinumab are presented in the country-specific prescribing information where ustekinumab is approved; for countries where ustekinumab is not yet approved, investigators should refer to the latest version of the ustekinumab IB.

3. OBJECTIVES AND ENDPOINTS

3.1. Phase 2 Dose-Ranging Study (GALAXI 1)

3.1.1. Objectives

Primary Objectives

- To evaluate the clinical efficacy of guselkumab in participants with Crohn's disease
- To evaluate the safety of guselkumab

Secondary Objectives

- To evaluate the dose-response of guselkumab to inform dose selection for the Phase 3 portion of this protocol
- To evaluate the efficacy of guselkumab on endoscopic improvement
- To evaluate the PK, immunogenicity, and pharmacodynamics (PD) of guselkumab therapy, including changes in C-reactive protein (CRP) and fecal calprotectin

Other Objectives

- To evaluate the impact of guselkumab on health-related quality of life (HRQOL) and health economics outcome measures
- To evaluate the efficacy of guselkumab on histologic improvement
- To evaluate the impact of treatment with guselkumab on intestinal mucosal gene expression profiles and cellular composition associated with Crohn's disease

3.1.2. Endpoints

The primary endpoint and major secondary endpoints evaluate the short-term efficacy of guselkumab versus placebo. These endpoints are described below. **Note: the final ordering of the major secondary endpoints will be provided in the Phase 2 Statistical Analysis Plan (SAP).**

Primary Endpoint

Change from baseline in the CDAI score at Week 12.

Major Secondary Endpoints

- Clinical remission at Week 12 (defined as CDAI score <150).
- Clinical response at Week 12 (defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150).
- PRO-2 remission at Week 12 (defined as an AP mean daily score at or below 1 [AP≤1] AND an SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline).
- Clinical-biomarker response at Week 12 (clinical response based on CDAI score and ≥50% reduction from baseline in CRP or fecal calprotectin).
- Endoscopic response at Week 12 (defined as at least 50% improvement from baseline in the Simple Endoscopic Score for Crohn's Disease [SES-CD] or SES-CD score ≤2).

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

3.1.3. Hypothesis

The primary hypothesis for GALAXI 1 is that guselkumab is superior to placebo in inducing a reduction from baseline in CDAI score in participants with moderately to severely active Crohn's disease.

3.2. Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)

GALAXI 2 and GALAXI 3 are identical studies and have the same objectives and endpoints, as described below.

3.2.1. Objectives

Primary Objectives

- To evaluate the clinical and endoscopic efficacy of guselkumab in participants with Crohn's disease
- To evaluate the safety of guselkumab

Secondary Objectives

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

Other Objectives

- To evaluate the impact of guselkumab on health economics outcome measures
- To evaluate the efficacy of guselkumab on histologic improvement
- To evaluate the impact of treatment with guselkumab on intestinal mucosal gene expression profiles and cellular composition associated with Crohn's disease

3.2.2. Endpoints and Hypotheses

The primary and major secondary endpoints and hypotheses found in Section 3.2.2.1 refer to the Global endpoints and hypotheses for the US and other countries/territories throughout the world as applicable. The primary and major secondary endpoints and hypotheses found in Section 3.2.2.2 refer to the Regional endpoints and hypotheses for other health authorities that preferred the Week 12 co-primary endpoints were retained. The definitions associated with the endpoints will be provided in Section 3.2.2.3.

3.2.2.1. Global Endpoints and Hypotheses

Co-primary Endpoints

The Global co-primary endpoints are:

- Clinical response at Week 12 and clinical remission at Week 48
- Clinical response at Week 12 and endoscopic response at Week 48

For these endpoints, comparisons will be made within each study between each guselkumab dose (guselkumab CCI [redacted] and placebo.

Major Secondary Endpoints

The Global major secondary endpoints are grouped into 3 categories based on timepoint and comparator; note that these are grouped for the purpose of categorization but are not presented in the order of testing in the multiplicity-controlled testing procedure (the specific order for the testing procedure will be provided in the statistical analysis plan).

The following Global major secondary endpoints evaluate the short-term efficacy of guselkumab versus placebo in each study:

- Clinical response at Week 4
- Clinical remission at Week 12
- Endoscopic response at Week 12
- Fatigue response at Week 12
- Clinical remission at Week 12 and endoscopic response at Week 12
- Endoscopic remission (Global definition) at Week 12

The following long-term endpoints evaluate guselkumab versus placebo in each study:

- Clinical response at Week 12 and corticosteroid-free clinical remission at Week 48
- Clinical response at Week 12 and endoscopic remission (Global definition) at Week 48

The following long-term endpoints evaluate guselkumab versus ustekinumab:

- Clinical remission at Week 48
- Endoscopic response at Week 48
- Clinical remission at Week 48 and endoscopic response at Week 48
- Endoscopic remission (Global definition) at Week 48
- Deep remission (Global definition) at Week 48

A list of the exploratory endpoints can be found in Section 9.4.1.2.

Global Hypotheses

The co-primary hypotheses will be tested within each of GALAXI 2 and GALAXI 3 separately.

The co-primary hypotheses are that guselkumab is superior to placebo in achieving:

- clinical response at Week 12 and clinical remission at Week 48
- clinical response at Week 12 and endoscopic response at Week 48

3.2.2.2. Regional Endpoints and Hypotheses

Co-primary Endpoints

The Regional co-primary endpoints are:

- Clinical remission at Week 12
- Endoscopic response at Week 12

For these endpoints, comparisons will be made within each study between the combined guselkumab induction dose group and placebo.

Major Secondary Endpoints

The Regional major secondary endpoints are grouped into 3 categories based on timepoint and comparator; note that these are grouped for the purpose of categorization but are not presented in the order of testing in the multiplicity-controlled testing procedure (the specific order for the testing procedure will be provided in the statistical analysis plan):

The following Regional major secondary endpoints evaluate the short-term efficacy of guselkumab versus placebo:

- PRO-2 remission at Week 12
- Fatigue response at Week 12
- Endoscopic remission (Regional definition) at Week 12

The following long-term endpoints evaluate guselkumab versus placebo:

- Corticosteroid-free clinical remission at Week 48
- Endoscopic response at Week 48

The following long-term endpoints evaluate guselkumab versus ustekinumab:

- Endoscopic remission (Regional definition) at Week 48
- Clinical remission at Week 48
- Endoscopic response at Week 48
- Durable clinical remission at Week 48
- PRO-2 remission at Week 48
- Clinical remission at Week 48 and endoscopic response at Week 48

- Corticosteroid-free remission at Week 48

A list of the exploratory endpoints can be found in Section 9.4.1.2.

Regional Hypotheses

The co-primary hypotheses will be tested within each of GALAXI 2 and GALAXI 3 separately.

The co-primary hypotheses are that guselkumab is superior to placebo in achieving:

- clinical remission at Week 12
- endoscopic response at Week 12

3.2.2.3. Definition of Endpoints

Definitions:

- Clinical response: ≥100-point reduction from baseline in CDAI score or CDAI score <150
- Clinical remission: CDAI <150
- Endoscopic response: at least 50% improvement from baseline in the SES-CD or SES-CD score ≤2
- Corticosteroid-free clinical remission at Week 48: CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48
- Fatigue response: an improvement of ≥ 7 points in PROMIS Fatigue Short Form 7a.
- Durable clinical remission: CDAI <150 for ≥80% of all visits between Week 12 and Week 48 [ie, at least 8 of 10 visits]), which must include Week 48
- PRO-2 remission: AP mean daily score at or below 1 [AP≤1] AND SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline

Global Definitions:

- Endoscopic remission: SES-CD ≤4 with at least a 2-point reduction from baseline and no subscore greater than 1 in any individual subcomponent
- Deep remission: Clinical remission and endoscopic remission (Global definition)

Regional Definitions:

- Endoscopic remission: SES-CD score ≤2
- Deep remission: Clinical remission and endoscopic remission (Regional definition)

4. STUDY DESIGN

4.1. Overall Design

The clinical development program for guselkumab in Crohn's disease will be conducted under this single protocol: a Phase 2/3, randomized, double-blind, placebo- and active-controlled

(ustekinumab), parallel-group, multicenter protocol to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active Crohn's disease who have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy.

An overview of this clinical development program is presented in Figure 1 and described briefly below. Under this protocol, there are 3 separate studies: a 48-week Phase 2 dose-ranging study (ie, GALAXI 1) and 2 identical 48-week Phase 3 confirmatory studies (ie, GALAXI 2 and GALAXI 3). All 3 studies will be conducted using a treat-through study design, ie, participants are randomized to treatment regimens at Week 0 and will remain on that treatment regimen through at least Week 48 of each study, unless otherwise indicated.

In the Phase 2 dose-ranging study (ie, GALAXI 1), the safety and efficacy of guselkumab dose regimens spanning a wide induction and maintenance dose range will be evaluated to support the selection of induction and maintenance dose regimens for confirmatory evaluation in Phase 3. It is estimated that 250 to 500 participants may be required to select the dose regimens that will be evaluated in Phase 3 (GALAXI 2 and GALAXI 3). Therefore, the first 250 participants in GALAXI 1 will be enrolled into an Initial Dose Decision Cohort; an interim analysis (IA) primarily based on this cohort will occur once these participants reach Week 12 (or terminate study participation prior to Week 12), as described in Section 9.5.1. Since data from more participants may be required to inform the dose decision, the sponsor may elect to continue enrollment and newly enrolled participants (ie, starting from participant #251) will be randomized into a Transition Cohort while data from the Initial Dose Decision Cohort are being collected and analyzed. The purpose of the Transition Cohort will be to continue accruing safety and efficacy data on the Phase 2 dose regimens without interrupting the study, thereby increasing the size of the overall safety database as well as possibly contributing additional information in making a dose decision should there be uncertainty on dose selection based on the results from the Initial Dose Decision Cohort. If the decision is made to proceed with enrollment into the Transition Cohort, it is anticipated that a maximum of approximately 250 additional participants will be enrolled into GALAXI 1 (ie, 250 in the Initial Dose Decision Cohort and up to 250 in the Transition Cohort) prior to the dose decision. If a dose decision for Phase 3 is not made by the time the 500th patient is randomized, enrollment will be paused until a decision for Phase 3 dosing, or a decision to terminate the development program, is made.

This is an operationally seamless protocol in countries where the local health authorities have approved a seamless transition. In the countries that have approved a seamless transition, there will be no break in enrollment between the Phase 2 and Phase 3 studies if enrollment continues into the Transition Cohort and a dose decision can be made before 500 patients are randomized. Transition from the Phase 2 portion to the Phase 3 portion of the protocol will occur once the dose decision for Phase 3 has been made and implemented. In countries where the local health authority requires additional regulatory approval prior to initiating the Phase 3 studies, enrollment will pause until approval is received. In all countries, all participants randomized after the dose decision has been implemented will be part of the Phase 3 studies.

In the Phase 3 dose-confirming studies (ie, GALAXI 2 and GALAXI 3), the safety and efficacy of the selected guselkumab dose regimens will be evaluated. A target of approximately 490 participants will be enrolled in each of the Phase 3 studies, for a total target sample size of approximately 980 participants in the Phase 3 portion of the protocol. Participants impacted by major disruptions may be replaced (see Section 10.14, Appendix 14).

Participants who complete the 48-week Phase 2 or Phase 3 studies may be eligible to enter the LTE to receive approximately 4 additional years of treatment.

The overall GALAXI Phase 2/3 protocol will enroll a total of approximately 1,340 participants, with a total duration for each participant of up to approximately 5 years.

Target Population

The target population in all 3 studies under this protocol will consist of men or women ≥18 years of age at the time of informed consent with moderately to severely active Crohn's disease (of at least 3 months' duration). Participants must have colitis, ileitis, or ileocolitis previously confirmed by radiography, histology, and/or endoscopy.

Active Disease Criteria

At baseline, participants must have active Crohn's disease, defined as follows:

1. **Clinically active Crohn's disease**
    a. CDAI score ≥220 but ≤450

    AND EITHER

    b. Mean daily SF count >3, based on the unweighted CDAI component of the number of liquid or very soft stools

    OR

    c. Mean daily AP score >1, based on the unweighted CDAI component of AP

    AND

2. **Endoscopic evidence of ileocolonic Crohn's disease**

    A SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease), as assessed by central endoscopy reading at the screening endoscopy, based on the presence of ulceration in at least 1 of the 5 ileocolonic segments, resulting in the following specified ulceration component scores:

    a. a minimum score of 1 for the component of "size of ulcers"

    AND

    b. a minimum score of 1 for the component of "ulcerated surface".

    Of note, before the implementation of Amendment 3, where the minimum SES-CD score was ≥3 based on the presence of ulceration, within each of the studies, a maximum of 10% of the total enrolled population could include participants who had baseline scores for SES-CD <4

(ie, for participants with isolated ileal disease), or SES-CD <7 (ie, for participants with colonic or ileocolonic disease).

Medication History Criteria

In addition, a broad participant population eligible for systemic therapy will be evaluated in this protocol and will include participants who have demonstrated an inadequate response or failed to tolerate previous conventional therapy or biologic therapy.

Detailed eligibility criteria for prior exposure to conventional therapy or biologic therapy are described in Appendix 2 (Section 10.2) and Appendix 3 (Section 10.3), respectively, and are summarized below.

Note that participants with prior exposure to IL-12/23 or IL-23 agents are ineligible for entry into this protocol, with the exception of participants who have had limited exposure to and who have not demonstrated failure or intolerance to ustekinumab, as described in Appendix 4 (Section 10.4).

- **Conventional therapy failure or intolerance (CON-Failure)**

  Participants must have demonstrated an inadequate response to, or have failed to tolerate, at least 1 of the following conventional Crohn's disease therapies: oral corticosteroids (including prednisone, budesonide, and beclomethasone dipropionate) or the immunomodulators azathioprine (AZA), 6-mercaptopurine (6-MP) or methotrexate (MTX). Participants who have demonstrated corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of Crohn's disease) are also eligible. Participants may be naïve to biologic therapy (ie, a TNF antagonist or vedolizumab or ustekinumab) or may have been exposed to biologic therapy but have not demonstrated inadequate response or intolerance.

  Within each of the studies, an approximate 25% to 50% of the total enrolled population will be participants who are CON-Failures.

- **Biologic therapy failure or intolerance (BIO-Failure)**

  Participants must have demonstrated an inadequate response to, or have failed to tolerate, at least 1 or more biologic therapies (ie, TNF antagonists or vedolizumab) at a dose approved for the treatment of Crohn's disease. Inadequate response is defined as: Primary non-response (ie, no initial response) or Secondary non-response (ie, response initially but subsequently lost response). Participants who have demonstrated an inadequate response to, or have failed to tolerate ustekinumab are not eligible.

The use of concomitant and prohibited therapies is described in Section 6.5. In general, concomitant therapies should maintain stable dosing (except for steroid tapering) and new concomitant therapies should not be initiated unless considered medically necessary by the investigator. Corticosteroids will be tapered beginning at Week 12. Initiation of prohibited therapies will result in study intervention discontinuation (SID). Finally, in the event of persistent inadequate response or clinically significant Crohn's disease worsening, discontinuation of study intervention should be strongly considered, as described in Section 7.1.

Evaluations

Throughout the 3 studies, efficacy, PK, biomarkers, and safety will be assessed at time points indicated in the appropriate Schedule of Activities (Section 1.3).

An overview of the endpoints for the 3 studies is presented in Section 3 and full details are presented in Section 9.4.1.

A pharmacogenomic blood sample will be collected from participants who consent to this component of the protocol (where local regulations permit; Section 1.3). Participation in pharmacogenomic research is optional. Deoxyribonucleic acid (DNA) samples will be analyzed for identification of genetic factors that may be associated with clinical response.

An external independent DMC, with defined roles and responsibilities as governed by a DMC charter, will assess the safety of participants across the 3 studies. The DMC's initial responsibility will be careful review of the safety data from the first 25 participants randomized and treated in GALAXI 1. After that, ongoing safety data reviews will continue as specified in the DMC charter. After each review, the DMC will make recommendations to the sponsor about the continuation of the studies (Section 9.5.2).

4.1.1. Phase 2 Dose-Ranging Study (GALAXI 1): Induction and Maintenance

4.1.1.1. Overview of Phase 2 Study Design and Dose Decision for Phase 3

At Week 0, participants will be randomized in a 1:1:1:1:1 ratio to receive 1 of 3 dose regimens of guselkumab, ustekinumab, or placebo. Participants will be allocated to a treatment group using a permuted block randomization with baseline CDAI score (≤300 or >300) and prior BIO-Failure status (Yes/No) as the stratification variables. An approximate 25% to 50% of the total enrolled population will be CON-Failure participants. In addition, a maximum of 10% of the total enrolled population will have baseline scores for SES-CD <4 (ie, for participants with isolated ileal disease), or SES-CD <7 (ie, for participants with colonic or ileocolonic disease). Allocation to treatment group will be performed using a central randomization center by means of an interactive web response system (IWRS).

As described in Section 4.1, it is anticipated that up to 500 participants may be enrolled into GALAXI 1 (ie, 250 in the Initial Dose Decision Cohort and up to 250 in the Transition Cohort) prior to the dose decision for Phase 3. If a dose decision for Phase 3 is not made by the time the 500th patient is randomized, enrollment will be paused until a decision for Phase 3 dosing, or a decision to terminate the development program, is made.

Interim analyses are planned at Week 12 (and at Week 24, if necessary) after all participants from the Initial Dose Decision Cohort have either completed the Week 12 (or Week 24) visit or terminated study participation prior to the Week 12 (or Week 24) visit to inform the dose decision for Phase 3. At the time of each IA, all available data from both the Initial Dose Decision Cohort and the Transition Cohort will be analyzed, including any data beyond Week 12. Additional data

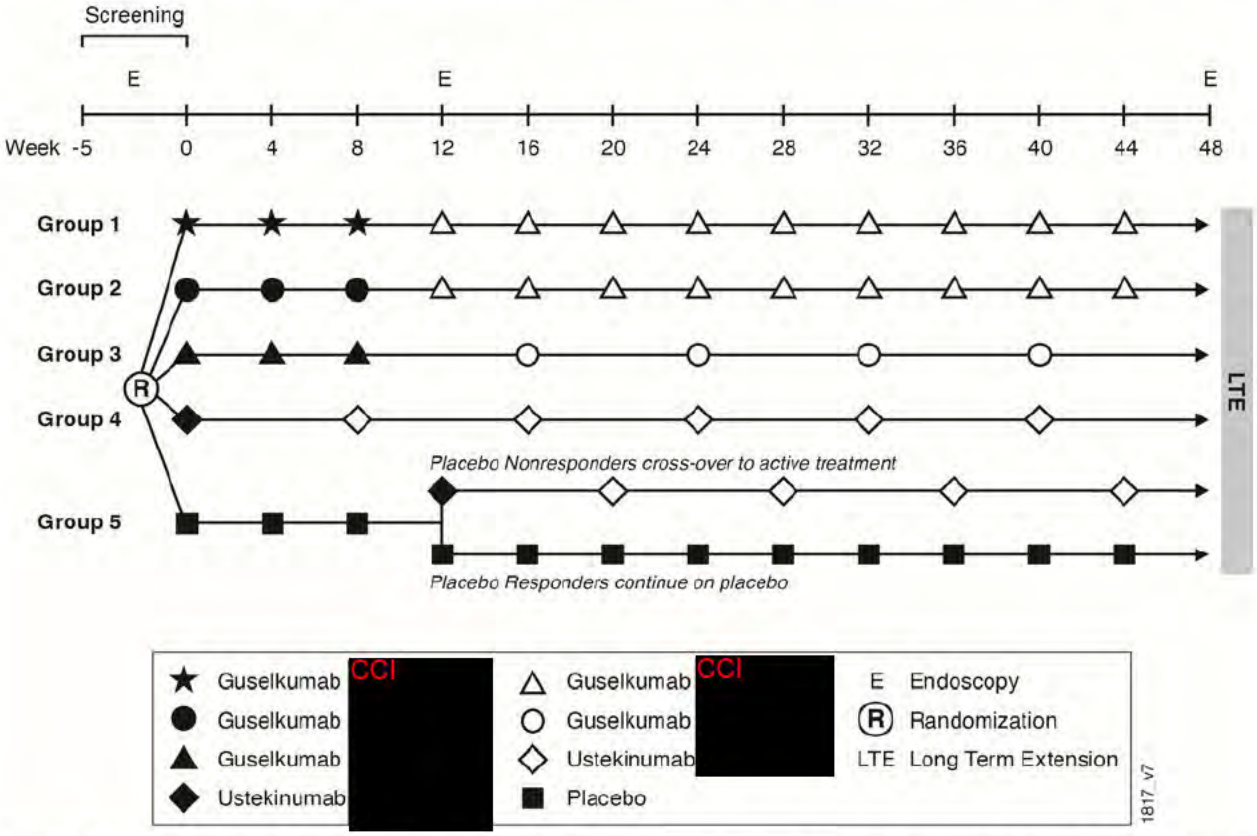
transfers and analyses may be performed at other time points if needed to enable the dose decision for Phase 3.

The goal is to select 2 guselkumab dose regimens for confirmatory evaluation in Phase 3. A Dose Selection Committee, composed of sponsor management representatives from Clinical, Safety, Biostatistics, and Clinical Pharmacology who are not associated with study conduct, will be responsible for deciding on the dose regimens of guselkumab to be evaluated in Phase 3. Further details regarding the dose decision process are described in Section 9.5.

4.1.1.2. Treatment Groups

An overview of the 5 treatment groups and their corresponding dosing schemes from Week 0 through Week 48 of the Phase 2 study is provided below and in Figure 2.

Figure 2: Design Schematic Illustrating the Dosing Schemes for the 5 Treatment Groups from Week 0 to Week 48 in Phase 2 (ie, GALAXI 1)



Note: This schematic only illustrates the dosing for the treatment groups. It does not provide a complete illustration of all blinding (placebo) administrations.

All participants in the Phase 2 study (ie, Initial Dose Decision Cohort and Transition Cohort) will be randomized to 1 of 5 treatment groups as described below. Participants will remain on their assigned treatment regimens through the end of the 48-week study, except for the Placebo group as outlined below.

Group 1: Guselkumab Regimen 1 [redacted]

Participants will receive guselkumab [redacted] from Week 0 through Week 8 (ie, total of 3 [redacted] doses). At Week 12, participants will continue treatment with guselkumab [redacted] through Week 44.

Group 2: Guselkumab Regimen 2 [redacted]

Participants will receive guselkumab [redacted] from Week 0 through Week 8 (ie, total of 3 [redacted] doses). At Week 12, participants will continue treatment with guselkumab [redacted] through Week 44.

Group 3: Guselkumab Regimen 3 [redacted]

Participants will receive guselkumab [redacted] from Week 0 through Week 8 (ie, total of 3 [redacted] doses). At Week 16, participants will continue treatment with guselkumab [redacted] through Week 40.

Group 4: Active Control, Ustekinumab [redacted]

Participants will receive a single ustekinumab [redacted] induction dose at Week 0 (weight-based [redacted] doses approximating [redacted] as outlined below). At Week 8, participants will receive ustekinumab [redacted] maintenance [redacted] through Week 40.

- Ustekinumab [redacted] (weight ≤55 kg)
- Ustekinumab [redacted] (weight >55 kg and ≤85 kg)
- Ustekinumab [redacted] (weight >85 kg)

Group 5: Placebo → Placebo or Ustekinumab crossover

Participants will receive placebo [redacted] from Week 0 through Week 8 (ie, total of 3 [redacted] doses). At Week 12, participants will continue treatment based on their clinical response status as follows:

- **Placebo responders:** Continue placebo treatment [redacted] from Week 12 through Week 44.
- **Placebo nonresponders:** Receive a single ustekinumab [redacted] induction dose at Week 12 (weight-based [redacted] doses approximating [redacted] as outlined above). At Week 20, participants will receive ustekinumab [redacted] maintenance [redacted] through Week 44.

Clinical response is defined as a reduction from baseline (ie, Week 0) in the CDAI score of ≥100 points or being in clinical remission (CDAI <150). To maintain the blind, participants in all treatment groups will be assessed for their clinical response status at Week 12.

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

No dosing adjustments are planned for any of the treatment groups from Week 0 through Week 48, except for Group 5 (Placebo) at Week 12 based on clinical response status as described above. Details of the dose rationale in support of the study design are presented in Section 4.3.

The use of concomitant and prohibited therapies is described in Section 6.5. In general, concomitant therapies should maintain stable dosing (except for steroid tapering) and new concomitant therapies should not be initiated, unless considered medically necessary by the investigator. Corticosteroids will be tapered beginning at Week 12. Initiation of prohibited therapies will result in SID. Finally, in the event of persistent inadequate response or clinically significant Crohn's disease worsening, discontinuation of study intervention should be strongly considered, as described in Section 7.

All participants who complete the Week 48 evaluations may be eligible to enter the LTE and continue to receive study intervention for approximately 4 additional years (Week 48 to Week 252), as described in Section 4.1.3.

4.1.1.3. Endpoints and Evaluations

The primary endpoint is change from baseline in the CDAI score at Week 12. The major secondary endpoints are clinical remission at Week 12, clinical response at Week 12, PRO-2 remission at Week 12, endoscopic response at Week 12, and clinical-biomarker response at Week 12. Analyses of these endpoints will be based on comparisons between each guselkumab group and the placebo group. Additional analyses of endpoints at other time points, including comparisons of guselkumab with ustekinumab at Week 48, will also be performed.

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

Database locks (DBLs) are planned for Week 12 and Week 48. Additional DBLs (eg, Week 24) may be added as necessary and will be specified in the SAP.

4.1.2. Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3): Induction and Maintenance

4.1.2.1. Overview of Phase 3 Design

GALAXI 2 and GALAXI 3 are identical studies from a study design perspective. The purpose of conducting two replicate studies is to achieve independent confirmation of clinical efficacy in two independent samples of patients, which is required by some health authorities. At Week 0, a target of approximately 980 participants will be randomly allocated to GALAXI 2 (n=approximately 490) or GALAXI 3 (n=approximately 490), using a permuted block randomization with baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), prior BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) as the stratification variables. Within each stratum, participants in each study will be randomized in a 2:2:2:1 ratio to receive 1 of 2 dose regimens of guselkumab, ustekinumab, or placebo, respectively. Within each study (GALAXI 2 and GALAXI 3), an approximate 25% to 50% of the total enrolled population will be participants who are CON-Failures. Allocation to treatment groups will be performed using a central randomization center by means of an IWRS.

4.1.2.2. Treatment Groups

The Phase 3 guselkumab dose regimens were selected based on the efficacy and safety of the induction dose range (ie, from CCI [redacted] evaluated in the Phase 2 study.

Based on the Phase 2 data, 2 guselkumab dose regimens CCI [redacted] were selected for confirmatory evaluation in Phase 3 and will be evaluated in both Phase 3 studies.

An overview of the 4 treatment groups in the two Phase 3 studies and their corresponding dosing schemes from Week 0 through Week 48 are summarized below and in Figure 3. Participants will remain on their assigned treatment regimens through the end of the 48-week study, except for the placebo group as outlined below.

Group 1: Guselkumab Regimen 1 CCI [redacted]

Participants will receive guselkumab CCI [redacted] from Week 0 through Week 8 (ie, total of 3 CCI doses). At Week 12, participants will continue treatment with guselkumab CCI [redacted] through Week 44.

Group 2: Guselkumab Regimen 2 CCI [redacted]

Participants will receive guselkumab CCI [redacted] from Week 0 through Week 8 (ie, total of 3 CCI doses). At Week 16, participants will continue treatment with guselkumab CCI [redacted] through Week 40.

Group 3: Active Control – Ustekinumab CCI [redacted]

Participants will receive a single ustekinumab CCI induction dose at Week 0 (weight-based CCI dose approximating CCI as outlined below). At Week 8, participants will receive ustekinumab CCI maintenance CCI [redacted] through Week 40.

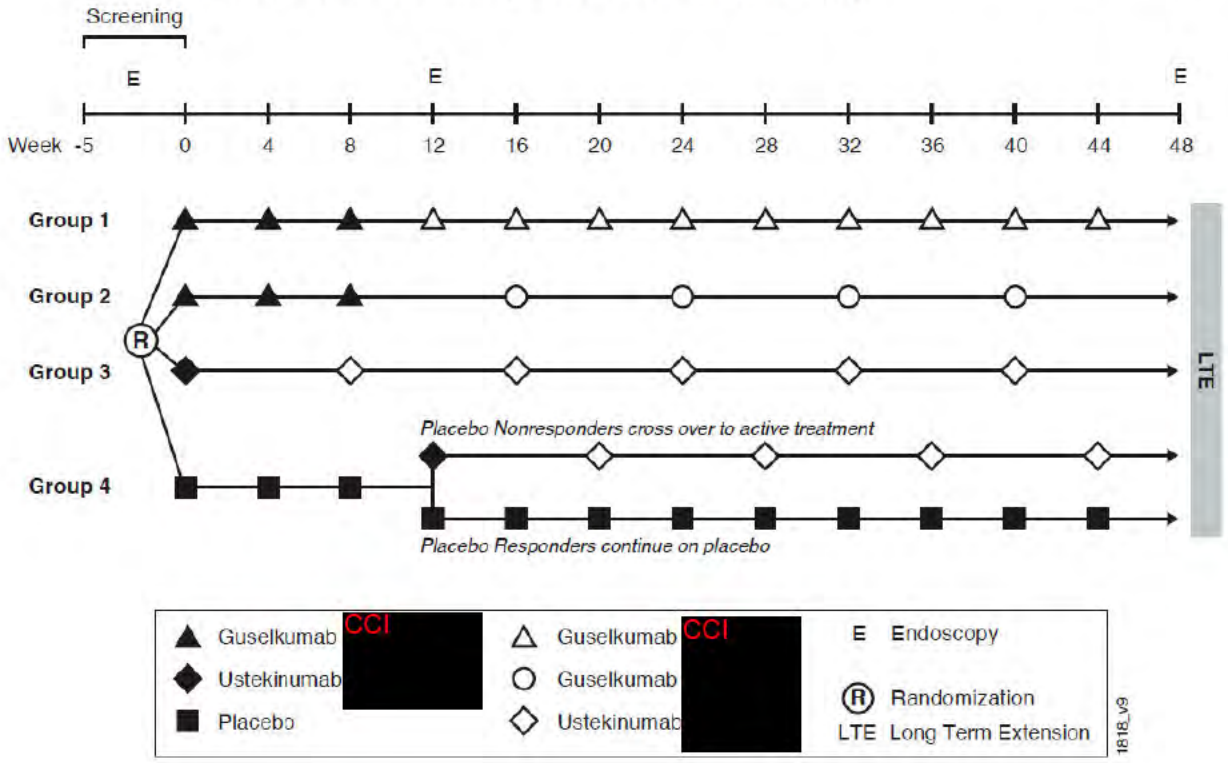
- Ustekinumab CCI (weight ≤55 kg)
- Ustekinumab CCI (weight >55 kg and ≤85 kg)
- Ustekinumab CCI (weight >85 kg)

Group 4: Placebo → Placebo or Ustekinumab Crossover

Participants will receive placebo CCI from Week 0 through Week 8 (ie, total of 3 CCI doses). At Week 12, participants will continue treatment based on their clinical response status as follows:

- **Placebo responders:** Continue placebo treatment from Week 12 through Week 44.
- **Placebo nonresponders:** Receive a single ustekinumab CCI induction dose at Week 12 (weight-based CCI doses approximating CCI as outlined above). At Week 20, participants will receive ustekinumab CCI maintenance CCI [redacted] through Week 44.

Figure 3: Design Schematic Illustrating the Dosing Schemes for the 4 Treatment Groups from Week 0 to Week 48 in the Phase 3 Studies (ie, GALAXI 2 and GALAXI 3)



Note: This schematic only illustrates the dosing for the treatment groups. It does not provide a complete illustration of all blinding (placebo) administrations.

Clinical response is defined as a reduction from baseline (ie, Week 0) in the CDAI score of ≥100 points or being in clinical remission (CDAI <150). To maintain the blind, participants in all treatment groups will be assessed for their clinical response status at Week 12.

In addition, placebo administrations (CCI and CCI will be given, as appropriate, to maintain the blind throughout the duration of the study. Refer to Study Interventions Administered (Section 6.1) for additional details.

No dosing adjustments are planned for any of the treatment groups from Week 0 through Week 48, except for Group 4 (Placebo) at Week 12 based on clinical response status as described above. Details of the dose rationale in support of the study design are presented in Section 4.3.

The use of concomitant and prohibited therapies is described in Section 6.5. In general, concomitant therapies should maintain stable dosing (except for steroid tapering) and new concomitant therapies should not be initiated unless considered medically necessary by the investigator. Corticosteroids will be tapered beginning at Week 12. Initiation of prohibited therapies will result in SID. Finally, in the event of persistent inadequate response or clinically significant Crohn's disease worsening, discontinuation of study intervention should be strongly considered, as described in Section 7.

All participants who complete the Week 48 evaluations may be eligible to enter the LTE and continue to receive approximately 4 additional years of treatment, as described in Section 4.1.3.

4.1.2.3. Endpoints and Evaluations

Both GALAXI 2 and GALAXI 3 have the same co-primary and major secondary endpoints, whether Global or Regional.

Within each study, the Global co-primary endpoints are:

- clinical response at Week 12 and clinical remission at Week 48
- clinical response at Week 12 and endoscopic response at Week 48

Within each study, the Regional co-primary endpoints are:

- clinical remission at Week 12
- endoscopic response at Week 12

For the Global co-primary endpoints, comparisons will be made within each study between each guselkumab dose group and placebo. For the Regional co-primary endpoints, comparisons will be made within each study between the combined guselkumab induction dose group and placebo, as the guselkumab induction dose is the same up to Week 12. All major secondary endpoints are listed in Section 3.2.2. Other efficacy endpoints are described in Section 9.4.1.2.

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

A DBL is planned for the Phase 3 Week 48 dataset. Additional DBLs may be added if necessary and will be specified in the SAP.

4.1.3. Long-Term Extension for GALAXI 1, 2, and 3

The LTE will be conducted for approximately 4 years, from Week 48 through Week 252.

At Week 48 of GALAXI 1, GALAXI 2, or GALAXI 3, all participants who, in the opinion of the investigator, will continue to benefit from treatment (ie, based on Week 48 clinical and endoscopic evaluations) are eligible to enter the LTE to receive approximately 4 additional years of treatment, during which time the longer-term efficacy and safety of guselkumab will be evaluated. All participants will be assessed according to the Schedule of Activities (Section 1.3). The final efficacy and safety follow-up (FES) visit of the LTE will occur at approximately Week 248 or 252 (ie, approximately 16 weeks after their last study intervention administration at Week 232 [for CCI dosing] or Week 236 [for CCI dosing]).

Participants who are not eligible to enter the LTE at Week 48 are to return for an FES visit 16 weeks after their last study intervention administration.

During the LTE, all participants will continue to receive the same treatment regimen (ie, guselkumab, ustekinumab, or placebo) that they were receiving at the end of GALAXI 1,

GALAXI 2, or GALAXI 3. The first study intervention administration in the LTE will occur at Week 48 and the last study intervention administration will occur at Week 236. Treatment adjustment for inadequate response is permitted between Week 52 and Week 80 of the LTE, as described in Section 4.1.3.1.

Beginning at Week 48, at the discretion of the investigator and participant, and after appropriate and documented training, participants may self-administer study intervention at the investigative site. A caregiver may also be trained to administer study intervention. After receiving training at Week 48, participants who are eligible for self- (or caregiver) administration of study intervention will be supplied with study intervention for at-home administration and will have their first at-home administration at Week 52. Participants who are unable or unwilling to have study intervention administered away from the investigative site will continue administration at the investigative site. See Section 4.1.3.2 for further details.

All participants will continue to receive active or placebo study intervention administration in the LTE in a blinded fashion until study unblinding, which will occur after the Week 48 DBL and the Week 48 analyses have been completed for the Phase 2 study (for participants entering the LTE from GALAXI 1) or for the Phase 3 studies (for participants entering the LTE from GALAXI 2 or GALAXI 3).

After study unblinding, all participants who are on active treatment (ie, guselkumab or ustekinumab) will continue to receive their assigned active treatment for the remaining duration of the LTE through Week 236. Participants who are on placebo will be discontinued from study intervention upon study unblinding and will have an FES visit at that time.

CCI [redacted]

4.1.3.1. Treatment Adjustment for Inadequate Response

Participants from all treatment groups (ie, guselkumab, ustekinumab, and placebo) who meet inadequate response criteria between Week 52 (ie, the first visit at which treatment adjustment is permitted) and Week 80 (ie, the last visit at which treatment adjustment is permitted) will be eligible for a single treatment adjustment (ie, the first-time inadequate response criteria are met).

Inadequate response is defined as not being in clinical response AND having a CDAI score of at least 220 points.

Clinical response is defined as a reduction from baseline (ie, Week 0) in the CDAI score of ≥100 points or being in clinical remission (CDAI <150).

CDAI assessments may be conducted at CCI visits between Weeks 52 and 80 (inclusive) to support the evaluation of CDAI response status. Participants who meet inadequate response criteria, and who are not already receiving the highest guselkumab CC maintenance dose regimen, are eligible to receive treatment adjustment as described below.

Participants (who are receiving placebo, ustekinumab, or the lower CC maintenance dose of guselkumab) will be eligible to receive a single, blinded, treatment adjustment to the highest guselkumab CC maintenance dose as defined in the Phase 2 or the Phase 3 portion of the protocol in which they are enrolled. Participants who are already receiving the highest guselkumab CC maintenance dose will receive a single, blinded, sham treatment adjustment. Participants who have received treatment adjustments will remain on their new treatment regimen through Week 92. At Week 96, the benefit of treatment adjustment will be evaluated. Continued participation in the remaining duration of the LTE will be decided on investigator's clinical judgment of the results of the Week 96, 144, and 192 clinical and endoscopic evaluations. Discontinuation of study intervention should be considered in participants with persistent unsatisfactory response or clinically significant worsening Crohn's disease where continuation of the study intervention is not in the best interest of the participant.

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

Study intervention will be administered at the investigative site by a health care professional (HCP) through Week 44.

Beginning at Week 48, at the discretion of the investigator and participant, and after appropriate and documented training, participants may self-administer study intervention at the investigative site according to regional/local regulations and instruction. A caregiver may also be trained to administer study intervention.

After receiving training at Week 48, participants who are eligible for self- (or caregiver) study intervention administration will be supplied with study intervention for at-home administration and will have their first at-home administration at Week 52. Participants will record all at-home study intervention administrations on a diary card. Participants will also be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding. Finally, participants will continue to have study visits and assessments at the investigative sites approximately CCI through Week 240, as outlined in Section 1.3.

Participants who are unable or unwilling to have injections administered away from the site will be required to return to the site for administration of study intervention injection(s). Participants will continue to have study visits and assessments at the investigative site approximately CCI (if receiving CCI dosing per protocol) or CCI (if receiving CCI dosing per protocol) through Week 240, as outlined in Section 1.3.

4.1.3.3. Concomitant and Prohibited Therapies for Crohn's Disease

During the LTE, all concomitant therapies for Crohn's disease may be adjusted at the discretion of the investigator.

At any time during the study, the initiation of prohibited therapies for Crohn's disease will result in discontinuation of study intervention administration.

For further details please refer to Section 6.5.

4.1.3.4. Endpoints and Evaluations

Through Week 252, the longer-term efficacy and safety of guselkumab will be evaluated. In addition, the benefit of treatment adjustment will be evaluated based on descriptive analysis of various efficacy endpoints (to be specified in the SAP).

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

Phase 2 LTE database locks are planned at Week 96 (to evaluate the durability of efficacy evaluations and the benefit of dose adjustment) and at the final efficacy and safety visit in the LTE. Phase 3 LTE database locks are planned at the final efficacy and safety visit in the LTE. Additional DBLs for Phase 2 and Phase 3 LTE may be added if necessary.

4.2. Scientific Rationale for Study Design

4.2.1. Use of Placebo- and Active-Control

The inclusion of both placebo and active controls in the same protocol has several advantages. A short-term placebo-control period facilitates the evaluation of the efficacy and safety of a new treatment compared with placebo within a timeframe for which the use of placebo in participants with active disease is considered clinically acceptable in support of scientific research. The use of an active comparator control can alleviate the concern over the extended use of placebo and can also provide an opportunity to evaluate comparative efficacy and safety in a randomized-controlled setting in addition to comparison to placebo. There is significant clinical value to determine whether a new treatment option will provide similar or greater benefit to patients compared with an approved treatment option.

Ustekinumab was selected as the active comparator because it targets an overlapping mechanism of action (ie, both IL-12/23 blockade) and the preclinical evidence suggests the potential for improved efficacy with more specific targeting of IL-23. Further, the proposed dosing of ustekinumab in this protocol is the highest currently approved induction-maintenance dose regimen and was one of the dose regimens evaluated in the ustekinumab Phase 3 clinical development program in Crohn's disease. Therefore, the inclusion of ustekinumab as an active comparator in this program will provide a valuable and relevant benchmark for comparison with guselkumab. For additional information on the ustekinumab dose rationale, see Section 4.3.2.

Ustekinumab is included as an active-reference arm in the Phase 2 study to collect data that will inform treatment effect size and sample size assumptions for the Phase 3 studies. Ustekinumab is included in the 2 Phase 3 studies as an active comparator control arm to enable the randomized-controlled evaluation of the long-term efficacy and safety of the 2 guselkumab dose regimens compared with ustekinumab in addition to comparison to placebo through approximately 1 year (ie, Week 48) of treatment.

4.2.2. Biomarker and DNA Collection

Biomarker samples will be collected to evaluate the cellular and molecular mechanism of action of guselkumab and ustekinumab, or help to explain interindividual variability in clinical outcomes, or may help to identify population subgroups that respond differently to either intervention. Serum biomarkers will be collected (where local regulations permit) from whole blood in all participants to assess PD markers associated with the response to guselkumab and ustekinumab. Whole blood samples will be collected from all participants to assess the effect of study intervention on ribonucleic acid (RNA) expression profiles. Ileocolonic biopsies will also be obtained from all participants pretreatment during screening and post-treatment at Weeks 12, 48, 96, 144, 192 and 240 to assess cellular and molecular changes within the intestinal mucosal tissue. The goal of the biomarker analyses is to further define the mechanism of action of the selective blockade of IL-23 with guselkumab compared with dual blockade of IL-12/23 with ustekinumab in Crohn's disease, and to aid in evaluating the intervention-clinical response relationship.

Two optional substudies are planned:

- **Optional Week 4 ileocolonoscopy substudy:** The optional ileocolonoscopy substudy will be performed at Week 4 in a subset of participants who consent to participate and will include endoscopic assessment and intestinal biopsy. This substudy will target approximately 200 study participants. Exploratory analyses of intestinal mucosal tissue obtained by biopsy at Week 4 will be performed to delineate the mechanisms of action of guselkumab and ustekinumab by establishing a sequence of molecular and cellular effects beginning at an early time point. In addition, data collected at Week 4 will be explored for correlation with clinical efficacy observations at later time points.
- **Optional pharmacogenomic substudy**: 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 DNA to allow for the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of guselkumab and to identify genetic factors associated with Crohn's disease or the response to guselkumab or ustekinumab treatment. The focus of this analysis will be the evaluation of genetic single nucleic polymorphisms (SNPs) associated with Crohn's disease and response to treatment with guselkumab.

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

Patient-reported outcome (PRO) evaluations (ie, Inflammatory Bowel Disease Questionnaire [IBDQ], PROMIS-29, PROMIS Fatigue 7-item Short Form, 5-level EuroQol 5 dimensions [EQ-5D-5L] instrument) will be used to assess the benefits of guselkumab treatment on disease-specific and general HRQOL. Patient-reported outcome evaluations are only being collected in countries where translations of the evaluations are available. See Section 8.1 for more details.

4.2.4. Medical Resource Utilization and Health Economics Data Collection

Medical resource utilization evaluations, including but not limited to Crohn's disease-related hospitalizations and Crohn's disease-related surgeries, will be collected for evaluation of the health economics of guselkumab treatment. Additionally, the impact of guselkumab treatment on work productivity will be assessed using the Work Productivity and Activity Impairment Questionnaire in Crohn's Disease (WPAI-CD).

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 adverse events (AEs) of the study and provide their consent voluntarily will be enrolled.

The total blood volume to be collected from each participant in each study (maximum of approximately 500 mL over approximately 252 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 period. For more details regarding blood collection, see Blood Sample Collection in Section 8.

4.3. Justification for Dose

4.3.1. Guselkumab

This section provides the rationale for the guselkumab dose regimens to be evaluated in the guselkumab Phase 2 dose-ranging study (GALAXI 1) and Phase 3 dose-confirming studies (GALAXI 2 and GALAXI 3) in participants with moderately to severely active Crohn's disease.

4.3.1.1. Phase 2 Dose-Ranging Study (GALAXI 1)

The following guselkumab dose regimens will be evaluated through Week 48 of GALAXI 1:

- **Guselkumab Regimen 1 –** Induction: CCI [redacted] at Weeks 0, 4, 8; followed by Maintenance: CCI [redacted] (ie, at Weeks 12, 16, 20, 24, 28, 32, 36, 40, and 44)
- **Guselkumab Regimen 2** – Induction: CCI [redacted] at Weeks 0, 4, 8; followed by Maintenance: CCI [redacted] (ie, at Weeks 12, 16, 20, 24, 28, 32, 36, 40, and 44)

- **Guselkumab Regimen 3 –** Induction: CCI at Weeks 0, 4, 8; followed by Maintenance: CCI (ie, at Weeks 16, 24, 32, and 40)

The guselkumab dose regimens selected for the Phase 2 dose-ranging study were identified based on dose-response data from studies of guselkumab in plaque psoriasis, and published information on risankizumab (another anti-IL-23 monoclonal antibody) on relative dosing requirements for anti-IL-23 mAbs in plaque psoriasis versus Crohn's disease. Supportive information from PK/PD modeling of ustekinumab and guselkumab, along with safety data from relevant preclinical and clinical studies with guselkumab, also contributed to the choice of these dose regimens. The basis for the choice of guselkumab induction and maintenance dose regimens in the Phase 2 dose-ranging study are presented in the next sections.

4.3.1.1.1. Induction Dose Regimens

Cross-study comparisons between the guselkumab and risankizumab Phase 2 studies in patients with plaque psoriasis suggest that comparable efficacy was attained at almost similar dose regimens. A model-based meta-analysis also suggests comparable clinical potency for these 2 compounds. In addition, the PK of guselkumab were found to be similar to those of risankizumab.[14,24] These dose-response and PK data suggest that comparable levels of IL-23 blockade and efficacy may be achieved in Crohn's disease at similar dose regimens or systemic exposures for these 2 compounds. Furthermore, a PK/PD model of ustekinumab (an IL-12/23 blocker), which is approved in Crohn's disease was considered applicable to predict efficacy following administration of different guselkumab dose regimens.

In the Phase 2 study of risankizumab in participants with moderately to severely active Crohn's disease, dose-dependent efficacy was demonstrated with a greater proportion of participants on the higher induction dose regimen of risankizumab (ie, CCI achieving remission at Week 12 compared with those receiving the lower dose regimen (ie, CCI ; however, it was not clear if maximum efficacy was attained with the risankizumab CCI induction dose regimen in this Phase 2 study.[7] Dose-dependent efficacy was further demonstrated with risankizumab as shown by an increased rate of remission in patients who switched from CCI in the second period of that study (Week 12 through Week 26). Based on these findings, along with the comparable PK and clinical potency of guselkumab and risankizumab, and coupled with the PK/PD predictions of guselkumab in Crohn' disease, induction dose regimens comprising guselkumab CCI CC CC each given at Weeks 0, 4, and 8, were selected for the Phase 2 dose-ranging study.

Additionally, a higher dose of guselkumab CCI induction dose regimen will evaluate the possibility of achieving a higher level of efficacy at Week 12 than that observed with the higher risankizumab dose regimen (ie, CCI CC tested in Phase 2. Overall, the 3 guselkumab CC induction dose regimens provide a 6-fold range of exposure that is likely to result in adequate separation between dose levels and consequently support guselkumab induction dose selection for Phase 3.

Regarding the safety of these higher CC induction guselkumab doses, single doses of guselkumab as high as CCI , with the highest single dose tested being CCI , have been previously

studied in a Phase 1 plaque psoriasis study in a limited number of participants. Since the initiation of the GALAXI protocol, higher doses of guselkumab (up to CCI CC) have been administered in two clinical studies (a Phase 1 PK study in healthy Japanese participants and a Phase 2 study in participants with hidradenitis suppurativa). Additionally, guselkumab C CI doses of up to CCI weekly for 5 weeks, and guselkumab CC doses of up to CCI weekly for 24 weeks, were well-tolerated in cynomolgus monkeys and did not result in any clinical or anatomic findings. These data suggest an acceptable exposure margin between predicted guselkumab exposures for the CCI C CI regimen compared with those observed in toxicology studies (Section 2.2.2). Furthermore, risankizumab was well-tolerated at dose regimens up to 6 doses of CCI ie, a total of CCI over a period of 26 weeks. Longer-term follow-up of these participants through Week 52 did not identify any significant safety concerns based on published data.[6] Nonetheless, an external DMC will be commissioned to monitor the benefit-risk of guselkumab, as described in Section 9.5.2.

4.3.1.1.2. Maintenance Dose Regimens

The posology of other biologics in Crohn's disease suggests that once the inflammatory burden of the disease is reduced, the drug exposures required to maintain efficacy may be lower than the exposures attained with initial induction doses.

In the ustekinumab Crohn's disease Phase 3 studies, among participants who were in remission at Week 8 following an induction regimen of CCI maintenance regimen resulted in 67% of participants maintaining remission at Week 52. In the risankizumab Crohn's disease Phase 2 study, among participants who were in remission at Week 26 after receiving up to 6 months of CCI induction dosing, the long-term uncontrolled data showed that a CCI regimen resulted in 71% of patients maintaining remission at Week 52.[6]

Accordingly, in this protocol, after 12 weeks of guselkumab C CI induction treatment, dose regimens providing lower guselkumab exposures will be evaluated during CC maintenance treatment through Week 48. The selected maintenance dose regimens provide reasonable maintenance:induction exposure ratios comparable to those of other biologics approved in Crohn's disease.

Regimens 1 and 2 evaluate guselkumab CCI induction, respectively. For each of these regimens, a maintenance regimen of CCI will be studied to evaluate if higher exposure than that tested in the risankizumab Phase 2 study (ie, CCI is necessary to optimize efficacy in maintenance.

For Regimen 3, which evaluates guselkumab CCI induction, a maintenance regimen of CCI will be studied. The guselkumab CCI regimen is expected to provide efficacy at least similar to, or greater than that observed with ustekinumab CCI the maintenance dose regimen for the active comparator being evaluated in this study.

Overall, the 2 guselkumab maintenance CC dose regimens provide a 4-fold range of exposure that should support dose selection for Phase 3.

No treatment adjustments are planned for any of the treatment groups from Week 0 through Week 48 of GALAXI 1, except for CCI induction placebo nonresponders who will cross over to receive the ustekinumab dose regimen being evaluated in this study (ie, CCI at Week 12 followed by CCI from Week 20). Participants randomized to placebo CCI who are responders at Week 12 will continue to receive CCI placebo through Week 44.

4.3.1.2. Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)

Based on the Phase 2 data, 2 guselkumab dose regimens (ie, CCI) were selected for confirmatory evaluation in Phase 3.

The goal was to select a single induction dose regimen from the induction dose range evaluated (ie, CCI to CCI at Week 0, Week 4, and Week 8) in the Phase 2 dose-ranging study based on the totality of the efficacy, safety, and exposure-response data at the time of dose decision. The goal of selecting a single induction regimen to be evaluated in the Phase 3 dose-confirming studies was based on the consideration that a sufficient amount of information would be available to establish an optimal induction dose regimen. In this scenario, the selected induction dose regimen was to be paired with 2 maintenance dose regimens selected from the range of exposures obtained from the guselkumab CCI dose regimens evaluated in Phase 2 (ie, between CCI. As described in Section 4.1.2, the goal of selecting a single induction dose regimen to be paired with 2 maintenance dose regimens was achieved.

No treatment adjustments are planned for any of the treatment groups from Week 0 through Week 48 of GALAXI 2 and GALAXI 3, except for CCI induction placebo nonresponders who will cross over to receive the ustekinumab dose regimen being evaluated in this study (ie, CCI at Week 12 followed by CCI from Week 20). Participants randomized to placebo CCI who are responders at Week 12 will continue to receive CCI placebo through Week 44.

4.3.1.3. Long-Term Extension (Week 48 to Week 240) for GALAXI 1, 2, and 3

Participants will continue on their assigned guselkumab maintenance dose during the LTE of GALAXI 1, GALAXI 2, and GALAXI 3. Participants who experience inadequate response between Week 52 through Week 80 while on the lower of the 2 maintenance dose regimens being evaluated in the applicable study will be eligible for a single dose adjustment and will receive the higher maintenance dose until the end of the LTE to assess if they can regain clinical response.

4.3.2. Ustekinumab

Ustekinumab (STELARA) is approved in many countries (including the US, EU, Canada, and Japan) for the treatment of Crohn's disease and is included in this study as an active comparator for comparisons with guselkumab after Week 12. The ustekinumab dosages selected for the study were found to be safe and effective in the pivotal Phase 3 studies of ustekinumab in patients with Crohn's disease.[8,22] All participants enrolled in the ustekinumab group will receive a single CCI induction dose of approximately CCI (based on weight tiers), which is the approved induction dose for patients with Crohn's disease. From Week 8, participants will receive a maintenance dose regimen of CCI Of note, the ustekinumab CCI regimen was chosen for the maintenance dose regimen as opposed to the every-12-weeks regimen as it more reliably demonstrated efficacy

across a range of clinical endpoints, especially with more stringent measures of efficacy such as sustained remission, in the pivotal ustekinumab Crohn's disease maintenance study (IM-UNITI). Evaluating the CCI regimen would, therefore, provide participants randomized to ustekinumab with the best chance for the highest levels of efficacy, thus allowing the fairest comparison for testing the superiority of guselkumab to ustekinumab.

4.4. End of Study Definition

For each of the 3 studies conducted under this protocol, the studies are considered completed when the last participant completes the last scheduled study assessment shown in the Schedule of Activities (Section 1.3) or if a decision has been made by the sponsor not to pursue an indication in Crohn's disease 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

A target of approximately 1,340 participants combined will be enrolled under the GALAXI protocol and will be randomized into the Phase 2 study (GALAXI 1) or one of the two Phase 3 studies (GALAXI 2 or GALAXI 3).

Screening for eligible participants will be performed within approximately 5 weeks before administration of the study intervention. Refer to Section 5.4, Screen Failures, for conditions under which repeating any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative or designee and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

The definition of baseline as applied to the inclusion and exclusion criteria below is defined as the Week 0 randomization visit.

5.1. Inclusion Criteria

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

1. Be male or female (according to their reproductive organs and functions assigned by chromosomal complement) ≥18 years of age.
2. Have Crohn's disease or fistulizing Crohn's disease of at least 3 months duration (defined as a minimum of 12 weeks), with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography, histology, and/or endoscopy.
3. Have clinically active Crohn's disease, defined as a baseline CDAI score ≥220 but ≤450 and either:
    a. Mean daily SF count >3, based on the unweighted CDAI component of the number of liquid or very soft stools

OR

b. Mean daily AP score >1, based on the unweighted CDAI component of AP

4. Criterion modified per Amendment 1.

4.1. Criterion modified per Amendment 3.

4.2. Criterion modified per Amendment 5.

4.3. Have endoscopic evidence of active ileocolonic Crohn's disease as assessed by central endoscopy reading at the screening endoscopy (Schedule of Activities, Table 4), defined as a screening SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease), based on the presence of ulceration in at least 1 of the 5 ileocolonic segments, resulting in the following specified ulceration component scores:

a. a minimum score of 1 for the component of "size of ulcers"

AND

b. a minimum score of 1 for the component of "ulcerated surface".

Of note, before the implementation of Amendment 3, where the minimum SES-CD score was ≥3 based on the presence of ulceration, within each of the studies, a maximum of 10% of the total enrolled population could include participants who had baseline scores for SES-CD <4 (ie, for participants with isolated ileal disease) or SES-CD <7 (ie, for participants with colonic or ileocolonic disease).

Note: Adenomatous polyps should be removed before the first administration of study agent. Histopathology for polyps or for any biopsies performed during the screening ileocolonoscopy due to concern or surveillance for malignancy should be negative for malignancy and dysplasia (low-grade, high-grade, or "indefinite dysplasia in reactive atypia") prior to the first dose of study intervention. Please refer to Exclusion Criterion #20 regarding metaplasia.

Concomitant or previous medical therapies received

5. Criterion modified per Amendment 4.

5.1. Criterion modified per Amendment 5.

5.2. Prior or current medication for Crohn's disease must include at least 1 of the following, and must fulfill additional criteria as described in Appendix 2 (Section 10.2), Appendix 3 (Section 10.3), and Appendix 4 (Section 10.4), as applicable:

a. Current treatment with oral corticosteroids (including budesonide and beclomethasone dipropionate) and/or immunomodulators (AZA, 6-MP, MTX)

OR

b. History of failure to respond to, or tolerate, at least 1 of the following therapies: oral corticosteroids (including budesonide and beclomethasone dipropionate) or immunomodulators (AZA, 6-MP, MTX).

OR

c. History of corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of Crohn's disease).

OR

d. Has previously demonstrated lack of initial response (ie, primary nonresponders), responded initially but then lost response with continued therapy (ie, secondary nonresponders), or were intolerant to 1 or more biologic agents with at least the minimum dose approved for the treatment of Crohn's disease (ie, infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars for these agents, see Appendix 3 [Section 10.3]).

Note: Participants meeting criteria 5a-c may also be naïve to biologic therapy (ie, a TNF antagonist or vedolizumab or ustekinumab) or may have been exposed to these biologic therapies but have not demonstrated inadequate response or intolerance. Participants with prior exposure to IL-12/23 or IL-23 agents are ineligible for entry into this protocol, with the exception of participants who have had exposure to ustekinumab at its approved labeled dosage **AND** have met the required washout criterion **AND** have not demonstrated failure or intolerance to ustekinumab (per Exclusion Criterion 7, Appendix 4 [Section 10.4]).

6. Adhere to the following requirements for concomitant medication for the treatment of Crohn's disease. The following medications are permitted provided that doses meeting the requirements listed below are stable or have been discontinued prior to baseline within the timeframes specified below:

   a. Oral 5-aminosalicylic acid (5-ASA) compounds on stable doses for at least 2 weeks; or if recently discontinued, must have been stopped for at least 2 weeks.

   b. Oral corticosteroids at a prednisone-equivalent dose at or below CCI day, or CCI /day of budesonide, or CCI /day beclomethasone dipropionate, and on stable dosing for at least 2 weeks; or if recently discontinued, must have been stopped for at least 2 weeks.

   c. Conventional immunomodulators (ie, AZA, 6-MP, or MTX) for at least 12 weeks and have been on a stable dose for at least 4 weeks; or if recently discontinued, must have been stopped for at least 4 weeks.

   d. If receiving antibiotics as a primary treatment of Crohn's disease, doses must be stable for at least 3 weeks; or if recently discontinued, must have been stopped for at least 3 weeks.

   e. If receiving enteral nutrition as a primary treatment for Crohn’s disease, must have been receiving for at least 2 weeks; or if recently discontinued, must have been stopped for at least 2 weeks.

Screening laboratory tests

7. Have screening laboratory test results within the following parameters, and if 1 or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted during the approximately 5-week screening period:

   a. Hemoglobin ≥8.0 g/dL.

   b. White blood cells (WBCs) ≥3.5 x 10^3/µL.

   c. Neutrophils ≥1.5 x 10^3/µL.

d. Platelets ≥100 x 10^3/µL.

e. Serum creatinine ≤1.5 mg/dL.

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

g. Direct (conjugated) bilirubin <1.0 mg/dL.

Tuberculosis

8. Criterion modified per Amendment 3.

8.1. Criterion modified per Amendment 5.

8.2. Are considered eligible according to the following tuberculosis (TB) screening criteria:

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

- currently receiving treatment for latent TB
- will initiate treatment for latent TB prior to the first administration of study intervention

  OR

- have documentation of having completed appropriate treatment for latent TB within 5 years prior to the first administration of study intervention. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculosis treatment and provide appropriate documentation.

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

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

d. Criterion modified per Amendment 3.

8.d.1. Criterion modified per Amendment 5.

8.d.2. Within 8 weeks prior to the first administration of study intervention, have a negative QuantiFERON®-TB test result (or T-SPOT® Test for sites in Japan where local regulations permit), or have a newly identified positive QuantiFERON-TB test (or T-SPOT Test for sites in Japan) in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first study intervention administration (see Section 8.2.6). Indeterminate or suspected false positive results should be handled as outlined in Section 8.2.6.

Note: A negative tuberculin skin test result (see Appendix 5 [Section 10.5]) is additionally required if the QuantiFERON-TB test is not approved/registered in the country in which this protocol is being conducted. In Ukraine, while the QuantiFERON-TB test is not approved/registered, it is acceptable, and an additional tuberculin skin test is not required.

The QuantiFERON-TB test (or T-SPOT test for sites in Japan where local regulations permit) and the tuberculin skin test are not required at screening for participants with a history of latent TB, if active TB has been ruled out, and if appropriate treatment has been initiated/completed as described above in Inclusion Criterion 8a.

e. Criterion modified per Amendment 3.

8.e.1. Have a chest radiograph (both posterior-anterior and lateral views, or per local/country regulations where applicable), taken ≤12 weeks before the first administration of study intervention and read by a qualified radiologist or qualified pulmonologist according to local clinical practice, with no evidence of current, active TB or old, inactive TB. A chest CT scan is also acceptable if obtained instead of a chest radiograph outside of the protocol.

Contraception

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

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

9. A female participant of childbearing potential must have a negative urine pregnancy test result at screening and baseline.
10. Before randomization, a female participant must be (as defined in Appendix 6 [Section 10.6], Contraceptive and Barrier Guidance and Collection of Pregnancy Information):
    a. Not of childbearing potential
    b. Of childbearing potential and:
        - 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 16 weeks after last dose (ie, the end of relevant systemic exposure). Examples of highly effective methods of contraception are located in Appendix 6 (Section 10.6), Contraceptive and Barrier Guidance and Collection of Pregnancy Information; however, the method selected must meet local/regional regulations/guidelines for highly effective contraception.

    Note: If a participant's childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin using a highly effective method of contraception, as described throughout the inclusion and exclusion criteria.
11. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 16 weeks after the last administration of study intervention.
12. During the study and for at least 16 weeks after the last administration of study intervention, a male participant

a. who is sexually active with a female of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository).

b. who is sexually active with a pregnant female must use a condom.

c. must agree not to donate sperm for the purpose of reproduction.

General

13. Criterion modified per Amendment 1.

    13.1. Criterion modified per Amendment 2.

    13.2. Be willing and able to adhere to all specified requirements, including but not limited to completion of assessments, adherence to visit schedule, and compliance with the lifestyle restrictions (Section 5.3), etc, as specified in this protocol.

14. 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.

15. Must sign a separate ICF if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample 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 protocol:

1. Has complications of Crohn's disease, such as symptomatic strictures or stenoses, short gut syndrome, or any other manifestation, that might be anticipated to require surgery, could preclude the use of the CDAI to assess response to therapy, or would possibly confound the ability to assess the effect of treatment with guselkumab or ustekinumab.

2. Currently has or is suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained and adequately treated at least 3 weeks before baseline, or 8 weeks before baseline for intra-abdominal abscesses, provided that there is no anticipated need for any further surgery. Participants with active fistulas may be included if there is no anticipation of a need for surgery and no abscesses are currently identified.

3. Criterion modified per Amendment 3.

    3.1. Has had any kind of bowel resection within 6 months, or any other intra-abdominal or other major surgery within 12 weeks before baseline.

4. Has a draining (ie, functioning) stoma or ostomy.

5. Criterion modified per Amendment 4.

    5.1. Has a stool culture or other examination positive for an enteric pathogen, including *Clostridioides difficile* (formerly known as *Clostridium difficile*) toxin, in the previous 4 months, unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen.

Concomitant or previous medical therapies received

6. Criterion modified per Amendment 3.

   6.1. Criterion modified per Amendment 4.

   6.2. Criterion modified per Amendment 5.

   6.3. Has received any of the following prescribed medications or therapies within the specified period:

      a. [redacted] corticosteroids received within 3 weeks of baseline

      b. Cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil received within 8 weeks of baseline

      c. 6-thioguanine received within 4 weeks of baseline

      d. Biologic agents:

         1) Anti-TNF therapy (eg, infliximab, etanercept, certolizumab pegol, adalimumab, golimumab) received within 8 weeks of baseline

         2) Vedolizumab received within 12 weeks of baseline

         3) Ustekinumab received within 16 weeks of baseline

      Note: A shorter washout duration for anti-TNF agents, ustekinumab or vedolizumab is acceptable if undetectable drug levels of the biologic can be demonstrated. Undetectable levels are defined as levels below the quantification limit using approved commercial testing.

         4) Other immunomodulatory biologic agents, including approved and investigational biologic agents, received within 12 weeks of baseline or within 5 half-lives of baseline, whichever is longer.

      e. Any investigational intervention received within 4 weeks of baseline or within 5 half-lives of baseline, whichever is longer. (Refer to Exclusion Criterion 6.d.4 for investigational biologic agents.)

      f. Nonautologous stem cell therapy (eg, Prochymal), natalizumab, efalizumab, or biologic agents that deplete B- or T-cells (eg, rituximab, alemtuzumab, or visilizumab) received within 12 months of baseline.

      g. Treatment with apheresis (eg, Adacolumn apheresis) or total parenteral nutrition for Crohn's disease within 3 weeks of baseline.

7. Criterion modified per Amendment 5.

   7.1. Has previously received a biologic agent targeting IL-12/23 or IL-23, including but not limited to briakinumab, brazikumab, guselkumab, mirikizumab (formerly LY3074828), and risankizumab.

   Exception: Participants who have had exposure to ustekinumab at its approved labeled dosage **AND** have met the required washout criterion **AND** have not demonstrated failure or intolerance to ustekinumab (criteria specified in Appendix 4 [Section 10.4]) are not excluded from this protocol provided that other inclusion criteria have been satisfied and no other exclusion criteria are met.

Infections or predisposition to infections:

8. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (eg, recurrent pyelonephritis or chronic non-remitting cystitis), or open, draining, or infected skin wounds or ulcers.
9. Has current signs or symptoms of a clinically significant infection. Established non-serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.
10. Has a history of serious infection (eg, hepatitis, sepsis, pneumonia, or pyelonephritis), including any infection requiring hospitalization or IV antibiotics, during the 8 weeks before baseline.
11. Has evidence of a herpes zoster infection within 8 weeks before baseline.
12. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Participants with radiographic evidence of possible prior histoplasmosis or coccidioidomycosis will be excluded.
13. Has a chest radiograph within 12 weeks prior to the first administration of study intervention that shows an abnormality suggestive of a malignancy or current active infection, including TB.
14. Has or has had a nontuberculous mycobacterial infection or clinically significant opportunistic infection (eg, cytomegalovirus colitis, pneumocystosis, invasive aspergillosis).
15. Participants must undergo screening for human immunodeficiency virus (HIV). Any participant who has a history of HIV antibody positivity, or tests positive for HIV at screening, is not eligible for this study.
16. Criterion revised per Amendment 1.

    16.1. Criterion revised per Amendment 4.

    16.2. Participants who are seropositive for antibodies to hepatitis C virus (HCV), unless they satisfy one of the following conditions:

        a. Have a history of successful treatment (defined as being negative for HCV RNA at least 12 weeks after completing antiviral treatment) and have a negative HCV RNA test result at screening, OR

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

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

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

18. Has received, or is expected to receive, any live virus or bacterial vaccination within 12 weeks before the first administration of study intervention. For Bacille Calmette-Guérin (BCG) vaccine, see Exclusion Criterion 19.
19. Has had a BCG vaccination within 12 months of screening.

Malignancy or increased potential for malignancy

20. Criterion modified per Amendment 5.

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

    Note: Premalignant conditions (eg, gastric or esophageal metaplasia) should be discussed with the sponsor for eligibility determination.

21. Has a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy, hepatomegaly, or splenomegaly, or monoclonal gammopathy of undetermined significance.

Coexisting medical conditions or past medical history

22. Has a history of severe, progressive, or uncontrolled renal, genitourinary, hepatic, hematologic, endocrine, cardiac, vascular, pulmonary, rheumatologic, neurologic, psychiatric, or metabolic disturbances, or signs and symptoms thereof.
23. Has a transplanted organ (with exception of a corneal transplant >12 weeks before screening).
24. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of adequate venous access.
25. Is known to have had a history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Disorders (5th edition) (DSM-V) criteria within 12 months before baseline.
26. 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.
27. Has known allergies, hypersensitivity, or intolerance to guselkumab or ustekinumab or any of their excipients (see guselkumab IB and ustekinumab IB).
28. Is a woman who is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 16 weeks after the last administration of study intervention.
29. Is a man who plans to father a child while enrolled in this study or within 16 weeks after the last administration of study intervention.

General

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

31. Criterion modified per Amendment 5.

    31.1. Has any condition for which, in the opinion of the investigator or sponsor, 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.

32. 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.

33. Has previously undergone allergy immunotherapy for prevention of anaphylactic reactions (eg, venom immunotherapy).

Infections or predisposition to infections:

34. Coronavirus Disease 2019 (COVID-19) infection

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

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

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

        AND

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

    Note on the COVID-related exclusion:

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

    Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

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

5.3. Lifestyle Considerations

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

1. Lifestyle consideration modified per Amendment 4.

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

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

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 not receive guselkumab or ustekinumab 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 undergo a SID visit before he or she terminates study participation.
4. Must agree not to receive a live virus or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention.
5. Lifestyle consideration modified per Amendment 4.

   5.1. Must agree not to receive a BCG vaccination during the study and for 16 weeks after receiving the last dose of study intervention.

6. Participants who require treatment for latent TB must complete the appropriate course of TB therapy.
7. Must be willing and able to complete a daily diary to document clinical symptoms, AEs, etc.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor or designee 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 date of birth (as allowed by local regulations). In cases where the participant is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

Completion of screening and randomization procedures within the specified screening window of approximately 5 weeks is required.

If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph, stool analysis, ileocolonoscopy), 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.

Additional criteria for retesting and rescreening are outlined below.

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 approximately 5 weeks.

Rescreening

Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then start a new screening phase including the collection and testing of new laboratory specimens. Previous TB evaluation results (including the QuantiFERON-TB test [or TSPOT test for sites in Japan where local regulations permit] and chest radiograph) and stool study results, and ileocolonoscopy results from the first screening event may be used if they meet the specified protocol criteria as described in Section 5.1. Medical Monitor approval is required prior to the study site obtaining a new informed consent for rescreening.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

In both the Phase 2 and Phase 3 portions of the protocol:

- All participants will receive 2 IV infusions at Week 0 (1 active + 1 placebo OR 2 placebo) and 1 IV infusion at Weeks 4, 8, and 12 (either active or placebo).
- All participants will receive 1 CC injection (either active or placebo) at Week 8 and up to 3 CC injections (either active or placebo) at each visit from Week 12 to Week 140.

CCI study intervention (including the flush) should be administered over a period of not less than 1 hour, and not more than 2 hours. The infusion (including the flush) should be completed within 6 hours of preparation.

At Week 0, the guselkumab/placebo in dextrose IV infusion (including the flush with dextrose) should be administered first. The IV infusion administration line set will be changed (ie, use a new line set) prior to the administration of the ustekinumab/placebo in saline IV infusion, followed by the flush with saline.

At Week 4, only guselkumab/placebo in dextrose IV infusion is administered (including the flush with dextrose).

At Week 8, the guselkumab/placebo in dextrose IV infusion (including the flush with dextrose) should be administered first, followed by CC injection with ustekinumab/placebo investigational product (IP).

At Week 12, the ustekinumab/placebo in saline IV infusion (including the flush with saline) should be administered first, followed by CC injection with guselkumab/placebo IP.

At Week 12 and beyond, multiple CC injections may be administered within the administration visit. Each injection of study intervention should be given at a different location of the body.

Detailed instructions on the preparation and administration of study intervention will be provided in the site Investigational Product Procedures Manual (IPPM).

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.14.

6.1.1. Combination Products

CCI

CCI

CCI

CCI

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Guselkumab

Guselkumab and placebo for guselkumab will be supplied to the study sites. All guselkumab and placebo for guselkumab must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. The sterile product does not contain preservatives and is designed for single use only. It should be clear to slightly yellow and may contain tiny white or clear particles. Do not use if the liquid is cloudy or discolored or has large particles. Protection

from light is not required during the preparation and administration of the study intervention material. Aseptic procedures must be used during the preparation and administration of the study intervention material.

Further details regarding the preparation and storage of guselkumab and placebo will be provided in the site IPPM.

6.2.2. Ustekinumab

All ustekinumab must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C), not frozen, and protected from light. Vigorous shaking of the product should be avoided. Prior to administration, the product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow color), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used.

Aseptic procedures must be used during the preparation and administration of the study intervention material. Exposure to direct sunlight should be avoided during preparation and administration.

The needle cover on the CCI contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Further details regarding the preparation and storage of ustekinumab and placebo will be provided in the site IPPM.

6.2.3. Accountability

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

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

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

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

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 GALAXI 1. Participants will be randomly assigned to 1 of 5 treatment groups (1:1:1:1:1 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 baseline CDAI score (≤300 or >300) and BIO-Failure status (Yes/No). The 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.

Central randomization will also be implemented in GALAXI 2 and GALAXI 3. Participants will be randomly assigned to GALAXI 2 (n=approximately 490) or GALAXI 3 (n=approximately 490), using a permuted block randomization with baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), prior BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) as the stratification variables. Within each stratum, participants in each study will then be randomized in a 2:2:2:1 ratio to receive 1 of 2 dose regimens of guselkumab, ustekinumab, or placebo, respectively, based on a computer-generated randomization schedule prepared before the studies by or under the supervision of the sponsor. The 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 protocol name, medication number, and reference number. The medication number will be entered in the electronic case report form (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 (ie, study intervention serum concentrations, antibodies to study intervention) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the study unblinding.

The post-baseline results of CRP and fecal calprotectin tests performed by the central laboratory will be blinded to the investigative sites. If an investigative site requests these data, it will be provided to them after the Week 48 analyses of both Phase 3 studies have been completed.

All participants will continue to receive active or placebo study intervention administration in the LTE in a blinded fashion until study unblinding, which will occur after the Week 48 DBL and the Week 48 analyses have been completed for the Phase 2 study (for participants entering the LTE from GALAXI 1) or for the Phase 3 studies (for participants entering the LTE from GALAXI 2 or GALAXI 3).

In GALAXI 1, the sponsor will remain blinded until the Week 48 DBL. However, a limited number of sponsor personnel will become unblinded at the Week 12 DBL for a dosing decision after the first 250 randomized participants have either completed the Week 12 visit or have terminated study participation before Week 12. If a dosing decision cannot be made, a subsequent DBL will occur after the first 250 randomized participants have either completed the Week 24 visit or have terminated study participation before Week 24. At the time of each analysis, selected sponsor personnel will be unblinded for all randomized participants from the Initial Dose Decision Cohort and for any available participants from the Transition Cohort. After the Week 48 DBL when all randomized participants (including both the Initial Dose Decision Cohort and the Transition Cohort) have either completed the Week 48 visit or have terminated study participation before Week 48, the treatment assignment information will be unblinded for all participants and released to the sponsor for analysis.

In GALAXI 2 or GALAXI 3, when all randomized participants in that study have either completed the Week 48 visit or have terminated study participation before Week 48, the treatment assignment information will be unblinded for all participants in that study and released to the sponsor for analysis. The sponsor will remain blinded until after the Week 48 DBL has occurred.

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 Schedule of Activities for participants who discontinue study intervention (Section 1.3).

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 [redacted] 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 [redacted] injections, this will include date and time of [redacted] injection.

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

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

6.5. Concomitant Therapy

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

All therapies (prescription or over the counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, 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 preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

6.5.1. Concomitant Medications

Participants who are receiving oral 5-ASA compounds, oral corticosteroids, conventional immunomodulators (ie, AZA, 6-MP, or MTX), antibiotics, and/or enteral nutrition for the treatment of Crohn's disease 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 Crohn's disease at baseline (ie, Week 0) of all 3 studies should maintain a stable dose through Week 48, 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. Corticosteroids must be maintained at baseline doses through Week 12, and all participants must begin tapering corticosteroids at Week 12, unless medically not feasible (see further details in Section 6.5.1.1, Oral Corticosteroids Tapering).

Week 0 through Week 48

From Week 0 through Week 48 of each study, enrolled participants should not initiate any of the following concomitant Crohn's disease-specific medical therapies:

- Oral or rectal 5-ASA compounds.
- Immunomodulators (ie, AZA, 6-MP, or MTX).
- Oral, parenteral, or rectal corticosteroids, including budesonide and beclomethasone dipropionate.
- Antibiotics as a primary treatment for Crohn's disease.
- Total parenteral nutrition or enteral nutrition as a treatment for Crohn's disease.

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 (guselkumab, ustekinumab, or placebo), it may be considered a treatment failure. Treatment failures will be defined in the SAP.

Week 12 and through Week 48

From Week 12 through Week 48 of each study, participants may transiently use (ie, for <4 weeks) increased doses of corticosteroids for reasons other than treatment for Crohn's disease (eg, stress doses of corticosteroids for surgery, asthma, adrenocortical insufficiency).

During treatment phase of LTE (ie, Week 48 through Week 240):

Concomitant therapies for Crohn's disease including 5-ASAs, corticosteroids, antibiotics, and immunomodulators (ie, AZA, 6-MP, or MTX), and/or total parenteral or enteral nutrition may be administered and changed at the discretion of the investigator.

6.5.1.1. Oral Corticosteroids Tapering

At Week 12, all participants who were taking 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 7. 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 7: Recommended Tapering Schedule for Oral Corticosteroids

Recommended Tapering Schedule for Oral Corticosteroids (Other than Budesonide)	
Dose CCI day prednisone or equivalent	Taper daily dose by CCI /week until receiving CCI day, then continue tapering at CCI week until CCI /day
Dose CCI /day prednisone or equivalent	Taper daily dose to CCI /day for 1 week, then continue at CCI week until CCI /day
Dose CC mg/day prednisone or equivalent:	Taper daily dose by CCI /week until CCI /day
Recommended Tapering Schedule for Oral Budesonide	
Participants receiving budesonide should have their daily dose tapered by CCI every 3 weeks until CCI /day	

6.5.2. Prohibited Concomitant Medications

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

- Immunomodulatory agents other than AZA, 6-MP, or MTX (including, but not limited to, 6-thioguanine, cyclosporine, mycophenolate mofetil, tacrolimus, and sirolimus).
- Immunomodulatory biologic agents (including, but not limited to, TNF antagonists, IL-23 antagonists, natalizumab, ustekinumab, rituximab, vedolizumab). Ustekinumab is permitted in this study only in participants randomly assigned to ustekinumab and only as stipulated in this protocol.
- Experimental Crohn's disease medications (including, but not limited to, upadacitinib, filgotinib, ozanimod, etrolizumab, brazikumab, mirikizumab [formerly LY3074828], risankizumab, GS5745).

- 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 a SID visit and an FES visit as described in Section 1.3.

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

6.5.3. Vaccinations (Including COVID-19)

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

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

Refer to Section 5.3 for additional vaccination details.

6.6. Dose Modification

No treatment/dose adjustment will be permitted through Week 48. After that time point, treatment/dose modification will be allowed as described in Section 4.1.3.1.

6.7. Intervention After the End of the Study

This protocol is designed to provide participants with up to approximately 5 years of treatment (ie, 48-week treatment under the Phase 2 or Phase 3 studies plus approximately 4 additional years of treatment in the LTE).

After completing the LTE, participants will be instructed that study intervention will not be made available to them as part of this protocol and that they should return to their treating physician for guidance.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

A participant will be considered to have completed the study if he or she has completed assessments through the FES visit as specified in the Schedule of Activities (Section 1.3).

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 Schedule of Activities (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 treatment must be discontinued under the following conditions:

1. The participant initiates treatment with prohibited therapies for Crohn's disease (Section 6.5.2).
2. The participant has a Crohn's disease-related surgery that represents a lack of efficacy of study intervention or that will preclude the future ability to assess efficacy using the CDAI or other instruments required for demonstration of efficacy endpoints.

   Note: Other permitted Crohn's disease-related surgeries (eg, to resolve long-standing complications such as strictures or for symptomatic nonhealing fistulas, in participants experiencing improvement on study intervention) other than minor procedures (eg, placement of a seton or cutaneous drainage of an abscess) should be postponed until after the FES visit, unless necessary to ensure participant well-being and/or safety.
3. The participant becomes pregnant or plans a pregnancy within the study period. Refer to Appendix 6 (Section 10.6), Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
4. The participant (or the participant's representative) withdraws consent for administration of study intervention.
5. The participant develops a systemic 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 QuantiFERON-TB (or T-SPOT for sites in Japan where local regulations permit) 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), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next study intervention administration and continued to completion (see also Section 8.2.6, Section 10.5, and Section 10.6). Indeterminate QuantiFERON-TB (or borderline T-SPOT for sites in Japan) test results

should be handled as described in Section 8.2.6. Participants with persistently indeterminate QuantiFERON-TB (or borderline T-SPOT for sites in Japan) test results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's or designee's medical monitor and recorded in the participant's source documents and initialed by the investigator.

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

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

7. Criterion revised per Amendment 1.

   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 liver test abnormalities that are not transient and are not explained by other etiologies, as described in Section 8.2.11 and Appendix 9 (Section 10.9). Such abnormalities would include:

   - ALT or AST >8 x ULN
   - ALT or AST >5 x ULN for more than 2 weeks
   - ALT or AST >3 x ULN and (TBL >2 x ULN or international normalized ratio [INR] >1.5)
   - ALT or AST >3 x ULN and symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash) and/or eosinophilia (>5%)

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

11. The 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. Criterion revised per Amendment 1.

   1.1. Persistent inadequate response or worsening of Crohn's disease:

a. The participant has a change from baseline in the CDAI score <70 points and has a CDAI score >220 at both Week 20 and Week 24.

OR

b. The participant experiences AEs consistent with clinically significant worsening of Crohn's disease at any time during the study.

These events must be evaluated by the investigator. A consultation with the study medical monitor may also be considered, at the investigator's discretion. Discontinuation of study intervention must be considered in participants with clinically significant worsening of Crohn's disease where continuation of the study intervention is not in the best interest of the participant.

2. The participant develops a serious infection, including but not limited to sepsis or pneumonia.
3. The participant reports Suicidal Ideation with Intention to Act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), or any suicidal behavior (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline C-SSRS assessment. If a participant can be adequately treated with psychotherapy and/or pharmacotherapy based on an evaluation by a mental health professional, then the participant, at the discretion of the investigator, may be continued with treatment if agreed to by the medical monitor or designee. Discussion of such participants with the medical monitor or designee is required.
4. Criterion revised per Amendment 1.

4.1. 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 Schedule of Activities (Section 1.3). If the reason for discontinuation of study intervention is withdrawal of consent, every effort should be made to conduct the SID visit assessments, as indicated in the Schedule of Activities, 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:

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

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 for the SID visit in the appropriate Schedule of Activities (Table 4) at the time they terminate study participation. No additional evaluations are performed after 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. Participants who withdraw will not be replaced.

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 for research activities 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. 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 future research (refer to Appendix 8 [Section 10.8], Long-Term Retention of Samples for Additional Future Research). 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 before considering the participant to be lost to follow-up. 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 Schedule of Activities (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker (PD), pharmacogenomic, medical resource utilization, health economic, and safety measurements applicable to this study.

Except at the screening visit, 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 completed as outlined in the Schedule of Activities (Section 1.3). 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 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 and health economics data will be collected. Refer to Section 8.9, Medical Resource Utilization and Health Economics for details.

Screening Phase

At the screening visit, written informed consent must be obtained from the participant for this program by the principal investigator or designee before performing any protocol-specific procedure. Procedures to be performed at the screening visit are outlined in the Schedule of Activities (Section 1.3).

The CDAI diary will be completed by participants during the screening period. The investigator or appropriate site personnel will use the hematocrit value obtained during screening to calculate the CDAI score at Week 0.

A minimum of 7 days of CDAI data during the screening period is required to calculate the CDAI score at baseline (Week 0).

Women of childbearing potential must have a negative urine pregnancy test result at screening. Participants must be reminded that they are required to use a highly effective method of contraception during the study (as described in Inclusion Criterion 10) and must continue taking such precautions for 16 weeks 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 8.2.6 and Appendix 5 [Section 10.5]) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

Participants with a negative QuantiFERON-TB (or T-SPOT for sites in Japan where local regulations permit) test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB [or T-SPOT for sites in Japan] test is not approved/registered or the tuberculin skin is mandated by local health authorities) are eligible to continue with prerandomization procedures. Note: A negative tuberculin skin test is additionally required if the QuantiFERON-TB (or T-SPOT for sites in Japan) 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 acceptable, and an additional tuberculin skin test is not required.

Participants with a newly identified positive QuantiFERON-TB (or tuberculin skin) test (or T-SPOT test for sites in Japan where local regulations permit) result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed, or the participant will be excluded from the study.

A participant whose first QuantiFERON-TB (or T-SPOT for sites in Japan where local regulations permit) test result is indeterminate should have the test repeated. If the second QuantiFERON-TB (or T-SPOT for sites in Japan) test result is also indeterminate, the participant may be enrolled without treatment for latent TB if his/her chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator and medical monitor.

An assessment of all screening laboratory test results, clinical data, and concomitant medication data will be made by the principal investigator or designee to confirm that the participant satisfies all inclusion criteria and does not violate any exclusion criteria.

Blood Sample Collection

Blood samples should be collected at the visits indicated in the Schedule of Activities (Section 1.3). The date and time of collection will be recorded. When blood samples are to be collected for safety, PK, efficacy, biomarkers, and pharmacogenomic evaluations at the same time point, the order of blood draws will be samples for CRP, chemistry/lipids, hematology, PK/Immunogenicity, serum biomarkers, pharmacogenomics, and RNA expression.

The maximum total blood volume to be collected from each participant in each study (GALAXI 1, GALAXI 2, or GALAXI 3) will be approximately 500 mL over approximately 252 weeks (Table 8). This total may vary due to:

- whether or not the participant consents to take part in the optional pharmacogenomics study (10 mL)
- which final visit the participant completes (SID [23 mL] versus FES [12 mL])
- repeat or unscheduled samples taken for safety reasons or technical issues with the samples
- regional or country-specific variation in blood collection systems

Table 8: Volume of Blood to be Collected from Each Participant per Study

Study Period or Type of Sample	Approximate Total Volume of Blood (mL)
Screening through Week 48	216
Pharmacogenomics sample [a]	10
Week 52 through Week 96	92
Week 100 through Week 144	69
Week 148 through Week 240	94
Final visit (SID or FES)	23 or 12 [b]
Approximate Total [c,d]	**500**

a. Sample to be collected only from participants who have consented to provide an optional pharmacogenomics (DNA) sample for research.
b. A participant's final visit will be either a study intervention discontinuation (SID) visit (23 mL) or a final efficacy and safety follow-up (FES) visit (12 mL).
c. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
d. May differ slightly due to regional or country-specific variation in blood collection systems.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Schedule of Activities (Section 1.3) for the timing and frequency of all sample collections.

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

Study-Specific Materials

Supplies provided to the investigator will include:

- Investigator Site File (includes protocol and IB)
- IPPM
- Central Laboratory Manual
- eCRF completion instructions
- Patient recruitment materials
- ICF
- Participant Diary Card including CDAI (including PRO-2), Bristol Stool Form Scale (BSFS), and Abdominal Pain – Numerical Rating Scale (AP-NRS)
- IWRS Manual
- Biopsy Manual
- ePRO equipment

- Endoscopy kit
- Imaging Manual
- Laboratory kits

8.1. Efficacy Assessments

Efficacy evaluations will include the following:

- CDAI
- PRO-2 (the unweighted CDAI components of the total number of liquid or very soft stools and the AP score)
- Endoscopic assessments of the intestinal mucosa based on the presence and absence of mucosal ulcerations and the SES-CD, and histologic assessments based on the Global Histology Activity Score (GHAS), Robarts histopathology index (RHI), and Geboes scores
- Inflammatory PD markers including CRP and fecal calprotectin
- Fistula assessment
- Patient-reported outcome (PRO) measures to assess HRQOL outcomes (ie, IBDQ, PROMIS-29, and PROMIS Fatigue 7-item Short Form [7a], and EQ-5D-5L), and health economics outcomes (ie, WPAI-CD)
- Exploratory patient-reported symptom measures including BSFS, AP-NRS, Patient's Global Impression of Severity (PGIS) of Crohn's Disease, and Patient's Global Impression of Change (PGIC) of Severity of Crohn's Disease

The **CDAI** (Appendix 10 [Section 10.10]) will be assessed by collecting information on 8 different Crohn's disease-related variables[2]: extraintestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid or very soft stools, AP/cramping, use of antidiarrheal drug(s) and/or opiates, and general well-being. The last 4 variables are scored over 7 days by the participant on a diary card that participants are to complete on a daily basis. The **PRO-2** includes the unweighted CDAI components of the total number of liquid or very soft stools and the AP score.

Endoscopic assessments of the intestinal mucosa will be evaluated during ileocolonoscopy in all participants. A video ileocolonoscopic examination will be performed at screening, Week 12, Week 48, Week 96, Week 144, Week 192, and Week 240. An optional substudy involving a Week 4 evaluation will be performed in consenting participants in addition to the above-specified evaluations. (See Biopsy Manual for more information.) Video endoscopies will be assessed by a central facility that will be blinded to treatment group and visit. A complete video endoscopic examination does not require assessment of the terminal ileum if it cannot be visualized. The **SES-CD** score will be used to evaluate **Endoscopic Improvement**.[4] The SES-CD is based on the evaluation of 4 endoscopic components (presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions, and presence/type of narrowing/strictures) across 5 ileocolonic segments. Each endoscopic component is scored from 0 to 3 for each segment, resulting in a total score of up to 15 for each component, except for the

narrowing component which can only attain a maximum total score of 11 because by definition, the presence of a narrowing that cannot be passed can be only observed once. In summary, an overall total SES-CD score is derived from the sum of all the component scores and can range from 0 to 56. **Endoscopic healing**, which is traditionally defined as the resolution (absence) of mucosal ulcers in response to a therapeutic intervention, will also be assessed.

Histologic assessments will be performed using biopsy samples collected during ileocolonoscopy. Biopsy samples will be collected at screening, Week 12, Week 48, Week 96, Week 144, Week 192, and Week 240 from each of 3 predefined anatomic locations: the terminal ileum, splenic flexure, and rectum, as clinically feasible. An optional substudy involving a Week 4 evaluation will be performed in consenting participants in addition to the above-specified evaluations. The biopsy samples collected post-baseline will be obtained near where the screening biopsy samples were collected from each of the 3 predefined locations, as clinically feasible. Histologic assessments will be conducted by a central reader who is blinded to treatment groups and visit. The GHAS will be used to evaluate histologic improvements and healing.[5] Additional histologic assessments (including RHI and Geboes scores) will also be implemented. Analyses will be specified in the SAP.

Fistula assessment will be performed in all participants on an ongoing basis throughout the duration of the studies. All participants will be assessed for fistulas at baseline. For participants with fistulizing disease, fistula closure will be assessed during the studies. Enterocutaneous fistulas (eg, perianal and abdominal) will be considered no longer draining (ie, closed) when there is absence of drainage despite gentle compression. Rectovaginal fistulas will be considered closed based on either physical examination or absence of relevant symptoms (eg, passage of rectal material or flatus from the vagina).

Patient-reported outcome measures will be evaluated at visits as indicated in the Schedule of Activities (Section 1.3):

- The **IBDQ** is a validated, 32-item, self-reported questionnaire for participants with IBD to evaluate PROs across 4 dimensions: bowel symptoms (loose stools, AP), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability).[12] Scores range from 32 to 224, with higher scores indicating better outcomes.
- 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 (NRS).
- The **PROMIS Fatigue 7-items Short Form** (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 with the fatigue scale of PROMIS-29, PROMIS Fatigue Short Form 7a provides additional information to evaluate severity of fatigue.

- The **EQ-5D-5L** is a validated instrument consisting of the EuroQol five dimensions descriptive system (EQ-5D) and the EuroQol visual analog scale (EQ-VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by checking the most appropriate statement in each of the 5 dimensions. The EQ-VAS records the respondent's self-rated health on a 20-cm vertical, visual analog scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. The respondents mark an "X" on the scale to indicate their health TODAY and then write the number marked on the scale in the box.
- The **WPAI-CD** is a validated instrument created as a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to Crohn's disease. The WPAI-CD consists of 6 questions to determine employment status, hours missed from work due to Crohn's disease, hours missed from work for other reasons, hours worked, the degree to which Crohn's disease affected work productivity while at work, and the degree to which Crohn's disease affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Higher scores indicate greater impairment.

Exploratory patient-reported symptom measures will be evaluated at visits as indicated in the Schedule of Activities (Section 1.3):

- The **BSFS** is a medical aid to classify the form (or consistency) of human feces into 7 categories.[15] It has been used as a research tool to evaluate the effectiveness of treatments for various diseases of the bowel (eg, irritable bowel syndrome [IBS]). Participants will complete the BSFS as a daily diary entry from Week 0 through Week 48.
- The **AP-NRS** is an 11-point (0-10) scale that will be used to evaluate AP. The score of 0 represents "no AP" and the score of 10 represents the "worst possible AP" with greater scores indicating greater pain severity and intensity. Participants will complete the AP-NRS as a daily diary entry from Week 0 through Week 48, selecting only one number that best reflects their pain at its worst.
- **PGIS of Crohn's Disease**: Participants will rate their Crohn's disease activity at baseline and each visit using a 5-point scale ("None", "Mild", "Moderate", "Severe", and "Very Severe"). The PGIS will be used as an anchor to establish and or validate response criteria of other clinical endpoints.
- **PGIC of Severity of Crohn's Disease**: Participants' perceived change (improvement or deterioration) in the severity of their Crohn's disease will be assessed using the PGIC. Participants will rate how their Crohn's disease 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"). The PGIC will be used as an anchor to establish and or validate response criteria of other clinical endpoints.

8.2. Safety Assessments

Details regarding the Independent Data Monitoring Committee are provided in Section 9.5.2.

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

Any clinically relevant changes occurring during the study must be recorded in 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 specified in the Schedule of Activities (Section 1.3):

8.2.1. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at screening.

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

8.2.2. Physical Examination

Physical examinations will be performed as specified in the Schedule of Activities. While assessment of the participants for safety and efficacy requires some physical examination by an investigator at all visits, a more complete, detailed physical examination will be performed at specified visits.

8.2.3. Height and Weight

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

8.2.4. Vital Signs

Through Week 48, vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be obtained before and approximately every 30 minutes during every IV infusion, and for 1 hour at approximately 30-minute intervals after completion of the final IV infusion. Vital signs should be obtained before and approximately 30 minutes after the final CC injection.

After Week 48, study participants receiving study intervention administration at the study site will have vital signs assessed at these visits as described above.

Study participants who are trained to self-inject (or will have a trained caregiver to inject) study intervention at home will be trained to perform self-evaluation for injection-site reactions and reporting of AEs after administering study interventions at home. Vital signs will only be assessed at the study site when study participants receive study intervention administration at the study site.

8.2.5. Infections

Study intervention administration should not be given to a participant with a clinically important, active infection. Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits (see Schedule of Activities, Section 1.3). If a participant develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study treatment (ie, no further study intervention administrations) must be considered.

8.2.6. Tuberculosis Evaluation(s)

8.2.6.1. Initial Tuberculosis Evaluation

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

Participants with a negative QuantiFERON-TB (or T-SPOT for sites in Japan where local regulations permit) 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 prerandomization procedures. Participants with a newly identified positive QuantiFERON-TB (or tuberculin skin) test (or T-SPOT test for sites in Japan) result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed, or the participant will be excluded from the study.

A participant whose first QuantiFERON-TB test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB test result is also indeterminate, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. For sites in Japan, a participant whose first T-SPOT test result (where local regulations permit) is borderline should have the test repeated. In the event that the second T-SPOT (for sites in Japan) test result is also

borderline, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's or designee's medical monitor and recorded in the participant's source documents and initialed by the investigator.

A suspected false-positive initial QuantiFERON-TB test must be repeated. If repeat testing is NOT positive, the participant should be referred to a physician specializing in TB to determine if the initial test can be considered a false-positive. This evaluation should be adequately documented prior to the first administration of study intervention. If repeat testing is positive, however, it will be considered a true-positive and the participant is only eligible if active TB has been ruled out and appropriate treatment for latent TB has been initiated as described above.

8.2.6.2. 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 Schedule of Activities in Section 1.3) or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

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

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

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON-TB (or T-SPOT for sites in Japan where local regulations permit) 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 for latent TB is warranted.

Study intervention administration should be interrupted during the investigation. A positive QuantiFERON-TB (or T-SPOT for sites in Japan where local regulations permit) test or tuberculin skin test result should be considered detection of latent TB. If the QuantiFERON-TB (or T-SPOT for sites in Japan) test result is indeterminate, the test should be repeated. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol. Participants who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study intervention and be encouraged to return for all subsequent scheduled study visits according to the Schedule of Activities (Section 1.3).

8.2.7. Allergic Reaction

Before any [redacted] injection or [redacted] infusion, appropriately trained personnel and medications must be available to treat allergic reactions, including anaphylaxis. All participants must be observed carefully for symptoms of an allergic reaction (eg, urticaria, itching, hives). If a mild or moderate allergic reaction is observed, acetaminophen, nonsteroidal anti-inflammatory drugs, and/or diphenhydramine may be administered.

In the case of a severe allergic reaction (eg, anaphylaxis), [redacted] aqueous epinephrine, corticosteroids, 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 should 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 will not be permitted to receive additional study intervention (see Section 7 and Table 4).

Participants who experience reactions suggestive of serum sickness-like reactions (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 an injection of study intervention, should be discontinued from further study intervention administrations. Note that these symptoms may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

8.2.8. Adverse Events Temporally Related to 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 stopped 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.

8.2.9. Injection-Site Reaction

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

8.2.10. 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.[17,19] 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, 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 procedure. 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. 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 11 [Section 10.11], Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

8.2.11. 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 AE 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.

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

  A medical monitor or delegate and the clinical site will be notified if prespecified abnormal laboratory values defined in the Laboratory Manual are identified in any participant during the conduct of the study.
- **Serology:** HIV antibody, HBV antibodies and surface antigen, and HCV antibody. For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines. Additional details are provided in Section 10.7 (Appendix 7).

- **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. Additional clinical and laboratory studies may be performed to evaluate the underlying etiology of abnormal findings. See Appendix 9 (Section 10.9; Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants With No Underlying Liver Disease) for additional information on monitoring and assessment of abnormal liver function tests. Also refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.
- **Pregnancy testing:** Female participants of childbearing potential will undergo a urine pregnancy test at screening before each study intervention administration, at a SID visit, and at the FES visit.

8.2.12. Immunogenicity Assessments (Antibodies to Guselkumab and Ustekinumab)

Serum samples will be screened for antibodies binding to guselkumab or ustekinumab and the titer of confirmed positive samples will be reported as applicable. Other analyses may be performed to further characterize the immunogenicity of guselkumab or ustekinumab. Antibodies to guselkumab or ustekinumab will be evaluated on blood drawn from all participants according to the Schedule of Activities (Section 1.3). Additionally, samples should also be collected at the final visit for participants who terminate from the study. These samples will be tested by the sponsor or sponsor's designee. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Evaluations

At visits where antibodies to study intervention will be evaluated in addition to serum concentration of study intervention, 1 venous blood sample of sufficient volume should be collected. Each serum sample will be divided into 3 aliquots (1 each for serum concentration of study intervention, antibodies to study intervention, and a back-up).

Analytical Procedures

The detection and characterization of antibodies to guselkumab and ustekinumab will be performed using validated assay methods by or under the supervision of the sponsor.

8.2.13. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

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 12 (Section 10.12).

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints (PQCs), refer to Appendix 11 (Section 10.11), 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

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

Information regarding SAEs will be transmitted to the sponsor or designee using the Serious Adverse Event Form, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor or designee within 24 hours.

Serious adverse events, including those spontaneously reported to the investigator within 16 weeks after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Any possible Hy's law case (AST or ALT ≥3xULN together with bilirubin ≥2xULN or INR >1.5) is considered an important medical event and must be reported to the sponsor in an expedited manner using the Serious Adverse Event Form, even before all other possible causes of liver injury have been excluded (INR criterion is not applicable to participants receiving anticoagulants).

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 11 (Section 10.11), Adverse Events: 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 AEs 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 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 SAEs 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 and Table 4).

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required (Section 10.6, Section 10.11).

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 participants 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 Section 10.11 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

Serum samples will be used to evaluate the PK of guselkumab and ustekinumab. Samples collected for the analyses of serum concentrations of guselkumab and ustekinumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Evaluations

At visits where only serum concentration of study intervention will be evaluated (ie, no antibodies to study intervention will be evaluated), 1 venous blood sample of sufficient volume should be collected, and each serum sample should be divided into 2 aliquots (1 for serum concentration of study intervention, and a back-up). At visits where serum concentration of study intervention and antibodies to study intervention will be evaluated, 1 venous blood sample of sufficient volume should be collected. Each serum sample will be divided into 3 aliquots (1 each for serum concentration of study intervention, antibodies to study intervention, and a back-up).

Analytical Procedures

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

Pharmacokinetic Parameters

Serum samples will be used to evaluate various guselkumab PK parameters based on blood drawn from all participants according to the Schedule of Activities.

8.6. Pharmacodynamics

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

- **CRP** has been demonstrated to be useful as a marker of inflammation in patients with IBD. In Crohn's disease, elevated CRP concentrations have been associated with severe clinical activity, elevated sedimentation rate, and active disease as detected by colonoscopy.[21] Blood samples for the measurement of CRP will be collected from all participants. CRP will be evaluated using a validated, high-sensitivity assay.
- **Fecal calprotectin** has been demonstrated to be a sensitive and specific marker in identifying intestinal inflammation and response to treatment in patients with IBD.[3] Stool samples for fecal calprotectin concentration will be collected from all participants. The assay for fecal calprotectin concentration will be performed using a validated method.

8.7. Genetics

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

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

DNA samples will be analyzed for identification of genetic factors that may be associated with clinical response. This research may consist of the analysis of 1 or more candidate genes, assessment of SNPs, or analysis of the entire genome (as appropriate) in relation to guselkumab or ustekinumab intervention and/or Crohn's disease. Whole blood samples of approximately 10 mL will be collected for genetic analyses as specified in the Schedule of Activities (Section 1.3).

8.8. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab or ustekinumab treatment and/or Crohn's disease. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, whole blood, stool, and ileocolonic biopsy samples collected as specified in the Schedule of Activities, where local regulations permit. Data collected from these samples will be used for exploratory research that will include the following objectives:

1. To understand the molecular effects of guselkumab and ustekinumab
2. To understand Crohn's disease pathogenesis
3. To understand why an individual may respond differently to guselkumab or ustekinumab
4. To understand the impact of treatment with guselkumab or ustekinumab on intestinal mucosal inflammation in participants with moderately to severely active Crohn's disease
5. To develop diagnostic tests to identify Crohn's disease populations that may be responsive or non-responsive to treatment with guselkumab or ustekinumab

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

8.8.1. Serum-based Biomarkers

Blood samples for serum-based biomarker analyses will be collected from all participants where local regulations permit. Assays to be performed may include proteins associated with

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

8.8.2. Whole Blood-based Biomarkers

Whole blood samples will be collected from all participants to assess the effect of study intervention on RNA expression profiles where local regulations permit. Whole blood analyses may also examine RNA expression associated with the pathogenesis of Crohn's disease. Transcriptome studies may be conducted using microarray, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each blood sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biologic response relating to Crohn's disease or the action of guselkumab.

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

8.8.3. Biopsy-based Biomarkers

Mucosal biopsy samples will be collected during ileocolonoscopy to study the effect of study intervention on the histological assessment of disease and healing. Biopsies will also be analyzed for exploratory gene and protein expression analysis where local regulations permit. Ileocolonic biopsy analyses may also examine gene and protein expression associated with the pathogenesis of Crohn's disease.

8.8.3.1. Optional Week 4 Biopsy Substudy

Ileocolonic biopsies will be obtained at Week 4 only from participants who agree to participate in the optional substudy. This optional substudy is included to investigate the mechanism of action of guselkumab and ustekinumab, 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. Approximately 200 study participants are defined for the Week 4 ileocolonoscopy substudy to provide sufficient power to support exploratory analyses.

8.8.4. Fecal Biomarkers

Fecal samples will be collected from all participants as specified in the Schedule of Activities. Where local regulations permit, microbiome and associated products analysis will be conducted to evaluate the association between inflammatory proteins, microbial activities and guselkumab, ustekinumab, and/or Crohn's disease. The relationships between microbiome, metabolites, and biomarkers in other tissue samples will also be assessed.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization, including but not limited to Crohn's disease-related hospitalizations and surgeries, will be collected in the studies. The WPAI-CD will also be utilized to evaluate work productivity (Section 8.1).

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 are outlined below. Specific details will be provided in the SAP. There will be 2 SAPs supporting this protocol: one for the Phase 2 study (ie, GALAXI 1) and one for the Phase 3 studies (ie, GALAXI 2 and GALAXI 3). A separate SAP will cover the LTE. In addition, an IA plan for Phase 2 will provide specific details for the dose selection analysis.

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] 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 efficacy endpoints that are collected at multiple post baseline time points will be compared using a MMRM model. Continuous endpoints that are measured only at a single time point will be compared using an ANCOVA.

All statistical testing will be performed at a significance level of 0.05 (2-sided) unless otherwise specified. For endpoints that are not multiplicity-controlled, nominal p-values will be displayed.

9.1. Statistical Hypotheses

9.1.1. Phase 2 Dose-Ranging Study (GALAXI 1)

The primary hypothesis is that guselkumab is superior to placebo as assessed by the reduction from baseline in CDAI at Week 12.

9.1.2. Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)

Refer to Section 3.2.2 for the co-primary and major secondary hypotheses.

9.2. Sample Size Determination

9.2.1. Assumptions for Phase 2 Study

Data from several sources informed the underlying assumptions for sample size determination in Phase 2, as summarized below. These include the ustekinumab Crohn's disease Phase 3 program consisting of 3 studies (ie, CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003), a program conducted by the sponsor in participants with Crohn's disease

who had previously failed or were intolerant to TNF antagonist therapy (referred to as TNF-Failure herein) or had previously failed or were intolerant to conventional therapies (referred to as CON-Failure herein), and the data from a risankizumab Crohn's disease Phase 2 study in which the majority of participants were those who had previously failed or were intolerant to biologic therapies (referred to as BIO-Failure herein).

Change in CDAI at Week 12

Assumptions for the BIO-Failure population and the CON-Failure population were based on the following:

- In CNTO1275CRD3001 (BIO-Failure population), the mean CDAI change from baseline at Week 8 was -25.1 (SD=91.41) and -78.7 (SD=91.79) for the placebo and ustekinumab [redacted] groups, respectively.[8]
- In CNTO1275CRD3002 (CON-Failure population), the mean CDAI change from baseline at Week 8 was -66.3 (SD=97.81) and -116.3 (SD=102.88) for the placebo and ustekinumab [redacted] groups, respectively.[8]

Taking into account a mixed BIO-Failure/CON-Failure population, the mean CDAI reduction from baseline at Week 12 is expected to be approximately 45 to 50 for placebo, approximately 85 to 95 for guselkumab [redacted] and approximately 105 to 115 for guselkumab [redacted] and guselkumab [redacted] at Week 12 with a common SD of 100 (considering increased variability in a relatively smaller Phase 2 study).

Clinical remission at Week 12

Assumptions for the BIO-Failure population at Week 12 were based on the following:

- In CNTO1275CRD3001, the proportions of participants in clinical remission (CDAI <150) at Week 8 were 7.3% and 20.9% for placebo and ustekinumab [redacted] respectively, for a treatment difference of 13.6%.[8]
- Based on a clinical remission rate of 15% for placebo at Week 12, the risankizumab Phase 2 study suggested an approximate 9% difference in clinical remission between [redacted] and placebo, and an approximate 21% difference between [redacted] and placebo at Week 12.[7]

Based on these data, the clinical remission rates are assumed to be 10% for placebo, 20% for guselkumab [redacted], and 30% for guselkumab [redacted] at Week 12 in the BIO-Failure population.

Assumptions for the CON-Failure population at Week 12 were based on the following:

- In CNTO1275CRD3002, the proportions of participants in clinical remission at Week 8 were 19.6% and 40.2% for placebo and ustekinumab [redacted], respectively, for a treatment difference of 20.6%.[8]
- Based on the data from CNTO1275CRD3002 and historical biologic studies in similar populations, it is reasonable to assume a greater treatment effect difference between active and placebo in the CON-Failure population compared with that observed in a BIO-Failure

population. In addition, the dose-response trend in the CON-Failure population is assumed to be similar to that observed in the BIO-Failure population.

Based on these data and assumptions, the clinical remission rates are assumed to be 20% for placebo, 40% for guselkumab CCI, and 50% for guselkumab CCI in the CON-Failure population.

In the absence of data for the CCI dose from guselkumab or from other anti-IL-23 agents, to be conservative, the clinical remission rate for guselkumab CCI is assumed to be similar to that for guselkumab CCI, at a minimum, for both BIO-Failure and CON-Failure populations.

Taking into account a mixed BIO-Failure/CON-Failure population, assumptions for the overall randomized population at Week 12 were based on the following:

- Based on the ratio of an approximate 25% to 50% of participants in the CON-Failure patient population, the proportions of participants in clinical remission at Week 12 is expected to be approximately 12% to 15% for placebo, approximately 25% to 30% for guselkumab CCI and approximately 35% to 40% for both guselkumab CCI and guselkumab CCI

9.2.2. Assumptions for Phase 3 Studies

As discussed in the Overall Rationale for Amendment 5, the co-primary endpoints in the original GALAXI Phase 3 studies were modified for the United States (US) and other countries/territories throughout the world as applicable, creating Global co-primary endpoints. As other health authorities preferred the Week 12 co-primary endpoints be retained, these endpoints are now labeled as Regional co-primary endpoints. Assumptions for the co-primary endpoints in Phase 3 studies were re-evaluated based on the data obtained from the Phase 2 (GALAXI 1) Week 48 DBL.

9.2.2.1. Global Endpoints

Clinical response at Week 12 and Clinical remission at Week 48

The placebo rate for the endpoint of clinical response at Week 12 and clinical remission at Week 48 was derived from the randomized placebo arm in the Phase 2 (GALAXI 1) Week 48 DBL results. In GALAXI 1, 5 out of 55 (9.1%) placebo participants meeting the GALAXI Phase 3 eligibility criteria were in clinical response at Week 12 and subsequently achieved clinical remission at Week 48. Therefore, a placebo rate of 8% to 10% is assumed. Guselkumab rates were derived from the guselkumab arms in the Phase 2 (GALAXI 1) Week 48 DBL results. For the combined guselkumab group, 87 out of 165 (52.7%) participants randomized at Week 0 achieved clinical response at Week 12 and clinical remission at Week 48. The overall treatment difference versus placebo was 44%. Based on these results, a difference of 40% to 45% between guselkumab and placebo is assumed.

Clinical response at Week 12 and Endoscopic response at Week 48

The placebo rate for the endpoint of clinical response at Week 12 and endoscopic response at Week 48 was derived by the randomized placebo arm from the Phase 2 (GALAXI 1)Week 48 DBL results. In GALAXI 1, 1 out of 55 (1.8%) placebo participants (meeting the GALAXI Phase 3 eligibility criteria) were in clinical response at Week 12 and subsequently achieved endoscopic response at Week 48. Therefore, a placebo rate of 2% to 5% is assumed. Guselkumab rates were derived by the guselkumab arms in the Phase 2 (GALAXI 1) Week 48 DBL results. For the combined guselkumab group, 61 out of 165 (37.0%) participants randomized at Week 0 achieved clinical response at Week 12 and endoscopic response at Week 48. The overall treatment difference versus placebo was 35%. Based on these results, a difference of 30% to 35% between guselkumab and placebo is assumed.

9.2.2.2. Regional Endpoints

The assumptions for the original co-primary endpoints were also re-evaluated based on the GALAXI 1 (Phase 2) Week 48 DBL.

Clinical remission at Week 12

The placebo rate for the endpoint of clinical remission at Week 12 was derived from the randomized placebo arm from the Phase 2 (GALAXI 1) Week 48 DBL. In GALAXI 1, 6 out of 55 (10.9%) placebo participants (meeting the GALAXI Phase 3 eligibility criteria) were in clinical remission at Week 12. Therefore, a placebo rate of 10% to 15% is assumed. Guselkumab rates were derived from the guselkumab arms in the Phase 2 (GALAXI 1) Week 48 DBL. For the combined guselkumab group, 86 out of 165 (52.1%) participants randomized at Week 0 achieved clinical remission at Week 12. The overall treatment difference versus placebo was 41%. Based on these results, a difference of 35% to 40% between guselkumab and placebo is assumed.

Endoscopic response at Week 12

The placebo rate for the endpoint of endoscopic response at Week 12 was derived from the randomized placebo arm from the Phase 2 (GALAXI 1) Week 48 DBL. In GALAXI 1, 7 out of 55 (12.7%) placebo participants (meeting the GALAXI Phase 3 eligibility criteria) were in endoscopic response at Week 12. Therefore, a placebo rate of 10% to 13% is assumed. Guselkumab rates were derived from the guselkumab arms in the Phase 2 (GALAXI 1) Week 48 DBL. For the combined guselkumab group, 57 out of 165 (34.5%) participants randomized at Week 0 achieved endoscopic response at Week 12. The overall treatment difference versus placebo was 22%. Based on these results, a difference of 20% to 25% between guselkumab and placebo is assumed.

9.2.3. Power and Sample Size Calculations

9.2.3.1. Phase 2 Dose-Ranging Study (GALAXI 1)

Power for Phase 2 was evaluated for the 2 analysis populations described below, using a 2-sample t-test (at the 0.05 level of significance) to detect a significant difference in the change from baseline in the CDAI score at Week 12 between the guselkumab high [redacted] induction dose and placebo.

Assuming the mean CDAI reductions from baseline at Week 12 of approximately 105 to 115 in the guselkumab high [redacted] induction dose group versus approximately 45 to 50 in the placebo group with a common SD of 100:

For the Initial Dose Decision Cohort: 50 participants in the guselkumab high [redacted] induction dose group and 50 participants in the placebo group will provide greater than 80% power to detect a treatment difference between guselkumab and placebo at a Type 1 error rate controlled at α=0.05 (2-sided) (Table 9). With 5 dose groups, the total sample size for the Initial Dose Decision Cohort is 250 participants.

For the Total Phase 2 Population: It is anticipated that 100 to 250 participants will be enrolled into the Transition Cohort by the time a dose decision is made for Phase 3. Thus, the sample size for the total Phase 2 study is expected to range from a minimum of 350 participants (70 per dose group) up to a maximum of 500 participants (100 per dose group). The power, based on the minimum number of participants, is greater than 90% for the change from baseline in the CDAI score at Week 12 and greater than 85% for clinical remission at Week 12 (Table 9).

Table 9: Power to Detect a Treatment Effect of Guselkumab Versus Placebo Based on Mean Change in CDAI and Proportion of Participants Achieving Clinical Remission at Week 12

Change in CDAI at Week 12*			Clinical remission at Week 12		
Initial Dose Decision Cohort					
Placebo (n=50)	Guselkumab (n=50)	Power	Placebo (n=50)	Guselkumab (n=50)	Power
45	95	70%	12%	30%	52%
45	**105**	**84%**	**12%**	**35%**	**73%**
50	105	78%	15%	35%	57%
50	**115**	**89%**	**15%**	**40%**	**76%**
Total Phase 2 Population (minimal sample size)					
Placebo (n=70)	Guselkumab (n=70)	Power	Placebo (n=70)	Guselkumab (n=70)	Power
45	95	83%	12%	30%	69%
45	**105**	**94%**	**12%**	**35%**	**87%**
50	105	90%	15%	35%	73%
50	**115**	**97%**	**15%**	**40%**	**89%**

*SD=100.

9.2.3.2. Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)

GALAXI 2 and GALAXI 3 are separate studies and will have separate type I error control at the 2-sided 0.05 significance level.

The power for the key endpoints in these Phase 3 studies (ie, Global co-primary endpoints, Regional co-primary endpoints, Regional endpoints of corticosteroid-free clinical remission at Week 48 and endoscopic response at Week 48 [which are meant to demonstrate the long-term efficacy of guselkumab versus placebo]), as well as the number of participants necessary to assess the safety of guselkumab, were considered in determining the appropriate sample size for these Phase 3 studies. Based on this, a total sample size of approximately 980 participants (approximately 490 participants per study, consisting of 140 participants in each of the two guselkumab treatment groups, 70 participants in the placebo treatment group, and 140 participants in the ustekinumab group) will provide at least 90% power for these key endpoints in each study.

9.2.3.2.1. Global Endpoints

For the co-primary endpoint of clinical response at Week 12 and clinical remission at Week 48: In each of the Phase 3 studies, assuming a rate of 8% to 10% for placebo and a 40% to 45% difference between guselkumab and placebo based on Phase 2 (GALAXI 1) results, 140 participants in each guselkumab dose group and 70 participants in the placebo group will provide >99% power for this endpoint at the 0.05 (2-sided) alpha level (Table 10).

For the co-primary endpoint of clinical response at Week 12 and endoscopic response at Week 48: In each of the Phase 3 studies, assuming a rate of approximately 2% to 5% for placebo and a 30% to 35% difference between guselkumab and placebo based on Phase 2 (GALAXI 1) results, 140 participants in each guselkumab dose group and 70 participants in the placebo group will provide >99% power for this endpoint at the 0.05 (2-sided) alpha level (Table 10).

Table 10: Power to Detect a Treatment Effect of Guselkumab versus Placebo for Global Co-primary Endpoints

Clinical Response at Week 12 and Clinical Remission at Week 48		
Placebo (n=70)	Guselkumab (n=140)	Power
8%	48%	>99%
10%	50%	>99%
8%	53%	>99%
10%	55%	>99%

Clinical Response at Week 12 and Endoscopic Response at Week 48		
Placebo (n=70)	Guselkumab (n=140)	Power
2%	32%	>99%
5%	35%	>99%
2%	37%	>99%
5%	40%	>99%

9.2.3.2.2. Regional Endpoints

Note that the 2 guselkumab dose groups will receive identical induction intervention, therefore, for short-term comparisons between guselkumab and placebo, the 2 guselkumab dose groups will be combined to compare to placebo. This comparison is applicable for all short-term endpoints, including regional co-primary endpoints, major secondary endpoints and exploratory endpoints. It will be referred to as the combined guselkumab induction dose group throughout the protocol.

For the co-primary endpoint of clinical remission at Week 12: In each of the Phase 3 studies, assuming a clinical remission at Week 12 rate of approximately 10% to 15% for placebo and a 35% to 40% difference between guselkumab and placebo based on Phase 2 (GALAXI 1) Week 48 DBL, 280 participants in the combined guselkumab induction dose group and 70 participants in the placebo group, respectively, will provide greater than 99% power for clinical remission at Week 12 at an overall Type 1 error rate controlled at 0.05 (2-sided) (Table 11).

For the co-primary endpoint of endoscopic response at Week 12: In each of the Phase 3 studies, assuming an endoscopic response at Week 12 rate of approximately 10% to 13% for placebo and a 20% to 25% difference between guselkumab and placebo based on Phase 2 (GALAXI 1) Week 48 DBL, 280 participants in the combined guselkumab induction dose group and 70 participants in the placebo group, respectively, will provide approximately 95% power for endoscopic response at Week 12 at an overall Type 1 error rate controlled at 0.05 (2-sided) (Table 11).

Table 11: Power to Detect a Treatment Effect of Guselkumab Versus Placebo for the Regional Co-primary Endpoints at Week 12

Co-Primary Endpoint of Clinical Remission at Week 12		
Placebo (n=70)	Guselkumab (n=280)	Power
10%	45%	>99%
10%	50%	>99%
15%	50%	>99%
15%	55%	>99%
Co-Primary Endpoint of Endoscopic Response at Week 12		
Placebo (n=70)	Guselkumab (n=280)	Power
10%	30%	97%
13%	33%	95%
10%	35%	>99%
13%	38%	>99%

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined for Phase 2 (Table 12) and Phase 3 (Table 13) studies. Note: Additional analysis populations may be defined in the SAP:

Table 12: Populations for Analyses for Phase 2 Study

Population	Description
Randomized Analysis Set	All participants who are randomized
Full Analysis Set	All participants who are randomized and receive at least 1 dose of study intervention.
Safety Analysis Set	All participants who are randomized and received at least 1 dose of study intervention (including a partial dose).

Table 13: Populations for Analyses for Phase 3 Studies

Analysis Sets	Description
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Primary Analysis Set (PAS)	The Primary analysis set **(PAS)** includes all randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease)).
Primary Safety Analysis Set	The Primary Safety analysis set includes all randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease)).
Primary Pharmacokinetics Analysis Set (PPK)	The Primary guselkumab PK analysis set **(GPPK)** is defined as all randomized participants who received at least 1 (partial or complete) dose of guselkumab and satisfied the SES-CD eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]) and have at least 1 valid post-baseline blood sample drawn for PK analysis. The Primary ustekinumab PK analysis set **(UPPK)** is defined as all randomized participants who received at least 1 (partial or complete) dose of ustekinumab and satisfied the SES-CD eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]) and have at least 1 valid post-baseline blood sample drawn for PK analysis.
Primary Immunogenicity Analysis Set (PIM)	The Primary guselkumab Immunogenicity analysis set **(GPIM)** is defined as all participants who received at least 1 (partial or complete) dose of guselkumab and satisfied the SES-CD eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]) and have appropriate samples for detection of antibodies to guselkumab (ie, participants with at least 1 sample obtained after their first dose of guselkumab). The Primary ustekinumab Immunogenicity analysis set **(UPIM)** is defined as all participants who received at least 1 (partial or complete) dose of ustekinumab and satisfied the SES-CD eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]) and have appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 sample obtained after their first dose of ustekinumab).
Note: Additional analysis sets used for supportive analyses (eg, those that include all treated participants, including those participants who do not meet the SES-CD entry criteria) will be identified and described in the SAP.	

9.4. Statistical Analyses

9.4.1. Endpoints

9.4.1.1. Phase 2 Dose-Ranging Study (GALAXI 1)

For the primary and major secondary endpoints, comparisons of each guselkumab group with the placebo group will be made. **Note that the final ordering of the major secondary endpoints will be provided in the Phase 2 SAP.**

Primary Endpoint

Change from baseline in the CDAI score at Week 12.

Major Secondary Endpoints

- Clinical remission at Week 12 (defined as CDAI score <150).
- Clinical response at Week 12 (defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150).
- PRO-2 remission at Week 12 (defined as an AP mean daily score at or below 1 [AP≤1] AND an SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline).
- Clinical-biomarker response at Week 12 (clinical response based on CDAI score and ≥50% reduction from baseline in CRP or fecal calprotectin).
- Endoscopic response at Week 12 (defined as at least 50% improvement from baseline in SES-CD score or SES-CD score ≤2).

Exploratory Endpoint(s)

Short-term Efficacy

The short-term endpoints for Phase 2 are the same as those for Phase 3 (refer to Section 9.4.1.2). In addition, the following endpoints will be assessed:

- Fatigue response at Week 12 (based on PROMIS Fatigue Short Form 7a; to be defined in the SAP).
- Change in SES-CD score from baseline at Week 12, endoscopic response at Week 12, endoscopic remission at Week 12, and endoscopic healing at Week 12, among participants with baseline SES-CD ≥4 (ie, for participants with isolated ileal disease) or SES-CD ≥6 (ie, for participants with colonic or ileocolonic disease).

The comparisons for these endpoints will be of each guselkumab group with the placebo group.

Long-term Efficacy

The long-term endpoints for Phase 2 are the same as those for Phase 3 (refer to Section 9.4.1.2). In addition, clinical remission and PRO-2 remission at Week 24 will be assessed based on the following:

- among participants in clinical response at Week 12

- among participants in clinical remission (or PRO-2 remission) at Week 12
- by CRP level (CRP ≤5 mg/L, >5 mg/L to ≤10 mg/L, and >10 mg/L) at Week 12
- by fecal calprotectin level (fecal calprotectin <250 µg/g, ≥250 µg/g) at Week 12

The comparisons for these endpoints will be of each guselkumab group with the ustekinumab group.

Endpoints (short-term and long-term) based on the following measures will also be defined in the Phase 2 SAP:

- AP-NRS
- BSFS
- Change from baseline in PGIS
- PGIC
- Assessments for histologic improvement and histologic healing

9.4.1.2. Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)

GALAXI 2 and GALAXI 3 are identical studies and have the same endpoints, as described below.

9.4.1.2.1. Global Endpoints

Co-primary Endpoints

The Global co-primary endpoints are:

- Clinical response at Week 12 and clinical remission at Week 48
- Clinical response at Week 12 and endoscopic response at Week 48

For these endpoints, comparisons will be made within each study between each guselkumab dose (guselkumab CCI [redacted] and placebo.

Major Secondary Endpoints

The Global major secondary endpoints are grouped into 3 categories based on timepoint and comparator; note that these are grouped for the purpose of categorization but are not presented in the order of testing in the multiplicity-controlled testing procedure (the specific order for the testing procedure will be provided in the statistical analysis plan).

The Global major secondary endpoints below evaluate the short-term efficacy of guselkumab versus placebo in each study:

- Clinical response at Week 4

- Clinical remission at Week 12
- Endoscopic response at Week 12
- Fatigue response at Week 12
- Clinical remission at Week 12 and endoscopic response at Week 12
- Endoscopic remission (Global definition) at Week 12

Note that the 2 guselkumab dose groups will receive identical induction intervention, therefore, for short-term comparisons between guselkumab and placebo, the 2 guselkumab dose groups will be combined to compare to placebo.

The following long-term endpoints evaluate guselkumab versus placebo in each study:

- Clinical response at Week 12 and corticosteroid-free clinical remission at Week 48
- Clinical response at Week 12 and endoscopic remission (Global definition) at Week 48

These following long-term endpoints evaluate guselkumab versus ustekinumab:

- Clinical remission at Week 48
- Endoscopic response at Week 48
- Clinical remission at Week 48 and endoscopic response at Week 48
- Endoscopic remission at Week 48
- Deep remission (Global definition) at Week 48

9.4.1.2.2. Regional Endpoints

Co-primary Endpoints

The Regional co-primary endpoints are:

- Clinical remission at Week 12
- Endoscopic response at Week 12

For these endpoints, comparisons will be made within each study between the combined guselkumab induction dose group and placebo.

Major Secondary Endpoints

The Regional major secondary endpoints are grouped into 3 categories based on timepoint and comparator; note that these are grouped for the purpose of categorization but are not presented in the order of testing in the multiplicity-controlled testing procedure (the specific order for the testing procedure will be provided in the statistical analysis plan).

The following Regional major secondary endpoints evaluate the short-term efficacy of guselkumab versus placebo:

- PRO-2 remission at Week 12
- Fatigue response at Week 12
- Endoscopic remission (Regional definition) at Week 12

The following long-term endpoints evaluate guselkumab versus placebo:

- Corticosteroid-free clinical remission at Week 48
- Endoscopic response at Week 48

The following long-term endpoints evaluate guselkumab versus ustekinumab:

- Endoscopic remission (Regional definition) at Week 48
- Clinical remission at Week 48
- Endoscopic response at Week 48
- Durable clinical remission at Week 48
- PRO-2 remission at Week 48
- Clinical remission at Week 48 and endoscopic response at Week 48
- Corticosteroid-free clinical remission at Week 48

9.4.1.2.3. Exploratory Endpoints

Exploratory endpoints include but are not limited to the endpoints below. A complete list of the exploratory endpoints will be provided in the SAP. The Regional and Global co-primary and major secondary endpoints are not the same. If a Global major secondary is not listed as a Regional major secondary endpoint, it will be considered exploratory for the Regional endpoints. If a Regional major secondary is not listed as a Global major secondary endpoint, it will be considered exploratory for the Global endpoints. Exploratory endpoints that include a component of endoscopic remission are specified as the Global and/or Regional definition of endoscopic remission.

Short-term Efficacy vs. Placebo

The following endpoints will be assessed, and the comparisons within each study will be of the combined guselkumab induction dose group with placebo.

- Change in CDAI score from baseline at all post-baseline visits through Week 12
- Clinical remission at all post-baseline visits through Week 12
- Clinical response at all post-baseline visits through Week 12

- Clinical-biomarker response (clinical response and ≥50% reduction from baseline in CRP or fecal calprotectin) at Week 12
- PRO-2 remission at all post-baseline visits through Week 12
- Abdominal pain score (daily average based on the CDAI assessment) ≤1 at all post-baseline visits through Week 12, among participants with daily average AP score >1 at baseline
- Number of liquid or very soft stools (daily average based on the CDAI assessment) ≤3 at all post-baseline visits through Week 12, among participants with daily average number of liquid or very soft stools >3 at baseline
- Change in SES-CD score from baseline at Week 12
- Endoscopic healing (defined as the absence of mucosal ulcerations) at Week 12
- Fistula response at all post-baseline visits through Week 12, defined as a ≥50% reduction from baseline in the number of draining fistulas, among participants with 1 or more fistulas at baseline
- Complete fistula response at all post-baseline visits through Week 12, among participants with 1 or more fistulas at baseline
- Change in CRP at all post-baseline visits through Week 12
- Normalization of CRP concentrations at Week 8 and Week 12, among participants with elevated CRP at baseline
- Change in fecal calprotectin from baseline at Week 8 and Week 12
- Fecal calprotectin concentration of ≤250 µg/g at Week 8 and Week 12, fecal calprotectin ≤100 µg/g at Weeks 8 and 12, and fecal calprotectin ≤50 µg/g at Weeks 8 and 12 among participants with fecal calprotectin >250 µg/g at baseline
- Change from baseline in IBDQ score (including IBDQ domains) at Week 8 and Week 12
- IBDQ remission (based on IBDQ ≥170) at Week 8 and Week 12
- IBDQ response (≥16-point improvement from baseline) at Week 8 and Week 12
- Change from baseline in the 7 domains and the pain NRS score of PROMIS-29 at Week 8 and Week 12
- Responses in the 7 domains and the pain NRS score of PROMIS-29 (to be defined in the SAP) at Week 8 and Week 12
- Change from baseline in the PROMIS Fatigue Short Form 7a total score at Week 8 and Week 12
- Change from baseline in the EQ-5D dimensions and EQ-VAS at Week 8 and Week 12
- Change from baseline in each of 4 impairments from WPAI-CD at Week 8 and Week 12
- Crohn's disease-related hospitalizations and/or Crohn's disease-related surgeries through Week 12

Long-Term Efficacy vs Placebo

The following endpoints will be assessed, and the comparisons will be for each guselkumab group with the placebo group.

- Clinical response at Week 12 and deep remission (Global definition) at Week 48
- Clinical response at Week 12 and clinical response at Week 48 (Sustained response)
- Clinical response at Week 12 and 90-day steroid free clinical remission at Week 48
- Clinical remission at Week 12 and clinical remission at Week 48 (Sustained remission)
- Deep remission (Regional definition) at Week 48

Long-Term Efficacy vs Ustekinumab

The following endpoints will be assessed, and the comparisons will be for each guselkumab group with the ustekinumab group.

- Corticosteroid-free (90-days) clinical remission at Week 48 (defined as CDAI <150 at Week 48 and not receiving corticosteroids for at least 90 days prior to Week 48)
- Change in CDAI score from baseline at all post-baseline visits from Week 16 to Week 48
- Clinical remission (CDAI score <150) at all post-baseline visits from Week 16 to Week 48
- Clinical remission at Week 12 and clinical remission at Week 48 (Sustained remission)
- Clinical response at all post-baseline visits from Week 16 to Week 48
- PRO-2 remission (AP ≤1 and SF ≤3 and no worsening of AP or SF from baseline) at all post-baseline visits from Week 16 to 48
- Abdominal pain score (daily average based on the CDAI assessment) ≤1 at all post-baseline visits from Week 16 to Week 48, among participants with daily average AP score >1 at baseline
- Number of liquid or very soft stools (daily average based on the CDAI assessment) ≤3 at all post-baseline visits from Week 16 to Week 48, among participants with daily average number of liquid or very soft stools >3 at baseline
- Fistula response at all post-baseline visits from Week 16 to 48, defined as a ≥50% reduction from baseline in the number of draining fistulas among participants with 1 or more fistulas at baseline
- Complete fistula response at all post-baseline visits from Week 16 to 48 among participants with 1 or more fistulas at baseline
- Change in SES-CD score from baseline at Week 48
- Endoscopic healing (defined as the absence of mucosal ulcerations) at Week 48
- Change in CRP from baseline at all post-baseline visits from Week 16 to Week 48
- Normalization of CRP concentrations at Week 24 and Week 48 among participants with elevated CRP at baseline

- Change in fecal calprotectin from baseline at Week 24 and Week 48
- Fecal calprotectin concentration ≤250 µg/g at Week 24 and Week 48, and fecal calprotectin ≤100 µg/g at Weeks 24 and 48, among participants with fecal calprotectin >250 µg/g at baseline
- Clinical-biomarker response (clinical response and ≥50% reduction from baseline in CRP or fecal calprotectin) at Week 24 and Week 48
- Clinical response and normalization of CRP concentration and fecal calprotectin concentration ≤250 µg/g at Week 24 and Week 48, among participants with elevated CRP or fecal calprotectin >250 µg/g at baseline
- Change in IBDQ score and domain scores from baseline at Week 24 and Week 48
- IBDQ remission (based on IBDQ ≥170) at Week 24 and Week 48
- IBDQ response (≥16-point improvement from baseline) at Week 24 and Week 48
- Change from baseline in the 7 domains and the pain NRS score of PROMIS-29 at Week 24 and Week 48
- Responses in the 7 domains and the pain NRS score of PROMIS-29 (to be defined in the SAP) at Week 24 and Week 48
- Change from baseline in the PROMIS Fatigue Short Form 7a total score at Weeks 24 and 48
- Fatigue response (defined as an improvement of ≥ 7 points in PROMIS Fatigue Short Form 7a) at Week 24
- Change from baseline in the EQ-5D dimensions and EQ-VAS at Week 24 and Week 48
- Change from baseline in each of 4 impairment percentages from WPAI-CD at Week 24 and Week 48
- Crohn's disease-related hospitalizations through Week 48 and Crohn's disease-related surgeries through Week 48

Endpoints (short-term and long-term) based on the following measures will be defined in the Phase 3 SAP:

- AP-NRS
- BSFS
- Assessments for histologic improvement and histologic healing

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

9.4.2. Phase 2 (GALAXI 1) Efficacy Analyses

9.4.2.1. Population for Efficacy Analysis

Unless otherwise noted, efficacy analyses will be based on the **Full Analysis Set**, which is defined as all randomized participants who had at least 1 study intervention administration in GALAXI 1

(including the Transition Cohort). Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment they received.

9.4.2.2. Primary Endpoint Analysis

The primary endpoint is the change from baseline in the CDAI score at Week 12.

Participants who have any of the following events before the Week 12 visit will be considered as treatment failures, and will be considered to have no change at Week 12 from their baseline CDAI score, regardless of the actual CDAI score:

- Specified changes in concomitant Crohn's disease medications (to be detailed in the Phase 2 SAP)
- A Crohn's disease-related surgery (with the exception of drainage of an abscess or seton placement)
- Discontinuation of study intervention due to lack of efficacy or due to an AE of worsening Crohn's disease

The CDAI score will be calculated for a visit if at least 4 of the 8 components are available at Week 12. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last available components. If the CDAI score cannot be calculated (ie, <4 components available) at a visit, the CDAI score will be considered missing for that visit. The missing data handling rules for the CDAI score will be described in the Phase 2 SAP.

The change from baseline in CDAI will be analyzed using a Mixed Model for Repeated Measures (MMRM) approach. Further details will be described in the Phase 2 SAP. A multiple testing procedure will be used to control the Type 1 error at α=0.05 (2-sided) over the comparisons of guselkumab with placebo (to be defined in the Phase 2 SAP).

Since there is no possibility that the study will stop early for positive efficacy, as the planned IA is only for making the dosing decision for the Phase 3 studies, there is no alpha spending penalty for this IA.

The study will be considered positive if the guselkumab CCI C induction dose group is significantly different from the placebo group for the primary endpoint.

To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint will be conducted using different missing data approaches; these analyses will be described in the Phase 2 SAP.

Subgroup analyses of the primary endpoint will be performed based on demographic and baseline disease characteristics, baseline use and history of Crohn's disease medications (including BIO-Failure status), and study cohorts (ie, Initial Dose Decision Cohort vs Transition Cohort).

9.4.2.3. Major Secondary Endpoint Analysis

The major secondary endpoints are:

- Clinical remission at Week 12 (defined as CDAI score <150)
- Clinical response at Week 12 (defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150)
- PRO-2 remission at Week 12 (defined as an AP mean daily score at or below 1 [AP≤1] AND an SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline)
- Clinical-biomarker response at Week 12 (clinical response based on CDAI score and ≥50% reduction from baseline in CRP or fecal calprotectin)
- Endoscopic response at Week 12 (defined as at least 50% improvement from baseline in SES-CD score or SES-CD score ≤2)

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 or clinical response, either based on CDAI or PRO-2. For endoscopic response, the same treatment failure rules apply, except for a modification of the "certain changes in concomitant Crohn's disease medications" rule, which will only consider prohibited medications as treatment failure. Details will be provided in the Phase 2 SAP.

The CDAI score will be calculated for a visit if at least 4 of the 8 components are available at that visit. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last available components. The clinical response or remission endpoints will be determined based on these imputed CDAI scores. If the CDAI score cannot be calculated (ie, <4 components available) at a visit, the CDAI score will be considered missing for that visit. Participants who do not return for evaluation or have a missing CDAI score at Week 12 will be considered not to be in clinical remission or clinical response as measured by the CDAI score. Participants who do not return for evaluation or have missing AP or SF scores at Week 12 will not be considered to have achieved clinical remission, as measured by PRO-2. Participants with a nonevaluable or missing endoscopy will be considered not in endoscopic response. The details for handling missing segments in the SES-CD score will be described in the Phase 2 SAP.

The major secondary endpoints of clinical remission (either based on CDAI or PRO-2), clinical response, and clinical-biomarker response at Week 12 will be compared between each guselkumab dose group and the placebo group using the CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300) and BIO-Failure status (Yes/No), at a significance level of 0.05. Endoscopic response at Week 12 will be compared between each guselkumab dose group and the placebo group using the CMH test (2-sided) stratified by SES-CD score (≤12 or >12) and BIO-Failure status (Yes/No), at a significance level of 0.05.

Details of the multiplicity control of these major secondary endpoints will be specified in the Phase 2 SAP.

9.4.2.4. Other Efficacy Endpoint Analyses

Pairwise comparisons of each guselkumab treatment group with the placebo treatment group or the ustekinumab treatment group will be made for certain endpoints (as specified in Section 9.4.1.1), with details that are to be specified in the Phase 2 SAP.

The treatment failures rules are the same as those specified for the primary endpoint except for the following addition:

- Protocol-specified recommendation for discontinuation of study intervention at Week 24 due to lack of efficacy.

No adjustments for multiple comparisons will be made and nominal p-values will be presented.

9.4.3. Phase 3 (GALAXI 2 and GALAXI 3) Efficacy Analyses

In this protocol, the co-primary and major secondary endpoints, as well as all other endpoints, are the same in GALAXI 2 and GALAXI 3. Each study will control the overall Type I error rate at the 0.05 level of significance (2-sided).

9.4.3.1. Population for Efficacy Analysis

Unless otherwise noted, efficacy analyses within each study will be based on the Primary Analysis Set for that study, which includes all randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]). Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment they received.

9.4.3.2. Primary Endpoint Analysis

9.4.3.2.1. Global Primary Endpoint Analysis

The Global co-primary endpoints in each Phase 3 study are:

- clinical response at Week 12 and clinical remission at Week 48
- clinical response at Week 12 and endoscopic response at Week 48

For testing of the co-primary endpoints, the efficacy of each dose of guselkumab versus placebo will be compared. A CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) will be used. Additional analysis considerations are provided in Section 9.4.3.2.3.

To control the Type I error at the 2-sided 0.05 significance level, a fixed sequence testing approach will be used for the co-primary endpoints for each study. Specifically, the sequential testing will begin with the guselkumab CCI [redacted] group with the following 2 co-primary endpoints tested sequentially:

- clinical response at Week 12 and clinical remission at Week 48
- clinical response at Week 12 and endoscopic response at Week 48

Followed by the guselkumab CCI group with the same co-primary endpoints tested sequentially:

- clinical response at Week 12 and clinical remission at Week 48
- clinical response at Week 12 and endoscopic response at Week 48

Each study will be considered positive if the guselkumab CCI group is significantly different from the placebo group for both of the co-primary endpoints.

9.4.3.2.2. Regional Primary Endpoint Analysis

The co-primary endpoints in each Phase 3 study are:

- clinical remission at Week 12
- endoscopic response at Week 12

For testing of the co-primary endpoints, the efficacy of the induction dose of guselkumab versus placebo will be compared. As such, within each study, the two guselkumab groups that are randomized to receive identical guselkumab induction treatment through Week 12 will be combined for these comparisons. To control the Type I error at the 2-sided 0.05 significance level, a fixed sequence testing approach will be used with the 2 co-primary endpoints tested sequentially:

- clinical remission at Week 12
- endoscopic response at Week 12

A CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) will be used. Additional analysis considerations are provided in Section 9.4.3.2.3.

9.4.3.2.3. Analysis Methods Applicable to both Global and Regional Co-primary Endpoints

Participants who have any of the following events before the Week 12 visit (for short-term endpoints) or before the Week 48 visit (for long-term endpoints) will be considered as treatment failures, and will not be considered to have achieved the endpoint:

- Specified changes in concomitant Crohn's disease medications (to be detailed in the Phase 3 SAP)
- A Crohn's disease-related surgery (except drainage of an abscess or seton placement)
- Discontinuation of study intervention due to lack of efficacy or due to an AE of worsening Crohn's disease (NOTE: For all endpoints [including major secondary and other endpoints] assessed at Week 24 and beyond, this includes discontinuation of study intervention at Week 24 due to Week 20/24 non-responder criteria)

The CDAI score will be calculated for a visit if at least 4 of the 8 components are available at that visit. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last available components. If the CDAI score cannot be calculated (ie, < 4 components available) at a visit, the CDAI score will be considered missing for that visit. Participants who do not return for evaluation or have a missing CDAI score at Week 12 and/or Week 48 will not be considered to have achieved the Global co-primary endpoint of clinical response at Week 12 and clinical remission at Week 48. Likewise, participants who do not return for evaluation or have a missing CDAI score at Week 12 will not be considered to have achieved the Regional co-primary endpoint of clinical remission at Week 12.

The total SES-CD score at a visit will be calculated based on all segments scored at the visit. If the total SES-CD score cannot be calculated (ie, no segment is scored) at a visit, the total SES-CD score will be considered missing. Participants who do not return for evaluation or who have a missing SES-CD score at Week 48 or a missing CDAI score at Week 12 will not be considered to have achieved the Global co-primary endpoint of clinical response at Week 12 and endoscopic response at Week 48. Similarly, participants who do not return for evaluation or who have a missing SES-CD score at Week 12 will not be considered to have achieved the Regional co-primary endpoint of endoscopic response at Week 12.

Treatment failure rules will overrule the missing data rules. The statistical analysis plan (SAP) will provide details on analysis rules for the data impacted by any major disruption.

To examine the robustness of the co-primary endpoint analyses, sensitivity analyses of the co-primary endpoints will be conducted using different missing data approaches; these analyses will be described in the Phase 3 SAP.

Subgroup analyses of the co-primary endpoints will be performed based on demographic and baseline disease characteristics and baseline use and history of Crohn's disease medications (including BIO-Failure status).

9.4.3.3. Major Secondary Endpoint Analysis

9.4.3.3.1. Global Major Secondary Endpoint Analyses

The Global major secondary endpoints are grouped into 3 categories as listed in Section 9.4.1.2.1 (note that these are grouped for the purpose of categorization but are not presented in the order of testing in the testing procedure).

The major secondary endpoints in the first category evaluate the short-term efficacy of the combined guselkumab induction dose group versus placebo; the major secondary endpoints in the second category evaluate the long-term efficacy of each guselkumab dose group versus placebo; and the major secondary endpoints in the third category evaluate the long-term efficacy of each guselkumab dose group vs. ustekinumab. For all 3 sets of comparisons, the CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) will be used.

Participants who meet 1 or more treatment failure rules before a visit will be considered not to have achieved any of the major secondary endpoints from that visit onward. The treatment failure rules and missing data rules will follow the principles of the rules specified for the co-primary endpoints. Additional analysis considerations will be specified in the SAP.

A Global testing procedure to control the Type-I error at the 2-sided 0.05 significance level for the co-primary endpoints and the major secondary endpoints will be performed for each study separately. Each study will be tested with a separate testing procedure, but some tests of each guselkumab group vs. ustekinumab within each studies' testing procedure may be based on data pooled across studies. An overview is described below, and more details are specified in the SAP.

The testing procedure begins with sequential tests (within each Phase 3 study) of superiority of each guselkumab dose group compared with placebo relative to the co-primary endpoints at the 2-sided 0.05 significance level for each study. If any of these tests of the co-primary endpoints within a study is not significant (ie, p>0.05), all subsequent p-values in the testing hierarchy will be considered nominal. The major secondary endpoints will be grouped into tiers for testing. Within each tier, the Hochberg procedure will be used. [10] The testing procedure will start with Tier 1. If all p-values in a tier are less than 0.05, all tests will be declared significant, and the procedure will move onto the next tier. If at least one p-value is greater than 0.05 in a tier, formal testing will stop, and other endpoints within the same tier could still be declared as significant if they meet the Hochberg thresholds, but all p-values in subsequent tiers would be considered as nominal.

9.4.3.3.2. Regional Major Secondary Endpoint Analyses

The Regional major secondary endpoints are listed in Section 9.4.1.2.2.

Within each study, the major secondary endpoints of clinical remission at Week 12 as measured by PRO-2, fatigue response at Week 12, and endoscopic remission at **Week 12 will be compared between the combined guselkumab induction dose group and the placebo group** using the CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No).

The major secondary endpoints of endoscopic response at Week 48 and corticosteroid-free clinical remission at **Week 48 will be compared between each guselkumab dose group and the placebo group using** the CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No). For these comparisons, clinical non-responders at Week 12 will be considered non-responders.

The major secondary endpoints of clinical remission at Week 48 (either based on CDAI or PRO-2), endoscopic response at Week 48, endoscopic remission at Week 48, clinical remission at Week 48 and endoscopic response at Week 48, durable clinical remission at Week 48, and corticosteroid-free remission at **Week 48 will be compared between each guselkumab dose group and the ustekinumab group** using the CMH test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No).

Participants who meet 1 or more treatment failure rules before a visit will be considered not to have achieved any of the major secondary endpoints from that visit onward. The treatment failure rules and the missing data rules will follow the principles of the rules specified for the co-primary endpoints. Additional analysis considerations will be specified in the SAP.

A Regional testing procedure to control the Type-I error at the 2-sided 0.05 significance level for the co-primary endpoints and major secondary endpoints will be performed for each study separately. This testing procedure is separate from the Global testing procedure. An overview is described below, and more details are specified in the SAP.

The testing procedure begins with sequential tests (within each Phase 3 study) of superiority of the combined guselkumab induction dose group compared with placebo relative to the co-primary endpoints at the 2-sided 0.05 significance level for each study. If either of the tests of the co-primary endpoints within a study is not significant (ie, p>0.05), all subsequent p-values in the testing hierarchy will be considered nominal. The major secondary endpoints will be grouped into tiers for testing. Within each tier, the Hochberg procedure will be used. [10] The testing procedure will start with Tier 1. If all p-values in a tier are less than 0.05, all tests will be declared significant, and the procedure will move onto the next tier. If at least one p-value is greater than 0.05 in a tier, formal testing will stop, and other endpoints within the same tier could still be declared as significant if they meet the Hochberg thresholds, but all p-values in subsequent tiers would be considered as nominal.

9.4.3.4. Exploratory Efficacy Endpoint Analyses

Exploratory efficacy endpoints defined in Section 9.4.1.2.3 will be analyzed based on the timepoint (short-term, long-term) and comparator (placebo, ustekinumab) as described in Section 9.4.3.3. Within each study, the endpoints defined at Week 12 will be compared between the combined guselkumab induction dose group and the placebo group. The endpoints defined at Week 48 will be compared between each guselkumab dose group and the placebo group, or between each guselkumab dose group and the ustekinumab group, as specified in Section 3. Details will be provided in the Phase 3 SAP.

All statistical testing will be performed at the 2-sided 0.05 significance level. No adjustments for multiple comparisons will be made for these other efficacy endpoints and nominal p-values will be presented.

9.4.4. Safety Analyses

Adverse Events

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

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

- Frequency and type of AEs.
- Frequency and type of SAEs.
- Frequency and type of reasonably related AEs as assessed by the investigator.
- Frequency and type of AEs leading to discontinuation of study intervention.
- Frequency and type of infections.
- Frequency and type of AEs temporally associated with infusion.
- Frequency and type of injection-site reactions.

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

Clinical Laboratory Tests

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

- Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry).
- Summary of maximum National Cancer Institute Common Terminology Criteria for Adverse Events toxicity grade for post-baseline laboratory values (hematology and chemistry).

Listings of participants with any abnormal post-baseline laboratory values of National Cancer Institute Common Terminology Criteria for Adverse Events 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.

9.4.5. Other Analyses

Pharmacokinetic Analyses

Descriptive statistics of the serum guselkumab and ustekinumab concentrations will be calculated at each sampling time point. These concentrations will be summarized over time for each treatment group.

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.

A population PK analysis approach using nonlinear mixed-effects modeling will be used to evaluate guselkumab PK parameters. The influence of important covariates on the population PK parameter estimates may be evaluated. Details will be provided in a population PK analysis plan and the results of the population PK analysis will be presented in a separate technical report.

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 SAPs.

Immunogenicity Analyses

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

A listing of participants who are positive for antibodies to guselkumab or ustekinumab will be provided. The maximum titers of antibodies to guselkumab or ustekinumab will be provided for participants who are positive for antibodies to guselkumab or ustekinumab.

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

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, excluded from the biomarker analysis.

Changes in serum protein analytes and whole blood RNA obtained over time will be summarized by treatment group where local regulations permit. Associations between baseline levels and changes from baseline in select markers and response to treatment will be explored. RNA analyses will be summarized in a separate technical report.

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

Pharmacokinetic/Pharmacodynamic Analyses

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

Medical Resource Utilization and Health Economics Analyses

Medical resource utilization and health economics, including work productivity, will be summarized by treatment group.

9.5. Interim Analysis

An IA is planned for the Phase 2 study (GALAXI 1) to support the selection of induction and maintenance guselkumab dose regimens that will be evaluated in Phase 3. Moreover, the IA will help to inform the hypothesis testing order of the major secondary endpoints in the Phase 3 studies. This IA will be referred to as the dose selection analysis.

No IA is planned for the Phase 3 studies.

9.5.1. Dose Selection Analysis for Phase 2 (GALAXI 1)

The IA for the Phase 2 study (dose selection analysis) will occur after the first 250 randomized participants (ie, the Initial Dose Decision Cohort) in GALAXI 1 have either completed the Week 12 visit or terminated study participation prior to the Week 12 visit. The objective is to select 2 guselkumab dose regimens for continued development in Phase 3. The selection of the guselkumab dose regimens will be based on the analyses of key efficacy endpoints, dose-response analysis, safety, and PK data (further details to be provided in the Phase 2 Dose Selection Analysis Plan). In addition, the Phase 2 data through Week 48 will help to refine the assumptions for endoscopy endpoints, and to inform the testing procedure and the final ordering of the major secondary endpoints in Phase 3. Statistical analyses will be primarily based on data from the Initial Dose Decision Cohort (ie, the first 250 randomized participants) in GALAXI 1, but will also include data from the Transition Cohort. All available data from both cohorts will be analyzed, including any data beyond Week 12.

A Dose Selection Committee, composed of sponsor management representatives from Clinical, Safety, Biostatistics, and Clinical Pharmacology who are not associated with study conduct, will be responsible for deciding on the dose regimens of guselkumab to be evaluated in Phase 3.

The Dose Selection Committee will have access to the unblinded safety and efficacy summary tables and figures, but it will not have access to individual participant treatment assignment, with the exception of a listing of SAEs, AEs leading to discontinuation of study intervention, and maximum post-baseline toxicity values for the purpose of safety evaluation.

In general, individual participant treatment assignment will remain blinded to the sponsor. However, to support the dose selection process, a limited number of sponsor personnel will be unblinded to individual participant treatment assignment. Those sponsor personnel will not have contact with the investigative sites. Details of which sponsor personnel will be unblinded to individual participant treatment assignments will be specified prior to unblinding.

Investigative sites and site monitors will remain blinded to individual participant treatment assignments.

If a dose selection cannot be made at the Week 12 IA, further evaluation will be conducted at the Week 24 IA, which would occur when all participants in the Initial Dose Decision Cohort (n=250) have reached Week 24 or terminated study participation prior to Week 24. For both the Week 12 IA and the Week 24 IA, all available data for both the Initial Dose Decision Cohort and the

Transition Cohort will be analyzed. Additional data transfers and analyses may be performed if needed to enable the dose decision for Phase 3.

Since the sponsor does not plan to stop the trial early for efficacy, there is no alpha spending penalty for the IA.

The Dose Selection Analysis Plan will describe the analyses to be performed, the prespecified dose selection criteria, and other operational plans in greater detail.

9.5.2. Data Monitoring Committee

An external independent DMC will be established and will meet periodically to review interim unblinded safety data from the Phase 2 and Phase 3 studies to ensure the continuing safety of the participants enrolled in this program. This DMC may also participate in the IA (see Section 9.5.1). The DMC will consist of a gastroenterologist familiar with the treatment of the adult IBD population, a physician familiar with the safety profile of guselkumab, 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 and treated in GALAXI 1. Based on the planned randomization ratio, this first 25 participants should include approximately 5 participants in each of the highest guselkumab dosing groups ([redacted] [redacted] similar to the cohort size for each dose in a typical single or multiple ascending dose Phase 1 study. Also 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 additionally perform a review of unblinded safety tables. In the event that the number of patients in either the [redacted] group or the [redacted] group for this review is less than 5, then the DMC will conduct another review of unblinded safety tables 1 month later, when at least 5 patients will have been treated in both the [redacted] and [redacted] groups. 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 4 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
AP	abdominal pain
AP-NRS	abdominal pain – numerical rating scale
AST	aspartate aminotransferase
AUC	area under the serum concentration versus time curve
AZA	azathioprine
BCG	Bacille Calmette-Guérin
BIO-Failure	biologic therapy failure or intolerance
BSFS	Bristol Stool Form Scale
CDAI	Crohn's Disease Activity Index
CMH	Cochran-Mantel-Haenszel
CON-Failure	conventional therapy failure or intolerance
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBL	database lock
DCS	data collection system
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	EuroQol five dimensions descriptive system
EQ-5D-5L	5-level EuroQol five dimensions instrument (consisting of the EuroQol five dimensions descriptive system [EQ-5D] and the EuroQol Visual Analog Scale [EQ-VAS])
EQ-VAS	EuroQol visual analog scale
EU	European Union
FDA	Food and Drug Administration (US)
FES	Final Efficacy and Safety
GCP	Good Clinical Practice
GHAS	Global Histology Activity Score
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HBV DNA	hepatitis B virus deoxyribonucleic acid
HCP	healthcare professional
HRQOL	health-related quality of life
HRT	hormonal replacement therapy
IA	interim analysis
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL	interleukin
INR	international normalized ratio

IPPM	Investigational Product Procedures Manual
IRB	Institutional Review Board
[redacted]	[redacted]
IWRS	interactive web response system
LTE	long-term extension
mAb	monoclonal antibody
MMRM	Mixed Model for Repeated Measures
MTX	methotrexate
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic
PGIC	Patient's Global Impression of Change (of Severity of Crohn's Disease)
PGIS	Patient's Global Impression of Severity (of Crohn's Disease)
PK	pharmacokinetic(s)
PPD	purified protein derivative
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PROMIS	Patient-Reported Outcomes Measurement Information System
PsA	psoriatic arthritis
[redacted]	[redacted]
RHI	Robarts histopathology index
[redacted]	[redacted]
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	[redacted]
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SID	study intervention discontinuation (visit)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TNF	tumor necrosis factor
TU	tuberculin unit
ULN	upper limit of normal
US	United States
WBC	white blood cell (count)
WPAI-CD	Work Productivity and Activity Impairment Questionnaire in Crohn's Disease

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 an eCRF as determined by the protocol. Data in this system may be considered source documentation.

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

CORTICOSTEROIDS

Participants have failed to respond to corticosteroids if they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving at least CCI of prednisone (or corticosteroid equivalent, given orally or intravenously) for 2 weeks; or CCI of budesonide or CCI of beclomethasone dipropionate given orally for at least 4 weeks. Evidence of CON-Failure must be documented in the participant's source documentation.

Participants are intolerant of corticosteroids if:

- They have developed clinically significant adverse events (eg, osteonecrosis or osteoporosis, psychosis, uncontrolled diabetes) unresponsive to dose reduction that, in the judgment of the investigator, precluded the use of corticosteroids to treat Crohn's disease.

OR

- They have a medical condition that precludes the use of corticosteroids as a treatment for Crohn's disease.

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

6-MERCAPTOPURINE (6-MP), AZATHIOPRINE (AZA), OR METHOTREXATE (MTX)

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

- At least 3 months of therapy with CCI of 6-MP, CCI of AZA, or CCI week (intramuscular or CCI of MTX.

OR

- A lower dosage of 6-MP, AZA, or MTX 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, AZA, or MTX confirmed to be therapeutic for the participant with whole blood thioguanine nucleotide levels >200 pmol/8 x 10^8 red blood cells.

OR

- The highest tolerated dosage due to leukopenia, elevated liver enzymes, or nausea.

Participants are intolerant of 6-MP, AZA, or MTX 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, AZA, or MTX to treat Crohn's disease.

OR

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

10.3. Appendix 3: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNF Antagonist Therapies (Infliximab, Adalimumab, or Certolizumab Pegol) or Vedolizumab

The criteria for inadequate initial response, response followed by loss of response, or intolerance to infliximab, adalimumab, certolizumab pegol, or vedolizumab are described in items 1, 2, and 3, below.

1. Inadequate initial response to current or prior therapy with infliximab, adalimumab, certolizumab pegol (primary non-response), or vedolizumab (primary non-response)

Eligible participants must satisfy criteria a, b, and c.

a. Have received, at minimum, a locally approved induction dose, for example:

1) Infliximab (2 or 3 doses of C [redacted] C

or

2) Adalimumab (at a dose of CCI [redacted] followed by a dose C [redacted] C **or** at a dose of CCI [redacted] followed by a dose C [redacted] C

or

3) Certolizumab pegol (2 or 3 doses of C [redacted] C

or

4) Vedolizumab (at least 2 and up to 4 doses of CCI [redacted]

AND

b. Did not initially respond to these induction doses of infliximab, adalimumab, certolizumab pegol, or vedolizumab, as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of Crohn's disease, as assessed by a treating physician:

1) Lack of improvement or worsening in stool frequency

2) Lack of improvement or worsening in daily abdominal pain

3) Occurrence, lack of improvement, or worsening of fever thought to be related to Crohn's disease

4) Lack of improvement or worsening in a draining fistula or development of a new draining fistula

5) Lack of improvement or worsening in rectal bleeding

6) Initiation or increase in antidiarrheal medication

These signs and symptoms of Crohn's disease must have occurred ≥2 weeks after receiving the last induction dose of infliximab, adalimumab, certolizumab pegol, or vedolizumab, and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having had an inadequate initial response to infliximab, adalimumab, certolizumab pegol, or vedolizumab therapy. This benchmark acknowledges that the CDAI is not routinely recorded in clinical practice.

AND

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

1) Provide the dates and doses of the failed infliximab, adalimumab, certolizumab pegol, or vedolizumab induction therapy.

2) Documents that the participant had persistence of disease activity following infliximab, adalimumab, certolizumab pegol, or vedolizumab induction therapy.

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

2. Initial response followed by loss of response to current or prior therapy with infliximab, adalimumab, certolizumab pegol, or vedolizumab (secondary non-response)

Eligible participants must satisfy criteria a, b, c, d.

a. Initially responded to induction therapy

AND

b. Have received, at minimum, 2 doses of a locally approved maintenance dose, for example:

1) Infliximab (at a dose of C [redacted] C

or

2) Adalimumab (at a dose of C [redacted] C

or

3) Certolizumab pegol (at a dose of C [redacted] C

or

4) Vedolizumab (at a dose of C [redacted] CI or CCI [redacted]

AND

c. Have or had at least 1 of the following signs or symptoms related to recurrence of Crohn's disease, as assessed by a treating physician:

1) Worsening in stool frequency

2) Worsening in daily abdominal pain

3) Occurrence or worsening in fever thought to be related to Crohn's disease

4) Recurring drainage from a previously nondraining fistula or development of a new draining fistula

5) Worsening in rectal bleeding

6) Initiation or increase in antidiarrheal medication

These signs and symptoms of Crohn's disease must have occurred ≥2 weeks after receiving the last maintenance dose of infliximab, adalimumab, certolizumab pegol, or vedolizumab, and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having lost response to infliximab, adalimumab, certolizumab pegol, or vedolizumab therapy. This benchmark acknowledges that the CDAI is not routinely recorded in clinical practice.

AND

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

1) Provide the dates and doses of the failed infliximab, adalimumab, certolizumab pegol, or vedolizumab maintenance therapy.

2) Documents that the participant had recurrence of disease activity despite infliximab, adalimumab, certolizumab pegol, or vedolizumab maintenance therapy.

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

If the above evidence is not sufficient to be considered for primary or secondary non-response, this may also be determined based on evaluation of other measures that may be indicative of worsening disease (eg, elevations of inflammatory markers including but not limited to CRP or fecal calprotectin, and/or evidence of disease flare based on clinical imaging modalities including but not limited to ileocolonoscopy, CT, and MRI). Under these circumstances, documentation of these specified measures of worsening disease activity can be accepted as evidence of loss of response or inadequate response to prior biologic treatment. However, investigators should note that participants must meet protocol-specified criteria for active disease (ie, clinical and endoscopic) during the current screening period, as described in Section 5.1, to be eligible for enrollment.

3. Current or prior intolerance to therapy with infliximab, adalimumab, certolizumab pegol, or vedolizumab

Eligible participants must satisfy criteria A and B.

a. Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum sickness-like reaction); or 3) significant injection-site reaction. Definitions of these 3 criteria are provided below. Adverse reactions also must have followed ≥1 dose of infliximab, adalimumab, certolizumab pegol, or vedolizumab, and, in the treating physician's opinion, precluded continued use of the therapy.

1) A significant acute infusion/administration reaction is defined as an adverse reaction that was:

a) Manifested through ≥ 1 of the following symptoms.

- Fever greater than 100°F (37.8°C)
- Chills or rigors
- Itching
- Rash
- Flushing
- Urticaria or angioedema
- Breathing difficulties (dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor)
- Clinical hypotension (pallor, diaphoresis, faintness, syncope), blood pressure less than 90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure of greater than 20 mm Hg

AND

b) Occurred ≤24 hours after infusion/administration of infliximab, adalimumab, certolizumab pegol, or vedolizumab

AND

c) Was considered related to the infusion/administration of infliximab, adalimumab, certolizumab pegol, or vedolizumab.

2) A significant delayed infusion/administration reaction is defined as an adverse reaction that:

a) Was manifested through 1 or more of the following symptoms:

- Myalgias
- Arthralgias
- Fever greater than 100°F (37.8°C)
- Malaise
- Rash

AND

b) Occurred >24 hours and <15 days after infusion/administration of infliximab, adalimumab, certolizumab pegol, or vedolizumab

AND

c) Was considered related to the infusion/administration of infliximab, adalimumab, certolizumab pegol, or vedolizumab.

3) A significant injection-site reaction is defined as an adverse reaction that:

d) Was manifested through 1 or more of the following symptoms:

- Significant bruising
- Erythema
- Hemorrhage
- Irritation
- Pain
- Pruritus
- "Injection-site reaction"

AND

- Occurred within 24 hours of an [redacted] injection of adalimumab or certolizumab pegol.

AND

- Was considered related to the injection.

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

1) Provides the date of discontinuation of infliximab, adalimumab, certolizumab pegol, or vedolizumab.

2) Documents that the participant had intolerance to infliximab, adalimumab, certolizumab pegol, or vedolizumab.

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

10.4. Appendix 4: Definition of Exposure to Ustekinumab

Participants who have had exposure to ustekinumab at its approved labeled dosage **AND** have met the required washout criterion **AND** have not demonstrated failure or intolerance to ustekinumab as defined further below are eligible for entry into this protocol.

Participants who have had exposure to ustekinumab as an investigational agent (ie, exposure to ustekinumab from participation in prior ustekinumab clinical studies) or exposure to ustekinumab as an off-label treatment at their physician's discretion **are ineligible** for entry into this protocol.

Participants with prior exposure to other anti-IL-12/23 (ie, briakinumab) or anti-IL-23 (ie, including but not limited to risankizumab, brazikumab, and mirikizumab) agents **are ineligible** for entry into this protocol.

Participants MUST meet all of criteria 1, 2, and 3 below to qualify for entry into this protocol as having had minimal exposure to ustekinumab, and provided that all other entry criteria as described in Sections 5.1 and 5.2 have been satisfied.

1. **The criteria for minimal exposure to ustekinumab at its approved label dosage is defined as follows:**
   a. No more than one induction dose of ustekinumab CCI [redacted]

      AND EITHER

   b. No more than one maintenance dose of ustekinumab CCI [redacted] after the single induction dose

      OR

   c. More than one maintenance dose with sponsor approval

   Note: Discussion with sponsor must occur to confirm participant did not have inadequate response or intolerance as referenced in #3 below.

2. **The required washout period from ustekinumab is defined as followed:**

   Participants must have been discontinued from ustekinumab for at least 16 weeks prior to the Week 0 dosing visit of this protocol

3. **The following documentation to confirm the discontinuation of ustekinumab treatment for Crohn's disease for reasons other than inadequate response or intolerance MUST be provided:**

   Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization / denial notifications) that:

   a. Provide the dates and doses of ustekinumab for the treatment of Crohn's disease; AND
   b. Provide the date of discontinuation of ustekinumab for the treatment of Crohn's disease; AND
   c. Indicate the participant had discontinued ustekinumab treatment for reasons other than inadequate response and/or intolerance (eg, loss of insurance); AND
   d. Indicate the participant **did not** discontinue ustekinumab treatment for Crohn's disease due to inadequate response and/or intolerance. See further details under the NOTE section below for evidence indicative of inadequate response and/or intolerance.

NOTE:

The following is considered evidence of inadequate response and/or intolerance to ustekinumab treatment for Crohn's disease. Participants who meet these criteria **are ineligible** to enter this protocol.

Evidence of inadequate response to ustekinumab that had precluded continuation of previous treatment with ustekinumab for Crohn's disease:

- Lack of improvement or worsening in stool frequency
- Lack of improvement or worsening in daily abdominal pain
- Occurrence, lack of improvement, or worsening of fever thought to be related to Crohn's disease
- Lack of improvement or worsening in a draining fistula or development of a new draining fistula
- Lack of improvement or worsening in rectal bleeding
- Initiation or increase in antidiarrheal medication

These signs and symptoms of Crohn's disease are offered only as a benchmark and acknowledges that the CDAI is not routinely recorded in clinical practice.

Evidence of intolerance to ustekinumab that had precluded continuation of previous treatment with ustekinumab for Crohn's disease:

Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum sickness-like reaction); or 3) significant injection-site reaction. Definitions of these 3 criteria are provided below.

- **A significant acute infusion/administration reaction is defined as an adverse reaction that was:**
  a. Manifested through ≥ 1 of the following symptoms.
     - Fever greater than 100°F (37.8°C)
     - Chills or rigors
     - Itching
     - Rash
     - Flushing
     - Urticaria or angioedema
     - Breathing difficulties (dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor)
     - Clinical hypotension (pallor, diaphoresis, faintness, syncope), blood pressure less than 90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure of greater than 20 mm Hg

     AND

  b. Occurred ≤24 hours after infusion/administration of ustekinumab

     AND

  c. Was considered related to the infusion/administration of ustekinumab
- **A significant delayed infusion/administration reaction is defined as an adverse reaction that:**
  a. Was manifested through 1 or more of the following symptoms:
     - Myalgias
     - Arthralgias
     - Fever greater than 100°F (37.8°C)

- Malaise
- Rash

AND

b. Occurred >24 hours and <15 days after infusion/administration of ustekinumab

AND

c. Was considered related to the infusion/administration of ustekinumab

- **A significant injection-site reaction is defined as an adverse reaction that:**

a. Was manifested through 1 or more of the following symptoms:

- Significant bruising
- Erythema
- Hemorrhage
- Irritation
- Pain
- Pruritus
- "Injection-site reaction"

AND

b. Occurred within 24 hours of an [redacted] injection of ustekinumab.

AND

c. Was considered related to the [redacted] injection of ustekinumab.

10.5. Appendix 5: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

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

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, 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.

10.6. Appendix 6: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4 (Pregnancy), and Appendix 10.11 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 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 hormone-replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single follicle stimulating hormone 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 10, 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 16 weeks 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.

10.7. Appendix 7: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

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

These eligibility criteria based on HBV test results are also represented in Table 1 below. For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines.

Table 1: Eligibility based on hepatitis B virus test results

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

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

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

10.8. Appendix 8: Regulatory, Ethical, and Study Oversight Considerations

10.8.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (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 or designee. 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 designee. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor or designee 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 or designee before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor or designee 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 or designee has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

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

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

- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

Country 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.

10.8.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor or designee 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.

10.8.3. 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 or designee 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 or designee 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 approximately 5-week window is required. If a participant is approaching the completion of that period, the medical monitor can be contacted to discuss eligibility.

If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph, stool analysis), 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.

10.8.4. 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 tests are only for research. They will not be used for medical care of the participant or to make a diagnosis about the participant's health. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.8.5. 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 ustekinumab, to understand Crohn's disease, to understand differential intervention responders, and to develop diagnostic tests to identify Crohn's disease populations that may be responsive or non-responsive to treatment with guselkumab or ustekinumab. 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).

10.8.6. Committees Structure

Data Monitoring Committee

Details regarding the DMC are presented in Section 9.5.2.

10.8.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not

previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

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

The results of the study will be reported in a Clinical Study Report (CSR) generated by the sponsor and will contain data from all study sites that participated in the study 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 and exploratory biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR.

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 guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors 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.

10.8.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor or designee, 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 or designee 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.

10.8.9. Data Collection

Data for each study participant will be collected in the eCRF or ancillary data collection systems such as the IWRS, patient-reported outcome (PRO) tablets, laboratory database, and imaging database. Case report forms are prepared and provided by the sponsor for each participant in eCRF. 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.

10.8.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

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

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

- Referral letter from treating physician or
- Complete history of medical notes at the site
- 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. These data are 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.

10.8.11. Monitoring

The sponsor designee will perform on-site monitoring visits as frequently as necessary. This will include blinded site monitors who will perform the majority of source data verification and unblinded site monitors who will specifically review drug preparation and dispensation. 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 or designee 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 or designee expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

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

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

10.8.12. On-Site Audits

Representatives of the sponsor's (or sponsor designee'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 or designee if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.8.13. 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 or designee.

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

10.8.14. 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.

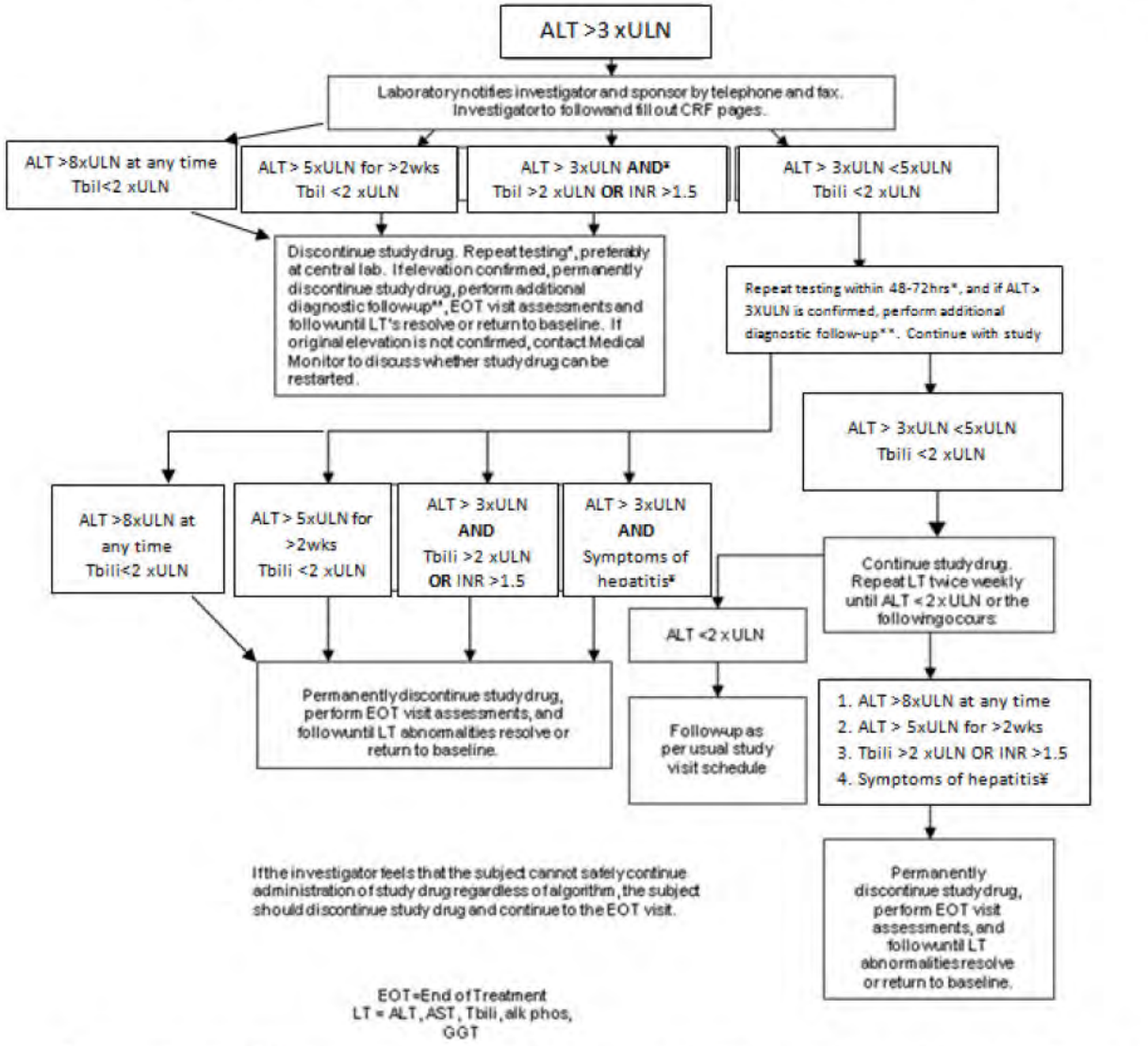
Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- 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

10.9. Appendix 9: Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants With No Underlying Liver Disease

The ALT criteria in this algorithm are also applicable to AST.

NOTE: "Liver tests" or "LT's" is the proper name for what are often called "liver function tests" or "LFT's"



*Repeat testing within 48-72 hours in patients with initial ALT elevations, particularly if these are not events reported previously with the drug. If ALT transient elevations have been already established as part of the safety profile, the required frequency of retesting can be decreased

¥ OR ALT >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

THE COMPLETE WORK-UP BELOW (ITEMS 1-5) SHOULD BE PERFORMED IN EVERY SITUATION WHERE "" APPEARS ABOVE. ITEMS 6-7 ARE OPTIONAL, TO BE CONSIDERED ON CASE-BY-CASE BASIS. ALL STUDIES SHOULD BE REPORTED WITH APPROPRIATE SOURCE DOCUMENTATION.**
THE STUDY MEDICAL MONITOR SHOULD BE NOTIFIED WHEN THE ABNORMALITIES ARE DETECTED AND PROVIDED WITH AN UPDATE OF THE RESULTS OF THE DIAGNOSTIC WORK-UP

The following definition of patterns of drug-induced liver injury (DILI) is used when directing the work-up for potential DILI based on elevations of common laboratory tests (LT). A hepatologist consultation should be considered if clinically indicated for the diagnosis and management of potential DILI.

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

1. Obtain detailed history of present illness (abnormal LT's) including (if not already obtained at baseline) height, weight, body mass index (BMI). Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure (CHF), occupational exposure to hepatotoxins, diabetes mellitus (DM), gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other meds including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAID), over the counter (OTC) herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical exam, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy). Allow free text in case report form for other relevant history and physical information.
2. Mandatory liver ultrasound with consideration of further imaging (eg, computerized tomography [CT], magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), Doppler studies of hepatic vessels, if indicated based on ultrasound findings or clinical situation).

3. If total bilirubin (Tbili) is >2xULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with white blood count (WBC) and eosinophil count platelet count, international normalized ratio (INR), and total protein and albumin (compute globulin fraction) should also be documented. If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.
4. If initial LTs and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin M (anti-HAV IgM), anti-HAV total, hepatitis B surface antigen (HBsAg), anti-HBs, anti-HB core total, anti-HB core IgM, anti-hepatitis C virus (anti-HCV), anti-hepatitis E virus IgM (anti-HEV IgM) (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) screen.
   - If patient is immunosuppressed, test for HCV RNA and HEV RNA.
   - If HBsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in patients who are immunosuppressed.
   - If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.
5. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: Total protein and albumin (estimate globulin fraction and obtain quantitative immunoglobulins if elevated), antinuclear antibody (ANA), anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-liver-kidney microsomal antibodies (anti-LKM antibodies), anti-smooth muscle antibodies (ASMA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then gamma-glutamyl transferase (GGT), anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody (pANCA) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/Total iron binding capacity (TIBC) and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If patient is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.
6. A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

   A liver biopsy may be considered:

   - if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.

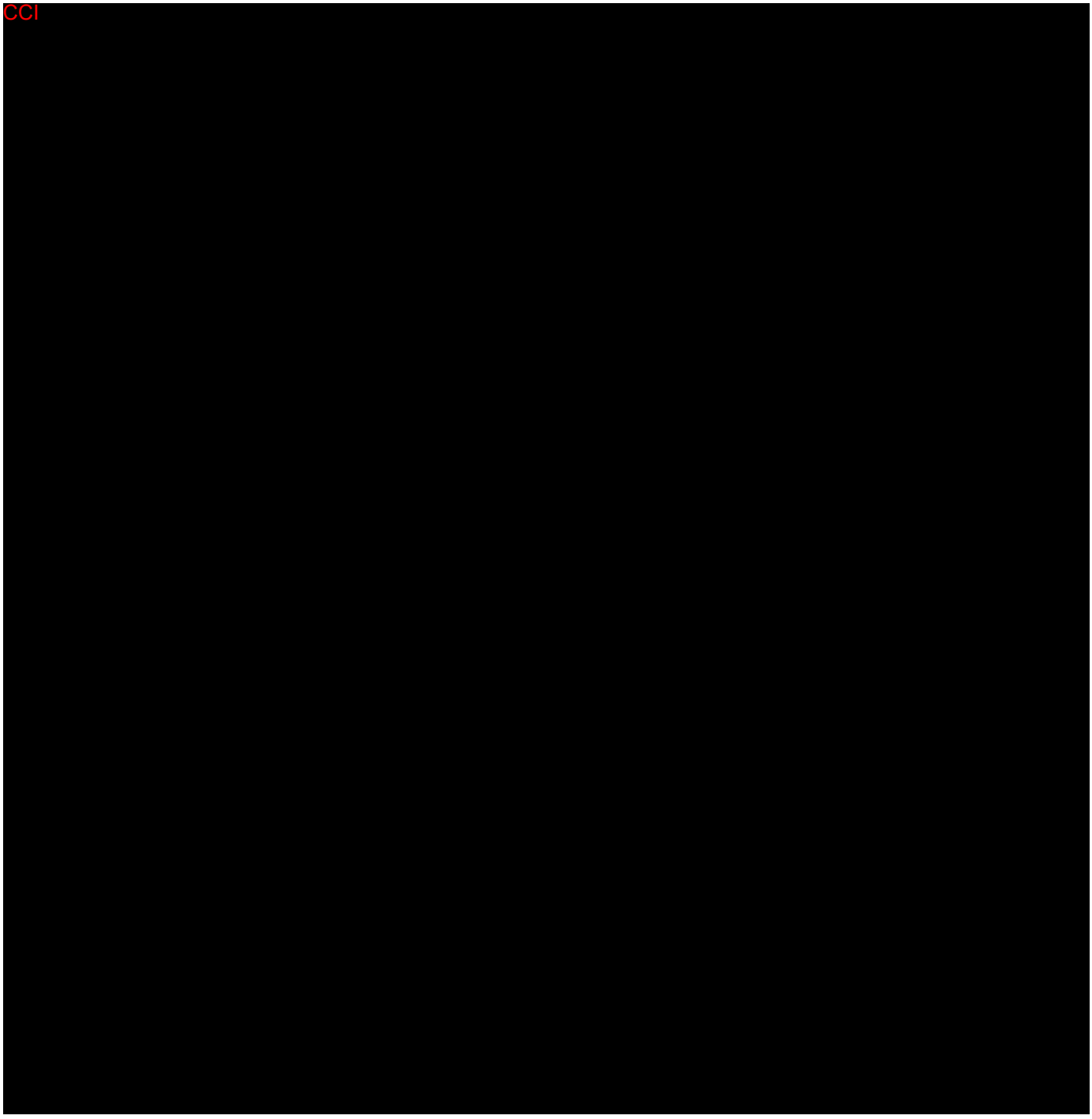
- if peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak Alk P has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
- in cases of DILI where continued use or re-exposure to the implicated agent is expected.
- if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

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

Abbreviations

AlkP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AMA	anti-mitochondrial antibody
ANA	antinuclear antibody
Anti-LKM1	anti-liver kidney microsomal antibody type 1
ASMA	anti-smooth muscle antibodies
AST	aspartate aminotransferase
BMI	body mass index
CBC	complete blood count
CHF	congestive heart failure
CMV	cytomegalovirus
CRP	C-reactive protein
CT	computerized tomography
DM	diabetes mellitus
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
EOI	end of intervention
GGT	gamma-glutamyltransferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HepB	hepatitis B virus
HEV	hepatitis E virus
IgM	immunoglobin M
INR	international normalized ratio
LT/LFT	liver tests/liver function tests
MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatography
NSAID	nonsteroidal anti-inflammatory drug
OTC	over the counter
PT	prothrombin time
PTT	partial thromboplastin time
RNA	ribonucleic acid
Tbili	total bilirubin
TIBC	total iron binding capacity
ULN	upper limit of normal
WBC	white blood count

10.10. Appendix 10: Crohn's Disease Activity Index



10.11. Appendix 11: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.11.1. 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 Council for 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).

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

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.

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

10.11.2. 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).

10.11.3. Severity Criteria

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

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

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

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

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

10.11.4. 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.

10.11.5. 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 or designee’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.

10.11.6. Product Quality Complaint Handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system. 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.

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

Procedures

All initial PQCs must be reported to the sponsor or designee 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 designee 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.

10.11.7. 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.

10.12. Appendix 12: Anticipated Events

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

- Adverse events related to symptoms of Crohn's disease
- Adverse events related to worsening or progression of Crohn's disease

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

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee. The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries/territories in which the studies are conducted.

10.13. Appendix 13: CCI

CCI

CCI
[redacted]

Table 14: CCI

CCI

Table 14: CCI

CCI

10.14. Appendix 14: Guidance on Study Conduct During a Major Disruption Event

It is recognized that the events causing major disruption such as COVID-19 pandemic, war, or natural disaster may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, relocated, or reassigned to critical tasks.

The sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be at unacceptable safety risk, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the major disruption on scheduled visits cannot be conducted in person at the study site, the study visit will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor.

Related to the COVID-19 pandemic, if a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee to discuss plans for administration of study intervention, performing study assessments, and follow-up.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the major disruption, should be summarized in the Clinical Study Report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the major disruption events. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of participant care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
    - remote (eg, by phone / telehealth) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures, eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration (including training where pertinent)
    - procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at-home administration (including the potential for self-administration of study intervention)
    - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
    - other procedures, eg, imaging, may be conducted at an appropriate facility
- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented in the case report form (CRF).
    - other relevant study data elements impacted by the major disruption, should also be documented in CRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of major disruption events on collection of key study data and additional data analyses will be outlined in study SAP(s).

10.15. Appendix 15: Protocol Amendment History

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

Amendment 4 (21 July 2021)

Overall Rationale for the Amendment: To extend the long-term extension (LTE) for the GALAXI 1, GALAXI 2, and GALAXI 3 studies from 2 years to 4 years, and therefore also add/update timepoints for assessments; to update/add Coronavirus Disease 2019 (COVID-19) language; to add administrative language for serious adverse event (SAE) monitoring and liver function tests; to update the CCI [redacted]

Corrections reflecting these changes, together with other minor clarifications, have been made.

Section Number and Name	Description of Change	Brief Rationale
The length of the LTE was extended from 2 years to 4 years, for a total duration of study participation for each participant of up to 5 years. Timepoints for assessments were added/updated accordingly.		
1.1. Synopsis: Overview of Protocol; 2.1. Study Rationale	Under this protocol, there are 3 separate studies: a 48-week Phase 2 dose-ranging study (ie, GALAXI 1) and 2 identical 48-week Phase 3 confirmatory studies (ie, GALAXI 2 and GALAXI 3). Participants who complete the 48-week Phase 2 or Phase 3 studies may be eligible to enter the long-term extension (LTE [Week 48 to Week ~~156~~252]) and receive approximately ~~2~~4 additional years of treatment. The overall Phase 2/3 development program will enroll approximately 2,000 participants with a total duration for each participant of up to approximately ~~3~~5 years.	There remains a high unmet need for the disease management and treatment of patients with Crohn's disease. The 2-year extension of the LTE (total 5 years of treatment) provides study participants further longevity with regards to treatment for the management of their disease. In addition, the extension allows for the evaluation of further long-term efficacy and safety of guselkumab.
1.1. Synopsis: Overall Design; 4.1. Overall Design	Participants who complete the 48-week Phase 2 or Phase 3 studies may be eligible to enter the LTE to receive approximately ~~2~~4 additional years of treatment.	
1.1. Synopsis: Number of Participants; 4.1. Overall Design	The overall GALAXI Phase 2/3 protocol will enroll a total of approximately 2,000 participants with a total duration for each participant of up to approximately ~~3~~5 years.	
Schedule of Activities (SoA); Table 3	[Table 3 title:] Table 3: SoA – Week 48 to Week ~~144~~240 (Long-Term Extension) for Eligible Participants Who Have Completed Week 48 of GALAXI 1, GALAXI 2, or GALAXI 3	
	[Notes in the following rows were revised to show updated study weeks and additional assessments for the extended LTE:] • Administer study intervention: Participants will receive their final study intervention administration at Week ~~140~~236. • Video ileocolonoscopy: Video ileocolonoscopy will ~~only~~ be performed at Weeks 96, 144, 192, and 240 ~~(not Week 144)~~.	

Section Number and Name	Description of Change	Brief Rationale
	• Stool sample (fecal calprotectin): Stool samples required for the Week 96, 144, 192, and 240 visits must be obtained before the start of the bowel preparation for the video ileocolonoscopy that is scheduled for the visit. • CRP: To be collected CCI from Week 48 to Week 96, and q16w from Week 96 to Week ~~144~~240. • Study intervention serum concentration: Study intervention serum concentration will be collected CCI from Week 48 to Week 96, and q16w from Week 96 to Week ~~144~~240. • Ileocolonoscopy biopsy sample collections for histology: Ileocolonoscopy biopsy sample will ~~only~~ be collected at Weeks 96, 144, 192, and 240 ~~(not Week 144)~~. • Crohn's disease-related hospitalizations and surgeries: Hospitalization for ileocolonoscopy at Weeks 96, 144, 192, and 240 is not included in this category.	
	[Whole blood sample collection for RNA analysis row deleted] ~~Whole blood sample and collection for RNA analysis (where local regulations permit)~~ [q16w visit column]: ~~X~~ [q48w visit column]: ~~X~~ ~~Whole blood for RNA analysis will be collected from all participants in the study to assess the RNA transcriptome related to both Crohn's disease and response to guselkumab and ustekinumab.~~	
	[Serum biomarkers row edited to show that samples will not be collected at the q16w visit; "X" removed from q16w visit column]	
	[Stool sample (microbiome; where local regulations permit) row deleted] ~~Stool sample (microbiome; where local regulations permit)~~ [q16w visit column]: ~~X~~ [q48w visit column]: ~~X~~	
	[Footnotes in Table 3 were revised:] b: (Third sentence) Upon study unblinding, study intervention administration will continue for all participants on active treatment through Week ~~144~~240. c: The CCI visits include scheduled visits at Weeks 56, 72, 88, 104, 120, ~~and~~ 136, 152, 168, 184, 200, 216, and 232. d: The q16w visits include scheduled visits at Weeks 64, 80, 112, ~~and~~ 128, 160, 176, 208, and 224. e: The q48w visits occur at Weeks 96, ~~and Week~~ 144, 192, and 240.	
Schedule of Activities (SoA); Table 4	[The following row headers and notes were revised to show updated study timepoints for the extended LTE:]	

Section Number and Name	Description of Change	Brief Rationale
	Participant discontinues study intervention after Week 48 and up to Week ~~144~~240: Discontinuation after Week 48 and before Week 96: The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 48, since these participants would have completed the procedure as part of the Week 48 visit. Discontinuation after Week 96 and before Week 144: The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 96, since these participants would have completed the procedure as part of the Week 96 visit. Discontinuation after Week 144 and before Week 192: The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 144, since these participants would have completed the procedure as part of the Week 144 visit. Discontinuation after Week 192 and before Week 240: The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 192, since these participants would have completed the procedure as part of the Week 192 visit. Participant completes LTE participation at Week ~~144~~240: Week ~~144~~240 (see Table 3) The FES should occur around Week ~~156~~248 or 252 (ie, approximately 16 weeks after the last study intervention administration at Week ~~140~~232 [for CCI dosing] or 236 [for CCI dosing]).	
Schedule of Activities (SoA); Table 5	[The note in the Patient-Reported Outcomes (PROs) row was edited] PRO assessments for efficacy (PGIC, PGIS, IBDQ, PROMIS-29, PROMIS Fatigue Short Form 7a, and EQ-5D-5L) and health economics (WPAI-CD) should be administered before the C-SSRS and before any clinical procedures or tests are performed. The IBDQ, PROMIS-29, and WPAI-CD assessments should be performed if a participant discontinues in the LTE.	
4.1.1. Phase 2 Dose-Ranging Study (GALAXI 1): Induction and Maintenance; 4.1.2. Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3): Induction and Maintenance; 4.1.3. Long-Term	[Edited subheaders] 4.1.1. Phase 2 Dose-Ranging Study (GALAXI 1): Induction and Maintenance 4.1.2. Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3): Induction and Maintenance 4.1.3. Long-Term Extension for GALAXI 1, 2, and 3	

Section Number and Name	Description of Change	Brief Rationale
Extension for GALAXI 1, 2, and 3		
4.1.1.2. Treatment Groups	All participants who complete the Week 48 evaluations may be eligible to enter the LTE and continue to receive study intervention for approximately ~~24~~ additional years (Week 48 to Week ~~156~~252), as described in Section 4.1.3.	
4.1.3. Long-Term Extension for GALAXI 1, 2, and 3	The LTE will be conducted for approximately ~~24~~ years, from Week 48 through Week ~~156~~252. At Week 48 of GALAXI 1, GALAXI 2, or GALAXI 3, all participants who, in the opinion of the investigator, will continue to benefit from treatment (ie, based on Week 48 clinical and endoscopic evaluations) are eligible to enter the LTE to receive approximately ~~24~~ additional years of treatment, during which time the longer-term efficacy and safety of guselkumab will be evaluated. All participants will be assessed according to the Schedule of Activities (Section 1.3). The final efficacy and safety follow-up (FES) visit of the LTE will occur at approximately Week ~~156~~248 or 252 (ie, approximately 16 weeks after their last study intervention administration at Week ~~140~~232 [for CCI dosing] or Week 236 [for CCI dosing]). [Paragraph 4] During the LTE, all participants will continue to receive the same treatment regimen (ie, guselkumab, ustekinumab, or placebo) that they were receiving at the end of GALAXI 1, GALAXI 2, or GALAXI 3. The first study intervention administration in the LTE will occur at Week 48 and the last study intervention administration will occur at Week ~~140~~236. Treatment adjustment for inadequate response is permitted between Week 52 and Week 80 of the LTE, as described in Section 4.1.3.1. [Paragraph 7] After study unblinding, all participants who are on active treatment (ie, guselkumab or ustekinumab) will continue to receive their assigned active treatment for the remaining duration of the LTE through Week ~~140~~236. Participants who are on placebo will be discontinued from study intervention upon study unblinding and will have an FES visit at that time.	
4.1.3.1. Treatment Adjustment for Inadequate Response	…[Paragraph 5, 2nd to last sentence] Continued participation in the remaining duration of the LTE will be decided on investigator's clinical judgment of the results of the Week 96, 144, and 192 clinical and endoscopic evaluations.	
4.1.3.2. Self-Administration of Study Intervention (or Administration	…[Paragraph 3, last sentence] Finally, participants will continue to have study visits and assessments at the investigative sites approximately CCI through Week ~~144~~240, as outlined in Section 1.3.	

Section Number and Name	Description of Change	Brief Rationale
by Caregiver) at Home	…[Paragraph 4, last sentence] Participants will continue to have study visits and assessments at the investigative site approximately CCI (if receiving CCI dosing per protocol) or CCI (if receiving CCI dosing per protocol) through Week ~~144~~240, as outlined in Section 1.3.	
4.2.1. Endpoints and Evaluations	[Paragraph 1, 1st sentence] Through Week ~~156~~252, the longer-term efficacy and safety of guselkumab will be evaluated. [Paragraph 3] Database locks are planned at Weeks 96 (to evaluate the durability of efficacy evaluations and the benefit of dose adjustment); Weeks 144 and 192, and when the final participant has completed the FES visit in the LTE (to provide longer-term safety and efficacy data). Additional DBLs may be added if necessary and will be specified in the Phase 3 SAP.	
4.2.3. Biomarker and DNA Collection	[Paragraph 1, 4th sentence] Ileocolonic biopsies will also be obtained from all participants pretreatment during screening and post-treatment at Weeks 12, 48, ~~and~~ 96, 144, 192 and 240 to assess cellular and molecular changes within the intestinal mucosal tissue.	
4.2.6. Study-Specific Ethical Design Considerations	[Paragraph 2, 1st sentence] The total blood volume to be collected from each participant in each study (maximum of approximately 500~~400~~ mL over approximately ~~156~~252 weeks) is far less than the American Red Cross standard limit for whole blood donation (approximately 475 mL CCI and is, therefore, considered an acceptable amount of blood to be collected over this time period.	
4.3.1.3. Long-Term Extension (Week 48 to Week 240) for GALAXI 1, 2, and 3	**Long-Term Extension (Week 48 to Week ~~144~~240) for GALAXI 1, 2, and 3** Participants will continue on their assigned guselkumab maintenance dose during the LTE of GALAXI 1, GALAXI 2, and GALAXI 3. Participants who experience inadequate response between Week 52 through Week 80 while on the lower of the 2 maintenance dose regimens being evaluated in the applicable ~~respective~~ study will be eligible for a single dose adjustment and will receive the higher maintenance dose until the end of the LTE to assess if they can regain clinical response.	
6.5.1. Concomitant Medications	[Subhead 3] **During treatment phase of LTE (ie, Week 48 through Week ~~144~~240):**	
6.7. Intervention After the End of the Study	[Paragraph 1] This protocol is designed to provide participants with up to approximately ~~3~~5 years of treatment (ie, 48-week treatment under the Phase 2 or Phase 3 studies plus approximately ~~2~~4 additional years of treatment in the LTE).	
8. Study Assessments and Procedures	[Blood Sample Collection subsection, 2nd paragraph] The maximum total blood volume to be collected from each participant in each study (GALAXI 1, GALAXI 2,	

Section Number and Name	Description of Change	Brief Rationale
	or GALAXI 3) will be approximately 500~~400~~ mL over approximately ~~156~~252 weeks (Table 8).	
8. Study Assessments and Procedures: Table 8	[Row 5 added] Week 148 through Week 240 94 [Row 7, Approximate Total Volume of Blood (mL) column] **500~~400~~**	
8.1. Efficacy Assessments	• Endoscopic assessments of the intestinal mucosa based on the presence and absence of mucosal ulcerations and the SES-CD, and histologic assessments based on the Global Histology Activity (GHAS), Robarts histopathology index (RHI), and Geboes scores [Endoscopic assessments paragraph] A video ileocolonoscopic examination will be performed at screening, Week 12, Week 48, ~~and~~ Week 96, Week 144, Week 192, and Week 240. An optional substudy involving a Week 4 evaluation will be performed in consenting participants in addition to the above-specified evaluations. (See Biopsy Manual for more information.) [Histologic assessments paragraph] Biopsy samples will be collected at screening, Week 12, Week 48, ~~and~~ Week 96, Week 144, Week 192, and Week 240 from each of 3 predefined anatomic locations… [Sentence added to end of paragraph on histologic assessments:] …The GHAS will be used to evaluate histologic improvements and healing.[5] Additional histologic assessments (including RHI and Geboes scores) will also be implemented. Analyses will be specified in the SAP.	
10.13. Appendix 13: CCI [redacted]	[Table 12 title revised:] SoA – CCI [redacted]	
Information regarding the impact of COVID-19 on clinical studies updated/added.		
5.2. Exclusion Criteria	[Criterion 34 added:] **Infections or predisposition to infections:** 34. Coronavirus Disease 2019 (COVID-19) infection During the 6 weeks prior to baseline, have had ANY of (a) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection • Exception: may be included with a documented negative result for a validated SARS-CoV-2 test (i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea) AND	To incorporate COVID-19-related guidance into the protocol.

Section Number and Name	Description of Change	Brief Rationale
	(ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit Note on the COVID-related exclusion: • The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care. Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.	
5.3. Lifestyle Considerations	[Lifestyle Consideration 1 modified:] 1.1. Refer to Section 6.5, Concomitant Therapy, for details regarding prohibited and restricted therapy during the study. It is recommended that participants are up-to-date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. For study participants who received locally approved (including emergency-use-authorized) COVID-19 vaccine(s) recently prior to study entry, follow applicable local vaccine labeling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.5.3 Vaccinations [Including COVID-19]).	
6.1. Study Interventions Administered	Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.14.	
6.5. Concomitant Therapy	Prestudy therapies administered up to 30 days before the first administration of study intervention must be recorded on the eCRF. Any COVID 19 vaccines administered, regardless of timing, must be recorded on the eCRF. Concomitant therapies must be recorded throughout the study, from signing of the informed consent to the last study visit.	
6.5.3. Vaccinations (Including COVID-19)	When considering use of locally approved (including emergency-use-authorized) COVID-19 vaccines in study participants, consider protocol lifestyle considerations (Section 5.3) and follow applicable local vaccine labeling, guidelines, and standards of care for participants receiving immune-targeted therapy. For study participants receiving a locally approved (including emergency-use-authorized) COVID-19 vaccine, in order to help identify acute reactions potentially related to the COVID-19 vaccine, it is recommended that, where possible, vaccine and study intervention be administered on different days, separated by as large an interval as is practical within the protocol.	

Section Number and Name	Description of Change	Brief Rationale
10.14. Appendix 14: Guidance on Study Conduct During the COVID-19 Pandemic	The previously standalone CNTO1959CRD3001 COVID-19 Appendix has been added to the protocol as Appendix 10.14, and subsequent appendices have been renumbered accordingly.	
Other Revisions in Protocol Amendment 4:		
Schedule of Activities (SoA); Table 2	[Note edited in the Collect and review participant diary row] CDAI: The most recent hematocrit value obtained during the screening window will be used to calculate CDAI at Week 0. For all other visits, the most recent hematocrit value obtained will be used to calculate the CDAI.	To clarify which hematocrit value will be used to calculate the Crohn's Disease Activity Index (CDAI)
4.1.3. Long-Term Extension for GALAXI 1, 2, and 3	[Paragraph 8] CCI [redacted]	CCI [redacted]
5.1. Inclusion Criteria	[Criterion 5d:] 5.1. Prior or current medication for Crohn's disease must… d. Has previously demonstrated lack of initial response (ie, primary nonresponders), responded initially but then lost response with continued therapy (ie, secondary nonresponders), or were intolerant to 1 or more biologic agents ~~at a~~with at least the minimum dose approved for the treatment of Crohn's disease (ie, infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars for these agents, see Appendix 3 [Section 10.3]). [Note, 1st sentence] Note: Participants meeting criteria 5a- ~~c~~d may also be naïve to biologic therapy (ie, a TNF antagonist or vedolizumab or ustekinumab) or may have been exposed to these biologic therapies but have not demonstrated inadequate response or intolerance.	To clarify that intolerance to 1 or more biologic agents must be demonstrated with at least the minimum dose approved for the treatment of Crohn's disease. Also criterion 5d is for participants who have failed a biologic therapy and therefore the note (for participants naïve to biologics) does not apply.
5.2 Exclusion Criteria	[Criterion 6:] 6.2. Has received any of the following prescribed medications or therapies within the specified period: d. Biologic agents: 1) Anti-TNF therapy…. 2) Vedolizumab received within ~~16~~12 weeks of baseline	To align the washout period for vedolizumab with updated recommendations.
	[Criterion 16:] 16.2. Participants who are seropositive for antibodies to hepatitis C virus (HCV), unless they satisfy one of the following conditions:	The duration of time required for being negative for HCV RNA was changed to align with guidelines (references

Section Number and Name	Description of Change	Brief Rationale
	a. Have a history of successful treatment (defined as being negative for HCV RNA at least ~~6 months~~ 12 weeks after completing antiviral treatment) and have a negative HCV RNA test result at screening, OR b. While seropositive have a negative HCV RNA test result at least ~~6 months~~ 12 weeks prior to screening and a negative HCV RNA test result at screening.	below) regarding HCV retesting in treated and untreated patients. • EASL Clinical Practice Guidelines: Management of hepatitis C virus infection Journal of Hepatology 2014 vol. 60 j 392–420 • Burgess, Sarah V et al. Concordance of sustained virologic response at weeks 4, 12 and 24 post-treatment of hepatitis C in the era of new oral direct-acting antivirals: A concise review. Annals of hepatology vol. 15,2 (2016): 154-9. doi:10.5604/16652681.1193693 • The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America Present HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C Last Updated: January 21, 2021 www.hcvguidelines.org
5.3. Lifestyle Considerations	[Lifestyle Consideration 5:] 5.1. Must agree not to receive a BCG vaccination during the study and for 1~~2~~6 weeks~~months~~ after receiving the last dose of study intervention.	To use ustekinumab half-life to determine the washout period.
8.2.11. Clinical Safety Laboratory Assessments	[Abnormal liver function tests paragraph, final sentence added.] See Appendix 9 (Section 10.9; Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants With No Underlying Liver Disease) for additional information on monitoring and assessment of abnormal liver function tests. Also refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.	Reference to Section 8.3.1. added for clarification.
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.~~	Administrative additions made for SAE monitoring.

Section Number and Name	Description of Change	Brief Rationale
	Serious Adverse Events [Two paragraphs added] …Serious adverse events, including those spontaneously reported to the investigator within 16 weeks after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. Any possible Hy's law case (AST or ALT >3xULN together with bilirubin >2xULN or INR >1.5) is considered an important medical event and must be reported to the sponsor in an expedited manner using the Serious Adverse Event Form, even before all other possible causes of liver injury have been excluded (INR criterion is not applicable to participants receiving anticoagulants).	
9.3. Populations for Analyses	For purposes of analysis, the following populations are defined (Table 11; the same definitions apply to all 3 studies. Note: Additional analysis populations will be defined in the SAP and could vary between the Phase 2 and Phase 3 studies): [Table 11, row 3, Safety Analysis Set description]: All ~~randomized~~ participants who are randomized and received at least 1 dose of study intervention (including a partial dose).	To provide more clarity on the population definitions.
10.3. Appendix 3: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNF Antagonist Therapies (Infliximab, Adalimumab, or Certolizumab Pegol) or Vedolizumab	[Edit made to criterion 1.a:] a. Have received, at minimum, a locally approved induction dose~~s~~, for example:~~of:~~	To align with edit to Inclusion Criterion #5.1 which clarifies that intolerance to 1 or more biologic agents must be demonstrated with at least the minimum dose approved for the treatment of Crohn's disease.
	[Edit made to criterion 2.b:] b. Have received, at ~~least~~ minimum, 2 doses of a locally approved maintenance dose~~s~~, for example:~~of:~~	
	[Edit made to criterion 1.a.4:] 4) Vedolizumab (~~3 or~~at least 2 and up to 4 doses of [redacted]	To update induction and maintenance dosing of vedolizumab to include subcutaneous dosing approved in the European Union.
	[Edit made to criterion 2.b.4:] Vedolizumab (at a dose of [redacted] or [redacted]	
10.9. Appendix 9: Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants With No Underlying Liver Disease	[Added to the start of the appendix:] The ALT criteria in this algorithm are also applicable to AST.	Administrative addition made to the liver function tests.

Section Number and Name	Description of Change	Brief Rationale
10.12. Appendix 12: Anticipated Events	[Sentence added to the end of the Reporting of Anticipated Events subsection] If an interim analysis leads to an unblinded, aggregate review of safety data by the study team (either for all studies or specific studies within this protocol), the sponsor may terminate the ARC review of the prespecified anticipated events outlined above, as applicable for any newly unblinded studies.	To clarify that the sponsor may terminate the review of prespecified anticipated events for a specific study once that study is unblinded.
10.13. Appendix 13: CCI	CCI [redacted]	[redacted]
Name of toxin updated to reflect new nomenclature.		
Schedule of Activities (SoA); Table 1	[Note in the "Stool studies to evaluate for enteric pathogens" row was edited to update the toxin name.] Stool studies for enteric pathogens may be performed at screening at either the central or a local laboratory and must include a stool culture and *Clostridioides difficile* (formerly known as *Clostridium difficile*) toxin assay.	The name of the toxin was clarified to reflect new nomenclature.
5.2. Exclusion Criteria	[Criterion 5:] 5.1. Has stool culture or other examination positive for an enteric pathogen, including *Clostridioides difficile* (formerly known as *Clostridium difficile*) toxin, in the previous 4 months, unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen.	
Edits were made to the numbering of inclusion/exclusion criteria to clearly indicate which criteria were modified in which previous protocol amendment.		

Section Number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	[Criterion 4:] 4.1. Criterion modified per Amendment 2. 4.2. Criterion modified per Amendment 3.	These edits were made to provide clarity for the eCRFs in the Phase 3 studies; no changes were made to actual inclusion and exclusion criteria.
	[Criterion 8 (Tuberculosis):] 8. Criterion modified per Amendment 3. 8.1. Are considered eligible according to the following tuberculosis (TB) screening criteria:… d. Criterion modified per Amendment 3. 8.d.1 Within 8 weeks prior to the first administration of study intervention,… e. Criterion modified per Amendment 3. 8.e.1. Have a chest radiograph…	
	[Criterion 13 (General):] 13. Criterion modified per Amendment 1. 13.1. Criterion modified per Amendment 2. 13.2. Be willing and able to adhere…	
5.2. Exclusion Criteria	[Criterion 3:] 3. Criterion modified per Amendment 3. 3.1. Has had any kind of bowel resection…	
	[Criterion 6 (Concomitant or previous medical therapies received):] 6. Criterion modified per Amendment 3. 6.1. Criterion modified per Amendment 4.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (20 October 2020)

Overall Rationale for the Amendment:

CCI [redacted]

Section Number, Name	Description of Change	Brief Rationale
CCI [redacted]		
10.11.1, Adverse Event Definitions and Classifications	Because of the addition of the CCI devices in the substudy, the following text was added: Paragraph 4 (under Adverse Event subhead): For combination products with a device constituent, adverse events include those resulting	

Section Number, Name	Description of Change	Brief Rationale
	from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any adverse event resulting from use error or from intentional misuse of the investigational device. Paragraph 3 (under Serious Adverse Event subhead): For combination products with a device constituent, serious adverse events include adverse device effects that resulted in any of the consequences characteristic of a serious adverse event. An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3. Benefit-Risk Assessment).	
10.11.6, Product Quality Complaint Handling	Text was revised/added: 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~~ or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system. 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. This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the study intervention or the comparator. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device	

Section Number, Name	Description of Change	Brief Rationale
	deficiencies include malfunctions, use errors, and inadequate labeling.	
For the Phase 3 studies, endoscopic response at Week 12 has been added as a co-primary endpoint and was therefore deleted as a major secondary endpoint; in addition, endoscopic remission at Week 12 and endoscopic remission at Week 48 were added as major secondary endpoints and therefore deleted from the list of other endpoints:		
CCI	CCI	CCI
	CCI	

Section Number, Name	Description of Change	Brief Rationale
	CCI [redacted]	
4.1.2.3, Endpoints and Evaluations	Both GALAXI 2 and GALAXI 3 have the same co-primary and major secondary endpoints. Within each study, the co-primary endpoints are clinical remission at Week 12 and endoscopic response at Week 12, which are based on comparisons between the combined guselkumab induction dose group and the placebo group. The major secondary endpoints of clinical remission at Week 48, endoscopic response at Week 48, durable clinical remission at Week 48, corticosteroid-free clinical remission at Week 48, PRO-2 remission at Week 48, ~~endoscopic response at Week 48,~~ and endoscopic remission at Week 48 are based on comparisons between each guselkumab group and ustekinumab. The major secondary endpoints of PRO-2 remission at Week 12~~, endoscopic response at Week 12,~~ endoscopic remission at Week 12, and fatigue response at Week 12 are based on comparisons between the combined guselkumab induction dose group and the placebo group. Other efficacy endpoints are described in Section 9.4.1.2.	
Synopsis	The additional co-primary endpoint was added to the subsection on Other Planned Analyses: The consistency of efficacy for the change from baseline in the CDAI score at Week 12 (GALAXI 1) and clinical remission at Week 12 and endoscopic response at Week 12 (GALAXI 2 and 3) will be examined in subgroups for each study based on demographic and baseline disease characteristics and baseline use and history of Crohn's disease medications (including BIO-Failure status).	
Synopsis	The primary hypothesis for both GALAXI 2 and GALAXI 3 is that guselkumab is superior to placebo in achieving clinical remission at Week 12 and endoscopic response at Week 12 in participants with moderately to severely active Crohn's disease.	
9.1.2, Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)	The primary hypothesis is that guselkumab treatment is superior to placebo as assessed by the proportion of participants achieving clinical remission at Week 12 and the proportion of participants with endoscopic response at Week 12. For the major secondary hypotheses for comparison with ustekinumab, while the ultimate goal is to demonstrate that the efficacy of guselkumab is superior to ustekinumab at Week 48, an initial test for non-inferiority is included because the overall profile of guselkumab may be	

Section Number, Name	Description of Change	Brief Rationale
	favorable compared with ustekinumab (in terms of overall efficacy and safety), even if final results only indicate the relative efficacy is non-inferior to ustekinumab for a certain endpoint.	
9.2.1, Assumptions	(Clinical remission at Week 12) … Taking into account a mixed BIO-Failure/CON-Failure population, assumptions for the overall randomized population at Week 12 were based on the following: • Based on the ratio of a minimum of 25% and up to 50% of participants in the CON-Failure patient population, the proportions of participants in clinical remission at Week 12 is expected to be approximately 12% to 15% for placebo, approximately 25% to 30% for guselkumab CCI and approximately 35% to 40% for both guselkumab CCI and guselkumab CCI **Endoscopic response at Week 12** Assumptions for endoscopic response at Week 12 were based on the following: • In the mirikizumab Phase 2 study for Crohn's disease, the proportions of participants in endoscopic response (based on SES-CD) at Week 12 were 10.9%, 25.8%, 37.5%, and 43.8% for placebo, mirikizumab CCI mirikizumab CCI , and mirikizumab CCI respectively, for a treatment difference of at least 15%. • In the risankizumab Phase 2 study for Crohn's disease, the proportions of participants in endoscopic response (based on CDEIS) at Week 12 were 13%, 27%, and 37% for placebo, risankizumab CCI , and risankizumab CCI , respectively, for a treatment different of at least 14%. Based on these data, the endoscopic response rates are assumed to be 13% for placebo and 28% for guselkumab CCI	
Synopsis	A new 3rd paragraph was added to the subsection on the sample size calculations for the Phase 3 studies: For the co-primary endpoint of endoscopic response at Week 12, assuming an endoscopic response rate of approximately 10% to 13% for placebo and a minimum of a 15% difference between guselkumab and placebo, 440 participants in the combined guselkumab induction dose group and 110 participants in the placebo group, respectively, will provide approximately 94%	

Section Number, Name	Description of Change	Brief Rationale
	power for endoscopic response at Week 12 at the α=0.05 (2-sided) level.	
9.2.2.2, Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)	Paragraph 3 was revised to add the co-primary endpoint: Therefore, the sample sizes for each of these studies were determined by the power to detect a significant difference in clinical remission at Week 12 and endoscopic response at Week 12 (co-primary endpoints) between the combined guselkumab induction dose group and placebo.	
	Paragraph 4 was revised and new fifth paragraph was added for co-primary endpoints: **For the co-primary endpoint of clinical remission at Week 12:** In each of the Phase 3 studies, assuming a clinical remission rate of approximately 12% to 15% for placebo and a minimum of a 20% difference between guselkumab and placebo, 440 participants in the combined guselkumab induction dose group and 110 participants in the placebo group, respectively, will provide greater than 99% power for clinical remission at Week 12 at an overall Type 1 error rate controlled at a 0.05 (2-sided) alpha level (Table 10). ~~If 2 guselkumab induction doses are chosen, based on the same assumptions 220 participants in each guselkumab induction dose group and 110 participants in the placebo group, respectively, will provide power ≥98%.~~ For the co-primary endpoint of endoscopic response at Week 12: In each of the Phase 3 studies, assuming an endoscopic response rate of approximately 10% to 13% for placebo and a minimum of a 15% difference between guselkumab and placebo, 440 participants in the combined guselkumab induction dose group and 110 participants in the placebo group, respectively, will provide approximately 94% power for endoscopic response at Week 12 at an overall Type 1 error rate controlled at a 0.05 (2-sided) alpha level (Table 10). ~~If 2 guselkumab induction doses are chosen, based on the same assumptions 220 participants in each guselkumab induction dose group and 110 participants in the placebo group, respectively, will provide approximately 89% power.~~	To add text for the co-primary endpoints, and to delete (in Section 9.2.2.2) hypothetical statements that were part of the protocol before the Phase 3 dose groups were chosen (these statements are no longer applicable because only 1 induction dose was chosen for the Phase 3 studies).
Table 10	Table 10 was revised to add power calculations for the co-primary endpoint of endoscopic response at Week 12 and for an additional major secondary endpoint. The table title was also updated.	
9.4.3.2, Primary Endpoint Analysis	Text was revised to incorporate the second co-primary endpoint: The co-primary endpoints in each Phase 3 study are clinical remission at Week 12 and endoscopic	

Section Number, Name	Description of Change	Brief Rationale
	response at Week 12. Clinical remission is defined as a CDAI score <150 points. Endoscopic response is defined as at least 50% improvement from baseline in SES-CD score or SES-CD score ≤2. Participants who have any of the following events before the Week 12 visit will be considered as treatment failures, and will not be considered to have achieved clinical remission at Week 12 or endoscopic response at Week 12: • Specified changes in concomitant Crohn's disease medications (to be detailed in the Phase 3 SAP) • A Crohn's disease-related surgery (except drainage of an abscess or seton placement) • Discontinuation of study intervention due to lack of efficacy or due to an AE of worsening Crohn's disease The CDAI score will be calculated for a visit if at least 4 of the 8 components are available at that visit. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last available components. If the CDAI score cannot be calculated (ie, < 4 components available) at a visit, the CDAI score will be considered missing for that visit. Participants who do not return for evaluation or have a missing CDAI score at Week 12 will not be considered to have achieved clinical remission at Week 12. The total SES-CD score at a visit will be calculated based on all segments scored at the visit. If the total SES-CD score cannot be calculated (ie, no segment is scored) at a visit, the total SES-CD score will be considered missing. The details for handling missing segments in the SES-CD score will be described in the Phase 3 SAP. Participants who do not return for evaluation or who have a missing SES-CD score at Week 12 will not be considered to have achieved endoscopic response at Week 12. Treatment failure rules will overrule the missing data rules. For testing of the co-primary endpoints, the efficacy of the induction dose of guselkumab versus placebo will be compared. As such, within each study, the two guselkumab groups that are randomized to receive identical guselkumab induction treatment through Week 12 will be combined for ~~this~~ these comparisons. A CMH chi-square test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) will be used. Each study will be considered positive if the combined guselkumab induction dose group (ie,	

Section Number, Name	Description of Change	Brief Rationale
	Treatment Group 1 and Treatment Group 2 that received the same guselkumab induction treatment through Week 8) for that study is significantly different from the placebo group for both of the co-primary endpoints. To examine the robustness of the co-primary endpoint analyses, sensitivity analyses of the co-primary endpoints will be conducted using different missing data approaches; these analyses will be described in the Phase 3 SAP. Subgroup analyses of the co-primary endpoints will be performed based on demographic and baseline disease characteristics and baseline use and history of Crohn's disease medications (including BIO-Failure status).	
Synopsis; 9.4.3.3, Major Secondary Endpoints	For the Phase 3 studies, endoscopic response at Week 12 was deleted, and endoscopic remission at Week 12 and endoscopic remission at Week 48 were added, as major secondary endpoints: • Clinical remission at Week 48 • Endoscopic response at Week 48 • Durable clinical remission at Week 48 (defined as CDAI score <150 for ≥80% of all visits between Week 12 and Week 48 [ie, at least 8 of 10 visits], which must include Week 48) • Corticosteroid-free clinical remission at Week 48 (defined as CDAI score <150 at Week 48 and not receiving corticosteroid at Week 48) • PRO-2 remission at Week 12 (defined as an AP mean daily score at or below 1 [AP≤1] AND an SF mean daily score at or below 3 [~~, ie, AP≤1 and~~ SF≤3], and no worsening of AP or SF from baseline) • PRO-2 remission at Week 48 • ~~Endoscopic response at Week 12 (defined as at least 50% improvement from baseline in SES-CD score or SES-CD score ≤2)~~ • ~~Endoscopic response at Week 48~~ • Endoscopic remission (defined as SES-CD score ≤2) at Week 12 • Endoscopic remission at Week 48 • Fatigue response at Week 12 (based on the PROMIS Fatigue Short Form 7a; to be defined in the SAP) Participants who meet 1 or more treatment failure rules before a visit will be considered not to have achieved any of the major secondary endpoints ~~be in clinical remission or fatigue response~~ from that visit onward. …	
	In Section 9.4.3.3, the following paragraph was also deleted:	To align the treatment failure rules among different efficacy endpoints.

Section Number, Name	Description of Change	Brief Rationale
	~~For endoscopic endpoints, the same treatment failure rules apply, except for a modification of the "certain changes in concomitant Crohn's disease medications" rule, which will only consider prohibited medications as treatment failure. Details will be provided in the Phase 3 SAP.~~	
	In Section 9.4.3.3, the following paragraphs were also edited: Within each study, the major secondary endpoints of clinical remission at Week 12 as measured by PRO-2, fatigue response at Week 12, and endoscopic remission ~~response~~ at Week 12 will be compared between the combined guselkumab induction dose group and the placebo group using the CMH chi-square test (2 sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No). The major secondary endpoints related to clinical remission at Week 48 (either based on CDAI or PRO-2), endoscopic response at Week 48, and endoscopic remission at Week 48 will be compared between each guselkumab dose group and the ustekinumab group using the CMH chi-square test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD (≤12 or >12), BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No).	
Synopsis; 3.2.1, Objectives	The first primary objective was edited to include endoscopic efficacy and the first secondary objective was deleted: **Primary Objectives** • To evaluate the clinical and endoscopic efficacy of guselkumab in participants with Crohn's disease • To evaluate the safety of guselkumab **Secondary Objectives** • ~~To evaluate the efficacy of guselkumab on endoscopic improvement~~ • To evaluate the impact of guselkumab on HRQOL • To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin	
Synopsis; 3.2.3, Hypothesis	Endoscopic response at Week 12 was added to the primary hypothesis: The primary hypothesis for both GALAXI 2 and GALAXI 3 is that guselkumab is superior to placebo in achieving clinical remission at Week 12 and endoscopic response at Week 12 in participants with moderately to severely active Crohn's disease.	

Section Number, Name	Description of Change	Brief Rationale
Synopsis; 3.1.2, Endpoints; 3.2.2, Endpoints; 9.4.1.1, Phase 2 Dose-Ranging Study (GALAXI 1); 9.4.1.2, Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3); 9.4.2.3, Major Secondary Endpoint Analysis; 9.4.3.3, Major Secondary Endpoint Analysis	The definition of PRO-2 remission was clarified: • PRO-2 remission at Week 12 (defined as an AP mean daily score at or below 1 [AP≤1] AND an SF mean daily score at or below 3 [~~ie, AP≤1 and~~ SF≤3], and no worsening of AP or SF from baseline).	Clarification
For the Phase 3 studies, SES-CD inclusion criteria were revised as follows:		
CCI [redacted]	[redacted]	CCI [redacted]
5.1, Inclusion Criterion	4. Criterion modified per Amendment 3: 4.2 Have endoscopic evidence of active ileocolonic Crohn's disease as assessed by central endoscopy reading at the screening endoscopy (Schedule of Activities, Table 4), defined as a SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease) ~~≥3~~,	

Section Number, Name	Description of Change	Brief Rationale
	based on the presence of ulceration in ~~any~~ at least 1 of the 5 ileocolonic segments, resulting in the following specified ulceration component scores: a. a minimum score of 1 for the component of "size of ulcers" AND b. a minimum score of 1 for the component of "ulcerated surface". Of note, before the implementation of Amendment 3, where the minimum SES-CD score was ≥3 based on the presence of ulceration, within each of the studies, a maximum of 10% of the total enrolled population ~~will be~~ could include participants who had ~~have~~ baseline scores for SES-CD <4 (ie, for participants with isolated ileal disease), or SES-CD <7 (ie, for participants with colonic or ileocolonic disease).	
4.1.2.1, Overview of Phase 3 Design	The second-last sentence in the following paragraph was deleted: GALAXI 2 and GALAXI 3 are identical studies from a study design perspective. The purpose of conducting two replicate studies is to achieve independent confirmation of clinical efficacy in two independent samples of patients, which is required by some health authorities. At Week 0, a target of 1,540 participants will be randomly allocated to GALAXI 2 (n=770) or GALAXI 3 (n=770), using a permuted block randomization with baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), prior BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) as the stratification variables. Within each stratum, participants in each study will be randomized in a 2:2:2:1 ratio to receive 1 of 2 dose regimens of guselkumab, ustekinumab, or placebo, respectively. Within each study (GALAXI 2 and GALAXI 3), a minimum of 25% and a maximum of 50% of the total enrolled population will be participants who are CON-Failures. ~~In addition, a maximum of 10% of the total enrolled population will have baseline scores for SES-CD <4 (ie, for participants with isolated ileal disease) or SES-CD <7 (ie, for participants with colonic or ileocolonic disease).~~ Allocation to treatment groups will be performed using a central randomization center by means of an IWRS.	This sentence is no longer necessary because of the change in SES-CD criteria.
9.4.1.1, Phase 2 Dose-Ranging Study (GALAXI 1) 9.4.1.2, Phase 3 Dose-Confirming	The following bullet was moved from the list of Other Endpoints (*Short-Term Efficacy*) for the Phase 3 studies to equivalent list for the Phase 2 study: • Change in SES-CD score from baseline at Week 12, endoscopic response at Week 12,	This analysis is no longer applicable for the Phase 3 studies because of the change to SES-CD enrollment criteria for the Phase 3 studies (but is still valid for the Phase 2 study).

Section Number, Name	Description of Change	Brief Rationale
Studies (GALAXI 2 and GALAXI 3)	endoscopic remission at Week 12, and endoscopic healing at Week 12, among participants with baseline SES-CD ≥4 (ie, for participants with isolated ileal disease) or SES-CD ≥6 (ie, for participants with colonic or ileocolonic disease).	
Other Revisions in Protocol Amendment 3:		
Synopsis; 9.4.2.2, Primary Endpoint Analysis	The MMRM definition was corrected: The change from baseline in CDAI will be analyzed using a Mixed Model for Repeated Measures ~~Mixed Effect Repeated Measures Model~~ (MMRM) approach.	MMRM was incorrectly spelled out in Amendment 2.
1.3, Schedule of Activities (Table 1, Table 2, Table 3, Table 5); 5.1, Inclusion Criterion 8d; 5.4, Screen Failures/Rescreening; 7.1, Discontinuation of Study Intervention, item 6; 8, Study Assessments and Procedures: Screening Phase; 8.2.6, Tuberculosis Evaluation(s)	The T-SPOT® test was added for sites in Japan, where local regulations permit, for the diagnosis of tuberculosis.	T-SPOT has been approved globally and is more convenient and more widely used as an assay test for TB assessment in Japan than the QuantiFERON-TB test.

Section Number, Name	Description of Change	Brief Rationale
1.3, Table 1	The Note for Chest radiograph item was edited: Chest radiograph (posterior-anterior and lateral views) must ~~may~~ be obtained within 12 weeks before the Week 0 visit.	To clarify that the time frame for obtaining this screening activity is required, not optional.
	The Note for Stool studies item was edited: Stool studies for enteric pathogens may be performed at screening at either the central or a local laboratory and must include a stool culture and *Clostridium difficile* toxin assay. Although stool studies may be processed at either the central or local laboratory, the central laboratory is preferred when available. Stool studies must have been performed within 4 months before Week 0. Additional testing, such as ova and parasites or *Escherichia coli* O157:H7 assessment, may be performed at the investigator's clinical discretion.	To clarify that central laboratory processing is preferred and to confirm the timing of screening stool studies.
1.3, Table 2	"Review medical history" row added to the SoA for Week 0 to Week 48.	Added as a double-check at Week 0 before participant randomization.
	Note added to the Randomization row: Randomization should be performed approximately 5 weeks after screening/informed consent signing.	Added as a reminder from the Screening SoA (Table 1).
1.3, Table 3	Clarification was added to Footnote a: a. Week 48 study procedures outlined in the SoA for Week 0 to Week 48 (Table 2) must be performed prior to study intervention administration. In participants who are considered appropriate for self-administration at home after being trained, at-home administration can begin after the Week 48 visit according to regional/local regulations and instructions.	Clarification
1.3, Table 4	A Note was added to the item about participant discontinuation after Week 12 but up to Week 48: Discontinuation after Week 12 (visit and ileocolonoscopy) and before Week 44: A video ileocolonoscopy (with biopsy samples) is optional (or can be performed as part of SID visit). Discontinuation at Week 44 or Week 48: A video ileocolonoscopy (with biopsy samples) is required (or can be performed as part of SID visit).	To clarify (depending on the time point) when video ileocolonoscopy is required for participants who discontinue study intervention after Week 12 but before Week 48.
1.3, Table 5	Two rows were added under the Pharmacodynamic and Biomarkers subsection of Table 5: Ileocolonoscopy biopsy sample collections for histology	To clarify that ileocolonoscopy biopsy sample collections are required as part of a Study Intervention Discontinuation (SID) visit.

Section Number, Name	Description of Change	Brief Rationale
	Ileocolonoscopy biopsy sample collections for exploratory RNA and protein assessments (where local regulations permit)	
4.1.2.2, Figure 3	A note was added to Figure 3: Note: This schematic only illustrates the dosing for the treatment groups. It does not provide a complete illustration of all blinding (placebo) administrations.	This note was added as clarification and parallels the note in the Phase 2 schematic (Figure 2).
5.1, Inclusion Criteria	Inclusion Criterion 8e: e.1 Have a chest radiograph (both posterior-anterior and lateral views, or per local/country regulations where applicable), taken ≤12 weeks before the first administration of study intervention and read by a qualified radiologist or qualified pulmonologist according to local clinical practice, with no evidence of current, active TB or old, inactive TB. A chest CT scan is also acceptable if obtained instead of a chest radiograph outside of the protocol.	Clarification
5.2, Exclusion Criteria	Exclusion Criterion 3: "Requiring general anesthesia" was removed as an example of other major surgery: 3. Has had any kind of bowel resection within 6 months, or any other intra-abdominal or other major surgery ~~(eg, requiring general anesthesia)~~ within 12 weeks, before baseline.	The example was removed to prevent confusion because general anesthesia may be administered for less invasive surgeries that would not be exclusionary.
	Exclusion Criterion 6.d.4: Clarification was added for other immunomodulatory biologic agents: 6. Has received any of the following prescribed medications or therapies within the specified period: …d. Biologic agents: …4) Other immunomodulatory biologic agents, <u>including approved and investigational biologic agents,</u> received within 12 weeks of baseline or within 5 half-lives of baseline, whichever is longer.	Clarification
	Exclusion Criterion 6.e: A clarification was added to the EC regarding investigational interventions: e. Any investigational intervention received within 4 weeks of baseline or within 5 half-lives of baseline, whichever is longer. <u>(Refer to Exclusion Criterion 6.d.4 for investigational biologic agents.)</u>	Clarification
	Exclusion Criterion 6.g:	Clarification

Section Number, Name	Description of Change	Brief Rationale
	"Total" was added to the EC: g. Treatment with apheresis (eg, Adacolumn apheresis) or total parenteral nutrition for Crohn's disease within 3 weeks of baseline.	
6.1, Study Interventions Administered	Text in this subsection was edited to clarify active and placebo administrations at various time points: In both the Phase 2 and Phase 3 portions of the protocol: • All participants will receive CC [redacted] at Week 0 (~~either~~ 1 active + 1 ~~or~~ placebo OR 2 placebo) and CC [redacted] at Weeks 4, 8, and 12 (either active or placebo). … At Week 4, only guselkumab/placebo in dextrose C [redacted] infusion is administered (including the flush with dextrose). At Week~~s~~ 8~~ and 12~~, the guselkumab/placebo in dextrose C [redacted] infusion (including the flush with dextrose) should be administered first, followed by SC injection~~(s)~~ with ~~active (guselkumab/placebo or~~ ustekinumab/placebo~~) or placebo~~ investigational product (IP). At Week 12, the ustekinumab/placebo in saline C [redacted] infusion (including the flush with saline) should be administered first, followed by C [redacted] injection with guselkumab/placebo IP.	Clarification
6.5.1, Concomitant Medications	A phrase was deleted from the following subsection: **Week 12 and through Week 48** From Week 12 through Week 48 of each study, participants may transiently use (ie, for <4 weeks) increased doses of corticosteroids for reasons other than ~~loss of response to~~ treatment for Crohn's disease (eg, stress doses of corticosteroids for surgery, asthma, adrenocortical insufficiency).	Clarification

Section Number, Name	Description of Change	Brief Rationale
CCI [redacted]	[redacted]	CCI [redacted]
9.2.1, Assumptions	A sentence was deleted from the 2nd bullet under "Assumptions for the CON-Failure population at Week 12…" • ~~No data are currently available for guselkumab or other anti IL-23 agents in the CON-Failure population.~~ Based on the data from CNTO1275CRD3002 and historical biologic studies in similar populations, it is reasonable to assume a greater treatment effect difference between active and placebo in the CON-Failure population compared with that observed in a BIO-Failure population. In addition, the dose-response trend in the CON-Failure population is assumed to be similar to that observed in the BIO-Failure population.	This sentence was deleted because data for IL-23 agents have become available since the protocol was originally written.
CCI [redacted]	[redacted]	[redacted]
Throughout the protocol	"Subject" was changed to "participant" where applicable.	For consistency with the rest of protocol.
Throughout the protocol	Minor grammatical, formatting, and/or spelling changes were made.	Minor errors were noted.

Amendment 2: 13 November 2019

Overall Rationale for the Amendment: To specify the guselkumab induction and maintenance doses to be administered in the Phase 3 studies (GALAXI 2 and GALAXI 3) and to clarify information related to management of liver test abnormalities.

Section number and Name	Description of Change	Brief Rationale
Synopsis: Intervention Groups and Duration: Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)	**Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)** ~~The Phase 3 guselkumab dose regimens will be selected based on the efficacy and safety of the induction dose range (ie, from CCI [redacted] evaluated in the Phase 2 study.~~ Based on the Phase 2 data, 2 guselkumab dose regimens (ie, C induction → C maintenance) were selected for confirmatory evaluation in Phase 3. Identical dose regimens are to be evaluated in both Phase 3 studies. ***Group 1: Guselkumab Regimen 1*** CCI [redacted] Participants will receive guselkumab CCI [redacted] from Week 0 through Week 8 (ie, total of 3 C doses). At Week 12, participants will continue treatment with guselkumab CCI [redacted] through Week 44. ***Group 2: Guselkumab Regimen 2*** CCI [redacted] Participants will receive guselkumab CCI [redacted] from Week 0 through Week 8 (ie, total of 3 C doses). At Week 16, participants will continue treatment with guselkumab CCI C [redacted] through Week 40.	The Phase 3 guselkumab dose regimens were added to the Synopsis.
4.1.2.2, Treatment Groups	The Phase 3 guselkumab dose regimens were selected based on the efficacy and safety of the induction dose range (ie, from CCI [redacted] evaluated in the Phase 2 study. Based on the Phase 2 data, 2 guselkumab dose regimens (ie, C induction → C maintenance) were selected for confirmatory evaluation in Phase 3 and will be evaluated in both Phase 3 studies. ~~See Section 4.3 for further details regarding the dose rationale.~~ … **Group 1: Guselkumab Regimen 1** CCI [redacted]	The Phase 3 guselkumab dose regimens were added to the text.

Section number and Name	Description of Change	Brief Rationale
	Participants will receive guselkumab CCI [redacted] from Week 0 through Week 8 (ie, total of 3 C doses). At Week 12, participants will continue treatment with guselkumab CCI [redacted] through Week 44. **Group 2: Guselkumab Regimen 2** CCI [redacted] Participants will receive guselkumab CCI [redacted] from Week 0 through Week 8 (ie, total of 3 C doses). At Week 16, participants will continue treatment with guselkumab CCI C [redacted] through Week 40.	
Figure 3	Figure 3 was revised to show all treatment groups and dose regimens to be evaluated in the Phase 3 studies.	The revised figure provides the dosing schemas for the treatment groups to be evaluated in the Phase 3 studies, ie, 2 guselkumab dose regimens, ustekinumab (active control), and placebo control.
4.3.1.2, Phase 3 Dose-Confirming Studies (GALAXI 2 and GALAXI 3)	Based on the Phase 2 data, 2 guselkumab dose regimens (ie, C induction → C maintenance) were selected for confirmatory evaluation in Phase 3. The goal was to select a single induction dose regimen from the induction dose range evaluated (ie, CCI [redacted] at Week 0, Week 4, and Week 8) in the Phase 2 dose-ranging study based on the totality of the efficacy, safety, and exposure-response data at the time of dose decision. The ~~choice~~ goal of selecting a single induction regimen to be evaluated in the Phase 3 dose-confirming studies was ~~is~~ based on the consideration that a sufficient amount of information ~~will~~ would be available to establish an optimal induction dose regimen. In this scenario, the selected induction dose regimen was to ~~will~~ be paired with 2 maintenance dose regimens selected from the range of exposures obtained from the guselkumab C dose regimens evaluated in Phase 2 (ie, between CCI [redacted] As described in Section 4.1.2, the goal of selecting a single induction dose regimen to be paired with 2 maintenance dose regimens was achieved. ~~It is also possible that the Phase 2 data may support the selection of more than one induction dose regimen for Phase 3 evaluation. In this case, each selected induction dose regimen will be paired with an appropriate maintenance dose regimen.~~	Text was updated to note that Phase 3 guselkumab dose regimens were selected. The third paragraph was deleted because, as planned, one dose regimen was selected for induction.

Section number and Name	Description of Change	Brief Rationale
6.1, Study Interventions Administered	Last paragraph: Detailed instructions on the preparation and administration of study intervention will be provided in the site Investigational Product Procedures Manual (IPPM). ~~Of note, instructions on the preparation and administration of study intervention in the Phase 3 portion of the protocol will be finalized and provided to investigative sites when the Phase 3 dose decision is made and implemented.~~	Text was deleted because the IPPM already includes instructions for the dose regimens in Phase 2 and Phase 3.
2.3.1, Benefit-Risk Assessment, Guselkumab	Fourth paragraph: … 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, as well as liver injury, based on an event of potential drug-induced liver injury (DILI) that occurred in a single participant at the highest Phase 2 induction dose administered.	Text was revised to indicate that information was added to the IB regarding the potential safety concern of liver injury.
7.1, Discontinuation of Study Intervention	Item 9 was revised: 6. The participant has severe ~~hepatic function~~ liver test abnormalities that are not transient and are not explained by other etiologies, as described in Section 8.2.1.1 and Appendix 9 (Section 10.9). Such abnormalities would include the following: • ALT or AST >8 x ULN • ALT or AST >5 x ULN for more than 2 weeks • ALT or AST >3 x ULN **and** (total bilirubin >2 x ULN **or** international normalized ratio [INR] >1.5) • ALT or AST >3 x ULN and symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%])	This item was revised to clarify the criteria for discontinuation of study intervention due to liver test abnormalities.
8.2.11, Clinical Safety Laboratory Assessments	• **Abnormal liver function tests:** If laboratory testing for a subject who is enrolled in the study and receiving study intervention reveals an increase of serum aminotransferases (ALT or AST) to >3 x ULN and an increase of bilirubin to >2 x ULN, study 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. Additional clinical and laboratory studies may be performed to evaluate the underlying	A sentence was added to clarify that additional testing may be requested, and the appendix number was corrected.

Section number and Name	Description of Change	Brief Rationale
	etiology of abnormal findings. See Appendix 9 (Section 10.9; Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants With No Underlying Liver Disease) for additional information on monitoring and assessment of abnormal liver function tests.	
10.9, Appendix 9	Updated Appendix.	This Appendix was updated with the most current version. The updated Appendix provides detailed guidance regarding additional tests and evaluations to be obtained in the setting of specific patterns of liver enzyme abnormalities.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 10 December 2018

Overall Rationale for the Amendment: The primary rationale for the amendment is to update the endoscopic inclusion criterion to more accurately define the contemporaneous Crohn's disease patient population based on the observed patient characteristics from this ongoing protocol and other protocols conducted by the sponsor. 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 and are indicated with an underline.

Section number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis, Overall Design; Section 4.1, Overall Design	Since data from more participants may be required to inform the dose decision, the sponsor may elect to continue enrollment and newly enrolled participants (ie, starting from participant #251) will be randomized into a Transition Cohort while the data from the Initial Dose Decision Cohort are being collected and analyzed.	Clarification of participant enrollment in the Phase 2 (GALAXI 1) study. The sponsor may elect to pause or to continue enrollment of participants into the transition cohort, depending on the sponsor's assessment of whether additional data are needed to inform the dose decision.
Section 1.1, Synopsis, Overall Design; Section 4.1, Overall Design	This is an operationally seamless protocol in countries where the local health authorities have approved a seamless transition. In the countries that have approved a seamless transition, there will be no break in enrollment between the Phase 2 and Phase 3 studies if enrollment continues into the Transition Cohort and a dose decision can be made before 500 patients are randomized. Transition from the Phase 2 portion to the Phase 3 portion of the protocol will occur once the dose decision for Phase 3 has been made and implemented. In countries where the local health authority requires additional regulatory approval prior to initiating the Phase 3 studies, enrollment will pause until approval is received. In all countries, all participants randomized after the dose decision has been implemented will be part of the Phase 3 studies.	Clarification to acknowledge that this protocol will be conducted based on the original operationally seamless design, in countries where this design is approved by the local health authority if enrollment continues into the Transition Cohort; and to acknowledge that in a number of countries, the local health authority requires a non-seamless transition and requires a separate approval prior to the initiation of the Phase 3 studies.

Section number and Name	Description of Change	Brief Rationale
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 1.3, Schedule of Activities, Table 1, Table 2, Table 3, Table 4b; Section 5.1, Inclusion Criteria; Section 7.1, Discontinuation of Study Intervention; Section 8, Study Assessments and Procedures; Section 8.2.6.1, Initial Tuberculosis Evaluation; Section 8.2.6.2, Ongoing Tuberculosis Evaluation	QuantiFERON-TB Gold test updated to QuantiFERON-TB test.	There may be region- or country-specific variability in the type of QuantiFERON-TB test used based on changes in the performance of the test by the central laboratory.
Section 1.3, Schedule of Activities, Table 1	The following sentence was added: During the initial screening visit the video ileocolonoscopy should be scheduled, if feasible.	This is considered a clarification, and not an additional procedure for the Screening Visit. The screening video ileocolonoscopy was always intended to be scheduled during the initial screening visit, if feasible. Specifying the scheduling activity as a screening visit procedure will ensure that study sites will plan the screening video ileocolonoscopy to be performed at least 8 days before but no more than approximately 3

Section number and Name	Description of Change	Brief Rationale
		weeks before the Week 0 visit to support randomization.
Section 1.3, Schedule of Activities, Table 1, Table 2, Table 3; Section 8.8.3, Biopsy-based Biomarkers	Ileocolonoscopy biopsy sample collections for histology and Ileocolonoscopy biopsy sample collections for exploratory RNA and protein assessments (where local regulations permit). Mucosal biopsy samples will be collected during ileocolonoscopy to study the effect of study intervention on the histological assessment of disease and healing. Biopsies will also be analyzed for exploratory gene and protein expression analysis where local regulations permit. Ileocolonic biopsy analyses may also examine gene and protein expression associated with the pathogenesis of Crohn's disease.	Clarification on the collection of ileocolonoscopy biopsy samples for RNA and protein analysis to be executed only in applicable countries where local regulations permit, since not all countries permit this testing on biopsy samples.
Section 1.3, Schedule of Activities, Table 1, Table 2, Table 3	Fecal biomarkers and microbiome moved from Efficacy Assessments to Pharmacodynamics and Biomarkers in Table 1 and Table 2. Microbiome moved from Efficacy Assessments to Pharmacodynamics and Biomarkers in Table 3.	Fecal biomarkers and microbiome analyses are considered part of the pharmacodynamics and biomarkers analyses.
Section 1.3, Schedule of Activities, Table 1, Table 2, Table 3, Table 4b; Section 4.2.2, Biomarker and DNA Collection; Section 8.8, Biomarkers; Section 8.8.1, Serum-based Biomarkers; Section 8.8.2, Whole Blood-based Biomarkers; Section 8.8.3, Biopsy-based Biomarkers; Section 8.8.4, Fecal Biomarkers; Section 9.4.5, Other Analyses, Biomarker Analyses	The following content was added: Where local regulations permit.	Clarification that whole blood samples for RNA analysis, serum biomarkers, and fecal biomarkers and microbiome will only be collected in applicable countries where local regulations permit, since not all countries permit the collection and/or testing of these samples.
Section 1.3, Schedule of Activities, Table 2	Optional Week 4: Only those participants who consent to participate in the optional substudy will undergo Week 4 video ileocolonoscopy and biopsy collection. Participation in the optional Week 4 substudy will target approximately 200 study participants.	Clarification on the number of study participants for the Week 4 substudy. The enrollment target is approximately 200 participants. Additional study participants will be accepted into the substudy if they consent.

Section number and Name	Description of Change	Brief Rationale
Section 4.2.2, Biomarker and DNA Collection Section 8.8.3.1 Optional Week 4 Biopsy Substudy	This substudy will target approximately 200 study participants. Approximately 200 study participants are defined for the Week 4 ileocolonoscopy substudy to provide sufficient power to support exploratory analyses.	
Section 1.3, Schedule of Activities, Table 3 Section 8.2.4, Vital Signs	Includes temperature, pulse/heart rate, respiratory rate, and blood pressure. Must be obtained prior to and approximately 30 minutes after the final [C] [CI] injection. For study participants receiving study intervention administration at the study site, vital signs will be assessed during the visit. For study participants who are trained to self-inject or have a caregiver who is trained to administer the study intervention at home, vital signs will only be assessed at the study site when these participants receive study intervention at the study site. Through Week 48, vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be obtained before and approximately every 30 minutes during every [C] [CI] infusion, and for 1 hour at approximately 30-minute intervals after completion of the final [C] [CI] infusion. Vital signs should be obtained before and approximately 30 minutes after the final [C] [CI] injection. After Week 48, study participants receiving study intervention administration at the study site will have vital signs assessed at these visits as described above. Study participants who are trained to self-inject (or will have a trained caregiver to inject) study intervention at home will be trained to perform self-evaluation for injection-site reactions and reporting of adverse events after administering study interventions at home. Vital signs will only be assessed at the study site when study participants receive study intervention administration at the study site.	No change to the originally planned assessments. Clarifications provided to indicate how study participants who will receive at-home study intervention administration will have their vital signs assessed at the study site vs at home.
Section 1.3, Schedule of Activities, Table 3	The following was added as a note to the injection-site evaluation line item: An injection-site reaction is any adverse reaction at any [C] [CI] study intervention injection site. Injection sites will be evaluated for reactions and any injection-site reaction will be recorded as an AE.	This content is included in Table 2 and was inadvertently omitted from Table 3 in the original protocol.
Section 1.3, Schedule of Activities, Table 3	The following was added as a note to the stool sample (fecal calprotectin) line item: Stool samples required for the Week 96 visit must be obtained before the start of the bowel preparation for	This content is included in Table 2 and was inadvertently omitted from Table 3 in the original protocol.

Section number and Name	Description of Change	Brief Rationale
	the video ileocolonoscopy that is scheduled for the visit.	
Section 1.3, Schedule of Activities, Table 3 Section 4.1.3.1, Treatment Adjustment for Inadequate Response	Footnote i added: CDAI assessments may be conducted at CCI visits between Weeks 52 and 80 (inclusive) to support the evaluation of CDAI response status. Participants who meet inadequate response criteria, and who are not already receiving the highest guselkumab C CI maintenance dose regimen, are eligible to receive treatment adjustment per protocol Section 4.1.3.1. The following paragraph was added: CDAI assessments may be conducted at CCI visits between Weeks 52 and 80 (inclusive) to support the evaluation of CDAI response status. Participants who meet inadequate response criteria, and who are not already receiving the highest guselkumab C CI maintenance dose regimen, are eligible to receive treatment adjustment as described below.	Clarification on the assessment of CDAI response status between Weeks 52 and 80 (inclusive). No change to the originally planned assessments. Clarifications are provided to indicate that study sites can perform CDAI response status evaluation at CCI visits to determine if participants meet inadequate response criteria to pursue the protocol-specified treatment adjustment.
Section 1.3, Schedule of Activities, Table 4a	Participant discontinues study intervention at or prior to the Week 12 visit The following notes were added: Discontinuation prior to Week 12: A video ileocolonoscopy at Week 12 is not required if already completed at the SID visit prior to Week 12. Discontinuation at Week 12: A video ileocolonoscopy is required at Week 12 (or can be performed as part of SID visit after Week 12).	No change to the originally planned assessments. Clarifications are provided to indicate the timing of discontinuation and the corresponding requirement to perform the video ileocolonoscopy.
Section 1.3, Schedule of Activities, Table 4a, Table 4b	The following note was added: The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 48, since these participants would have completed the procedure as part of the Week 48 visit.	The requirement of the video ileocolonoscopy for participants who discontinue study intervention after Week 48 is modified from “required” to “optional”. Study participants will have completed the procedure already at Week 48, and the endoscopy endpoints planned at Week 96 are considered exploratory. Therefore, to limit the number of unnecessary procedures in study participants who will be discontinuing study intervention after Week 48, the sponsor considers it important for study participants to be given the option to have this procedure, or not, as part of the discontinuation visit after Week 48.
Section 2.2.1, Guselkumab Clinical Experience; Section 2.2.2,	The following sentence was added: Since the initiation of the GALAXI protocol, higher doses of guselkumab (up to CCI	The description of available clinical experience with guselkumab in other study populations, at the dose range under study in the GALAXI

Section number and Name	Description of Change	Brief Rationale
Guselkumab Nonclinical Studies; Section 2.3.1, Guselkumab; Section 4.3.1.1.1, Induction Dose Regimens	have been administered in two clinical studies (a Phase 1 PK study in healthy Japanese participants and a Phase 2 study in participants with hidradenitis suppurativa).	protocol, is included to provide additional background information to investigators.
Section 2.3.1, Guselkumab	Since there is limited clinical information available for the higher dose regimens of guselkumab (as proposed in this protocol), safety will be evaluated in an initial cohort of 25 patients by an independent Data Monitoring Committee (DMC).	The description of available clinical experience with guselkumab in other study populations, at the dose range under study in the GALAXI protocol, is included to provide additional background information to investigators.
Section 4.1, Overall Design; Section 5.1, Inclusion Criteria	**Endoscopic evidence of ileocolonic Crohn's disease** A SES-CD score ≥3, as assessed by central endoscopy reading at the screening endoscopy, based on the presence of any ulceration in any 1 of the 5 ileocolonic segments, resulting in the following specified ulceration component scores: a. a minimum score of 1 for the component of "size of ulcers" AND b. a minimum score of 1 for the component of "ulcerated surface". Within each of the studies, a maximum of 10% of the total enrolled population will be participants who have baseline scores for SES-CD <4 (ie, for participants with isolated ileal disease), or SES-CD <7 (ie, for participants with colonic or ileocolonic disease).	Based on the scoring mechanism of the SES-CD, there are various endoscopic presentations of moderately to severely active Crohn's disease that would meet the originally specified protocol criteria (ie, achieving a minimum SES-CD score ≥3), and would also maintain consistency with the originally specified protocol criteria that were established after scientific consultation with several major health authorities. Therefore, the endoscopic inclusion criterion has been revised to enroll study participants with any evidence of ulceration in any 1 of the 5 ileocolonic segments. The revised criterion is intended to more accurately define the contemporaneous Crohn's disease patient population with moderately to severely active disease based on the observed patient characteristics from this ongoing protocol and other protocols conducted by the sponsor.
Section 4.1.1.2, Treatment Groups, Phase 2 Dose-Ranging Study (GALAXI 1), Figure 2	The following note was added to Figure 2, design schematic of the Phase 2 (GALAXI 1) study: Note: This schematic only illustrates the dosing for the treatment groups. It does not provide a complete illustration of all blinding (placebo) administrations.	Clarification is provided to indicate that the specified dosing only accounts for the planned treatment groups. The schematic is not intended to provide a complete account of both the assigned treatment administrations as well as the blinding (placebo) administrations.

Section number and Name	Description of Change	Brief Rationale
Section 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, 5-level EuroQol 5 dimensions [EQ-5D-5L] instrument) will be used to assess the benefits of guselkumab treatment on disease-specific and general HRQOL. Patient-reported outcome evaluations are only being collected in countries where translations of the evaluations are available. See Section 8.1 for more details.	Clarification is provided to indicate that PROs will be only be done in those countries where the PRO is available in the local language.
Section 5.1, Inclusion Criteria	Criterion #13: Be willing and able to adhere to all specified requirements, including but not limited to completion of required assessments, adherence to visit schedule, compliance with lifestyle restrictions (Section 5.3), etc 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 into the protocol.
Section 5.2, Exclusion Criteria	Criterion #16: Participants who are seropositive for antibodies to hepatitis C virus (HCV), unless they satisfy one of the following conditions: • have a history of successful treatment (defined as being negative for HCV RNA at least 6 months after completing antiviral treatment) and have a negative HCV RNA test result at screening, OR • while seropositive have a negative HCV RNA test result at least 6 months prior to screening and a negative HCV RNA test result at screening.	The objective of the HCV exclusion criteria is to identify participants with HCV infections who should not be enrolled into the protocol. The original specified criterion is not consistent with current practice and has been updated based on current HCV screening and treatment guidelines.
Section 5.2, Exclusion Criteria	Criterion #33 was added: 7. Has previously undergone allergy immunotherapy for prevention of anaphylactic reactions (eg, venom immunotherapy).	This exclusion criterion was inadvertently omitted from the original protocol.
Section 5.4, Screen Failures	**Rescreening** Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then start a new screening phase, including the collection and testing of new laboratory specimens. Previous TB evaluation results (including the QuantiFERON-TB test and chest radiograph) and stool study results, and ileocolonoscopy results from the first screening event may be used if they meet the specified protocol criteria as described in Section 5.1. Medical Monitor approval is required prior to the study site obtaining a new informed consent for rescreening.	Clarifications are provided regarding rescreening requirements, including specifications of which screening tests need to be performed again during rescreening and which screening test results from the previous screening event may be considered acceptable, provided that these previous tests were conducted in accordance with the protocol and meet the specified criteria.

Section number and Name	Description of Change	Brief Rationale
Section 6.1, Study Interventions Administered	In both the Phase 2 and Phase 3 portions of the protocol: • All participants will receive 2 [redacted] infusions at Week 0 (either active or placebo) and 1 [redacted] infusion at Weeks 4, 8, and 12 (either active or placebo). • All participants will receive 1 [redacted] injection (either active or placebo) at Week 8 and up to 3 [redacted] injections (either active or placebo) at each visit from Week 12 to Week 140. [redacted] study intervention (including the flush) should be administered over a period of not less than 1 hour, and not more than 2 hours. The infusion (including the flush) should be completed within 6 hours of preparation. At Week 0, the guselkumab/placebo in dextrose [redacted] infusion (including the flush with dextrose) should be administered first. The [redacted] infusion administration line set will be changed (ie, use a new line set) prior to the administration of the ustekinumab/placebo in saline [redacted] infusion, followed by the flush with saline. At Week 4, only guselkumab/placebo in dextrose [redacted] infusion is administered. At Weeks 8 and 12, the guselkumab/placebo in dextrose [redacted] infusion (including the flush with dextrose) should be administered first, followed by the [redacted] injection(s) with active (guselkumab/placebo or ustekinumab/placebo) or placebo investigational product (IP). At Week 12 and beyond, multiple [redacted] injections may be administered within the administration visit. Each injection of study intervention should be given at a different location of the body. Detailed instructions on the preparation and administration of study intervention will be provided in the site Investigational Product Procedures Manual (IPPM). Of note, instructions on the preparation and administration of study intervention in the Phase 3 portion of the protocol will be finalized and provided to investigative sites when the Phase 3 dose decision is made and implemented.	Clarifications are provided regarding [redacted] study intervention administration procedures for specific study visits. These clarifications are intended to provide a high-level summary only, and investigators and site staff are to refer to the IPPM for further details.
Section 6.2.2, Ustekinumab	The following sentence was added: The needle cover on the [redacted] contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.	This statement was inadvertently omitted from the original protocol.

Section number and Name	Description of Change	Brief Rationale
Section 6.2.3, Accountability	The following sentence was removed: Study site personnel must not combine contents of the study intervention containers.	Clarification is provided regarding IP preparation. The protocol-specified IP preparation method requires the pooling of multiple vials and syringes.
Section 6.3, Measures to Minimize Bias: Randomization and Blinding	The following paragraph was deleted and replaced with the paragraph below: [Deleted] Treatment assignment blinding will be maintained for investigative sites, site monitors, and participants until the Week 48 DBL and analyses are completed for both Phase 3 studies. [Replacement] All participants will continue to receive active or placebo study intervention administration in the LTE in a blinded fashion until study unblinding, which will occur after the Week 48 DBL and the Week 48 analyses have been completed for the Phase 2 study (for participants entering the LTE from GALAXI 1) or for the Phase 3 studies (for participants entering the LTE from GALAXI 2 or GALAXI 3).	The original text was incorrect in stating that all 3 studies under the protocol will be fully blinded until the Phase 3 study Week 48 DBL.
Section 7.1, Discontinuation of Study Intervention,	The following sentences were removed or relocated 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.~~	Removal of the CTCAE statement was necessary because grading of adverse events is not being performed in this study. Relocation of the specified statement is necessary because injection-site or infusion reactions are not mandatory discontinuation requirements.
Section 7.1, Discontinuation of Study Intervention	The following criterion was relocated from Criterion #1 in the section entitled "Discontinuation of a participant's study intervention must be strongly considered under the following conditions" to become Criterion #11 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.

Section number and Name	Description of Change	Brief Rationale
Section 7.1, Discontinuation of Study Intervention	Criterion #1: **Discontinuation of a participant's study intervention must be strongly considered under the following conditions:** 8. Persistent inadequate response or worsening of Crohn's disease: f. The participant has a change from baseline in the CDAI score <70 points and has a CDAI score >220 at both Week 20 and Week 24. OR g. The participant experiences AEs consistent with clinically significant worsening of Crohn's disease at any time during the study. These events must be evaluated by the investigator. A consultation with the study medical monitor may also be considered, at the investigator's discretion. Discontinuation of study intervention must be considered in participants with clinically significant worsening of Crohn's disease where continuation of the study intervention is not in the best interest of the participant.	Clarifications were provided to ensure that discontinuation of study intervention is strongly considered by the investigator and that the investigator may also consult with the study medical monitor if necessary.
Section 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 #4 in the section entitled "Discontinuation of a participant's study intervention must be strongly considered under the following conditions": The participant develops a severe injection-site or infusion reaction.	Relocation of the specified criterion was necessary since injection-site or infusion reactions are not mandatory discontinuation requirements.
Section 8.1, Efficacy Assessments	**Histologic assessments** will be performed using biopsy samples collected during ileocolonoscopy. Biopsy samples will be collected at screening, Week 12, Week 48, and Week 96 from each of 3 predefined anatomic locations: the terminal ileum, splenic flexure, and rectum, as clinically feasible. An optional substudy involving a Week 4 evaluation will be performed in consenting participants in addition to the above-specified evaluations. The biopsy samples collected post-baseline will be obtained near where the screening biopsy samples were collected from each of the 3 predefined locations, as clinically feasible. Histologic assessments will be conducted by a central reader who is blinded to treatment groups and visit. The Global Histology Activity Score (GHAS) will be used to evaluate histologic	Text clarified to acknowledge the collection of the specified ileocolonic biopsy samples may not be always clinically feasible.

Section number and Name	Description of Change	Brief Rationale
	improvements and healing.[5] Analyses will be specified in the SAP.	
Section 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 participants 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 Section 10.11 for serious adverse events. 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.	Clarification to specify the time period in which investigators or site staff personnel must report an event of special interest and special reporting situations.
Section 10.11, Appendix 11 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The following was added as the first sentence under Special Reporting Situation: 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.	Clarification to specify the time period in which investigators or site staff personnel must report an event of special interest and special reporting situations.
Section 1.1, Synopsis, Primary Efficacy Analysis	The primary efficacy analysis is based on the Full Analysis Set, defined as all participants who are randomized and who have received at least 1 dose of study intervention in GALAXI 1. The primary endpoint of the change from baseline in the CDAI score at Week 12 will be analyzed using a Mixed Effect Repeated Measures Model (MMRM) approach.	Text was updated to reflect planned alternate approaches to handling missing data to align with regulatory guidelines on missing data handling, and to indicate that additional details will be provided in the SAP.
Section 9.4.2.2, Primary Endpoint Analysis	The CDAI score will be calculated for a visit if at least 4 of the 8 components are available at Week 12. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last available components. If the CDAI score cannot be calculated (ie, <4 components available) at a visit, the CDAI score will be considered missing for that visit. The missing data handling rules for the CDAI score will be described in the Phase 2 SAP. The change from baseline in CDAI will be analyzed using a Mixed Effect Repeated Measures Model (MMRM) approach. Further details will be described in the Phase 2 SAP. A multiple testing procedure will be used to control the Type 1 error at α=0.05 (2-sided) over the comparisons of guselkumab with placebo (to be defined in the Phase 2 SAP).	
Section 9.4.2.3, Major Secondary Endpoint Analysis	The CDAI score will be calculated for a visit if at least 4 of the 8 components are available at that visit. When at least 4 of the 8 components are	

Section number and Name	Description of Change	Brief Rationale
	available, any missing components will be imputed by carrying forward the last available components. The clinical response or remission endpoints will be determined based on these imputed CDAI scores. If the CDAI score cannot be calculated (ie, <4 components available) at a visit, the CDAI score will be considered missing for that visit. Participants who do not return for evaluation or have a missing CDAI score at Week 12 will be considered not to be in clinical remission or clinical response as measured by the CDAI score. Participants who do not return for evaluation or have missing AP or SF scores at Week 12 will not be considered to have achieved clinical remission, as measured by PRO-2. Participants with a nonevaluable or missing endoscopy will be considered not in endoscopic response. The details for handling missing segments in the SES-CD score will be described in the Phase 2 SAP.	
Section 9.4.3.2, Primary Endpoint Analysis	The CDAI score will be calculated for a visit if at least 4 of the 8 components are available at that visit. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last available components. If the CDAI score cannot be calculated (ie, <4 components available) at a visit, the CDAI score will be considered missing for that visit. Participants who do not return for evaluation or have a missing CDAI score at Week 12 will not be considered to have achieved clinical remission at Week 12. Treatment failure rules will overrule the missing data rules.	
Section 9.4.3.3, Major Secondary Endpoint Analysis	The CDAI score will be calculated for a visit if at least 4 of the 8 components are available at that visit. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last available components. The clinical remission endpoints will be determined based on these imputed CDAI scores. If the CDAI score cannot be calculated (ie, <4 components available) at a visit, the CDAI score will be considered missing for that visit. Participants who do not return for evaluation or have a missing CDAI score at any visit will be considered not to be in clinical remission based on CDAI for that visit. Participants who do not return for evaluation or have missing AP or SF scores at the analysis time point will not be considered to have achieved clinical remission, as measured by PRO-2 for that analysis time point. Participants with a nonevaluable or missing endoscopy will be considered to be not in endoscopic response. The details for handling missing segments in the SES-CD score will be described in the SAP. In addition,	

Section number and Name	Description of Change	Brief Rationale
	for durable remission, participants with missing values for a visit will be considered not in clinical remission for that visit. The missing-data rules for fatigue response will be specified in the SAP.	
Section 10.2, Appendix 2: Definitions of Inadequate Response to or Intolerance of Corticosteroids or 6-MP/AZA/MTX and Corticosteroid Dependence	Appendix 2: Definitions of Inadequate Response to or Intolerance of Corticosteroids or 6-MP/AZA/MTX and Corticosteroid Dependence Methotrexate (MTX) added throughout the appendix: **6-MERCAPTOPURINE (6-MP), AZATHIOPRINE (AZA), OR METHOTREXATE (MTX)** **Subjects have failed to respond to 6-MP, AZA, OR MTX if** they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving: • At least 3 months of therapy with [redacted] day of 6-MP, [redacted] /day of AZA, or [redacted] week (intramuscular or [redacted] of MTX. **OR** • A lower dosage of 6-MP, AZA, or MTX 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, AZA, or MTX confirmed to be therapeutic for the subject with whole blood thioguanine nucleotide levels >200 pmol/8 x 10^8 red blood cells. **OR** • The highest tolerated dosage due to leukopenia, elevated liver enzymes, or nausea. **Subjects are intolerant of 6-MP, AZA, or MTX 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, AZA, or MTX to treat Crohn's disease within the past 5 years. **OR** • They have a medical condition that precludes the use of 6-MP, AZA, or MTX.	No change to the originally intended protocol criteria. The specified criteria for MTX were erroneously omitted in the original protocol.

Section number and Name	Description of Change	Brief Rationale
Section 10.3, Appendix 3: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNF Antagonist Therapies (Infliximab, Adalimumab, or Certolizumab Pegol) or Vedolizumab	The following content was added to Appendix 3: It is also acknowledged that previous treatment decisions could have been made based on evaluation of other measures that may be indicative of worsening disease (eg, elevations of inflammatory markers including but not limited to CRP or fecal calprotectin, etc, and/or evidence of disease flare based on clinical imaging modalities including but not limited to ileocolonoscopy, CT, MRI). Under these circumstances, documentations of these specified measures of worsening disease activity can be accepted as evidence of inadequate response to prior biologic treatment. However, investigators should note that participants must meet protocol-specified criteria for active disease (ie, clinical and endoscopic) during the current screening period as described in Section 5.1 to be eligible for enrollment.	Based on current clinical practice, clarifications are provided to acknowledge that additional measures of worsening disease activity indicative of inadequate response to previous biologic treatments may be acceptable.
Section 10.5, Appendix 5: QuantiFERON®-TB Gold Testing	Appendix 5 was removed and Appendices 6 through 13 were renumbered accordingly.	Appendix 5 QuantiFERON®-TB Gold Testing was removed since most of this information is already included in the Site Laboratory Manual and is not necessary to be included in the protocol.
Section 10.8, Appendix 8: Regulatory, Ethical, and Study Oversight Considerations	**Investigator Responsibilities** subsection 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 Helsinki, and applicable regulatory and country-specific requirements.	Clarification to specify that investigators are required to comply with the principles of Declaration of Helsinki as requested by a health authority.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

CNTO 1959 (guselkumab) Clinical Protocol CNTO1959CRD3001 Amendment 5

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: _____

_____

_____

_____

[redacted]

PPD

Institution: PPD Development

Signature: _____ 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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Status: Approved, Date: 12 July 2022

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

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

GALAXI

[A Study of the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Crohn's Disease]

Protocol CNTO1959CRD3001; Phase 2/3

CNTO 1959 (guselkumab)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

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

Status: Approved
Date: 27 April 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-38072

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL CNTO1959CRD3001

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of participant care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
    - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures, eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration (including training where pertinent)
    - procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at home administration (including the potential for self-administration of study intervention)
    - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
    - other procedures, eg, imaging, may be conducted at an appropriate facility
- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).
    - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in CRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).
- Exclusion: a potential participant with the following features will be excluded from participating in the study protocol:
    - During the 6 weeks prior to baseline, have had ANY of (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection
        - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

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

AND

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

- NOTES on COVID-related exclusion:

1. If a participant is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the CRF under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.

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

- Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
CNTO 1959 (guselkumab)
Clinical Protocol CNTO1959CRD3001

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

PPD

Signature: _____ Date: PPD
(Day Month Year)

Note: If the ad nber of the investigator changes during the course of the study, written notification wil vestigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 27 April 2020