Janssen Research & Development *

Clinical Protocol

Protocol Title
A Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Guselkumab for the Treatment of Participants with Crohn's Disease After Surgical Resection

Prevention of Recurrence post Operatively with Guselkumab Relative to Endoscopy and SymptomS: The PROGRESS Study

Protocol CNTO1959CRD3007; Phase 3
Version: Amendment 1
CNTO1959 (guselkumab)

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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 1	02 December 2022
Original Protocol	08 July 2022

Amendment 1 (02 December 2022)

Overall Rationale for the Amendment: The overall rationale for the amendment was to further clarify how cross over to open-label guselkumab treatment for participants is handled, which includes the addition of a separate Schedule of Activities for participants who cross over to guselkumab. Additional reasons for the amendment were to:

- Correct mentions of clinical recurrence to be consistent with Health Authority recommendation to use "disease recurrence" instead of "clinical recurrence"
- Add clarification to the statistical analysis including (1) adding cross over to open-label guselkumab induction as an intercurrent event, (2) censoring participants at cross over for the time to disease recurrence endpoint if they have confirmed endoscopic recurrence at Week 24 or 48 and cross over to open-label guselkumab treatment, (3) censoring participants who cross over for endoscopic recurrence at Week 24 rather than being included in the definition for disease recurrence.
- Make changes to the original Schedule of Activities relating to visits.

The changes made to the clinical protocol CNTO1959CRD3007 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
Synopsis/3 Objectives and Endpoints, Secondary Objectives	Reworded the secondary objective for evaluating steroid use. Pharmacokinetics analyses added to secondary objectives.	Clarification. Clarification.
Synopsis/9.1 Statistical Hypotheses; 4.1 Endpoints; 9.2 Sample Size Determination; 9.4.2 Primary Endpoint	Wording altered to state superiority based on endoscopic recurrence prior to or at Week 48 (rather than at Week 48).	Correction.
1.2 Study Schema	Corrected symbols for CCI dose (will be CCI doses)	Clarification.
1.3 Schedule of Activities	Created a separate SOA for participants who cross over to guselkumab treatment, such that there is one SOA for participants who do not cross over (and separating the Flare and End of Treatment visits for clarity), and one for participants who do.	Clarification.
	Added vital signs collection Week 24.	Inadvertently omitted in original protocol.
	Added physical exam for Flare and Early Termination visits.	Inadvertently omitted in original protocol.

Section Number and Name	Description of Change	Brief Rationale
	Separated the Flare and Early Termination visits, and removed PROs (WPAI, PROMIS-29, and PROMIS-Fatigue 7a) from the Flare visit.	The PROs were intended to be completed at the Early Termination visit only.
	Split the row pertaining to the CDAI assessment into 2 rows, one for reminder to complete the electronic CDAI and one for calculation of CDAI.	Clarification.
	Added footnote for final visit: If clinically appropriate and allowed by local regulations, the Week 156 visit can be done by telephone.	Reducing participant burden of frequent site visits, since they will have an on-site visit for the Week 152 Final Efficacy Visit.
	Details added for footnote for the Flare visit.	Clarification.
Throughout protocol	Where relevant, changed "clinical recurrence" to "endoscopic" or "disease recurrence," as appropriate.	To align with Health Authority feedback.
2.3.1 Risks for Study Participation, Risks Table: For risk of clinical worsening of CD	Added all criteria for cross over to open-label induction and removed mention of clinical recurrence.	Clarification.
4.1 Overall Design, Overall Design	Edited to clarify that the optional cross over at Week 24 is at the discretion of the investigator when there is ONLY endoscopic recurrence.	Clarification.
4.1 Overall Design, Study Length	Clarified that participation follow-up may vary for the main study period.	Clarification.
4.3 Justification for Dose	Added all criteria for cross over to open-label induction and removed mention of clinical recurrence.	Clarification
4.4 End of Study Definition, Participant Study Completion Definition	Added details for study completion criteria.	Clarification.
5.1 Inclusion Criteria, #3	Clarified that participants can have undergone an ileocolonic surgical resection for CD prior to the baseline visit.	Added to allow for screening/consent of participants prior to surgery.
5.1 Inclusion Criteria, #13	Edited criterion pertaining to adherence to all specified requirements in this protocol to include an ileocolonoscopy at 1 year or upon concern for clinical flare.	Clarification.
6.1 Study Interventions Administered, Table 1: Description of Interventions, Dose Formulation, Unit Dose Strength, Dosing Instructions	Details added for dosing upon cross over, and to clarify induction vs maintenance dosing details. Clarifications added for induction vs maintenance dosing.	Clarification and to allow for cross over guselkumab doses 1 and 3 to be administered at a scheduled visit in order to correspond with cross over visit schedule. Clarification.

Section Number and Name	Description of Change	Brief Rationale
6.2 Preparation/Handling/Storage/ Accountability	Added that guselkumab will also be supplied as [redacted].	Correction.
6.5.1 Open Label/Cross Over Treatment	Added criteria for not needing an ileocolonoscopy before crossing over.	Clarification.
6.7 Treatment of Overdose	Deleted text about considering dose reduction, and for the duration of overdosing. Removed bullet requiring obtaining a serum sample for PK analysis if requested by Medical Monitor.	Corrections. There is no clinical indication for, or analysis needed for this serum sample.
6.8 Concomitant Therapy	Deleted requirement to record dose of concomitant therapies.	There is no clinical or analysis need for these data (other than corticosteroid dosing, which will be recorded in the CRF).
8 Study Assessments and Procedures, Week 0 Visit	Deleted mention of informed consent (is already mentioned under Screening).	Correction.
8 Study Assessments and Procedures, Post-baseline Visits	Changed last CDAI diary completion to Week 152 (from Week 156).	Correction.
8 Study Assessments and Procedures, Cross Over Visit	Added details describing dosing and subsequent study visits for participants who cross over to guselkumab treatment.	To simplify and clarify the cross over schedule and procedures for sites, a separate cross over schedule was added.
8 Study Assessments and Procedures, Study-Specific Materials	Clarified the instructions for use. Deleted Symptom and Health Diary Cards. Added that study medication diary is for home dosing. Added Laboratory Manual and Source Documents as applicable, as well as manual and quick reference guide for PROs.	Clarification. An electronic diary will instead be used for PROs. Clarifications.
8.1.3 Endoscopic Assessments of the Intestinal Mucosa	Edits made to clarify endoscopic vs disease recurrence.	Clarification.
8.4.6 Injection Site Reactions	Noted that injection sites will be evaluated for reactions only at on-site visits.	Clarification.
8.4.8 Infections	Deleted requirement to discuss any serious infections with the medical monitor or designee.	Clarification so decision to discontinue study intervention is at the discretion of the investigator without requirement to consult with sponsor.
8.8.2 Mucosal Biopsy (Histology, RNA, and Single Cell Isolation)	Added details for protein and gene expression measurement.	For completeness.
8.8.3 Serum-based Biomarkers	Clarified language and noted analyses will include IL-17A and IL-22.	Clarification.
1.3 Schedule of Activities; 8.8 Biomarkers	Reorganized text to clarify samples to be taken for analysis of DNA vs RNA, and added details to align with current sponsor's text for	Clarification and additional details.

Section Number and Name	Description of Change	Brief Rationale
	protocols describing procedures for these.	
9.4.2 Primary Endpoint, Primary Estimand of Endoscopic Recurrence prior to or at Week 48, Treatment by Week 48	Added cross over to open-label guselkumab as an intercurrent event.	For completeness.
9.4.3 Secondary Endpoints	Edited details regarding censoring at cross over for time to disease recurrence endpoint.	Clarification.
9.4.3 Secondary Endpoints, Estimands and Estimators (for Clinical Remission without Disease Recurrence at Week 48) Estimators (for Disease Recurrence)	Changed mention of primary endpoint to first secondary endpoint. Updated details for ICEs and estimators. Added the (specific) list of other secondary endpoints; however, frequency of AEs and SAEs was deleted as another secondary endpoint.	Correction. For completeness and to eliminate redundancy. Correction.
9.4.4 Other/Exploratory Endpoints	Added endpoint of endoscopic recurrence prior to or at Week 24. Added exploratory analysis for risk factors of endoscopic and disease recurrence. Added a sensitivity analysis of the primary endpoint using a Rutgeerts score of $\geq$ i3 to define endoscopic recurrence.	Inadvertently omitted from original protocol. Inadvertently omitted from original protocol. For completeness.
9.4.6.2 Pharmacogenomic Analyses; 9.4.6.3 Biomarker Analyses	Deleted text that was redundant with text in Sections 8.7 and 8.8, and added text pertaining to the analyses.	Clarification and more complete descriptions of analyses.
Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments	Replaced prior version of appendix with a version with similar instructions but in a format that is easier to follow.	Clarification.
New Appendix 9: Clinical Disease Activity Index	Added a sample CDAI measure as Appendix 9.	Information added as tools to aid sites in calculating CDAI.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Guselkumab for the Treatment of Participants with Crohn's Disease After Surgical Resection: PROGRESS

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1 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 the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, thus inhibiting IL-23 specific intracellular signaling and downstream activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

BENEFIT-RISK ASSESSMENT

The benefit-risk assessment is described in detail in Section 2.3. Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with guselkumab are justified by the anticipated benefits that may be afforded to participants to prevent recurrence of Crohn's disease (CD) postoperatively based on promising efficacy results in a Phase 2 study (CNTO1959CRD3001).

Risks of the study intervention include clinical worsening of CD, serious infection or reactivation of latent infection, hypersensitivity reactions, malignancy, liver injury and immunosuppression. Risks associated with study procedures include rare risks of associated with video ileocolonoscopy (eg bleeding, intestinal perforation) or risk of minimal radiation exposure from a chest x-ray.

Potential benefits to study participation include possible prevention of recurrence of CD postoperatively, improved disease control related to the frequent study visits and medical care, and the satisfaction of contributing to scientific research.

The use of placebo is justified because there are currently no approved treatments for the indication of reducing the risk of recurrent CD after surgical resection and therefore a placebo comparator is necessary to establish whether there is meaningful benefit from the study intervention. Furthermore, the study population consists of participants with inactive CD at baseline, and participants who experience disease recurrence will then receive open-label, full subcutaneous guselkumab induction.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of guselkumab treatment versus placebo in preventing endoscopic recurrence of CD in participants after surgery	• Endoscopic recurrence prior to or at Week 48 (as defined by modified Rutgeerts score ≥ i2a in the neo-terminal ileum, anastomotic site, or its equivalent elsewhere in the GI tract [eg colonic ulceration])
Secondary	
• To evaluate clinical remission without disease recurrence in participants treated with guselkumab versus placebo after surgery	• Clinical remission (CDAI < 150) without disease recurrence at Week 48 (as defined in Section 9.4.3)

Objectives	Endpoints
• To evaluate disease recurrence in participants treated with guselkumab versus placebo after surgery	• Time-to-disease recurrence (as defined by CDAI/event driven criteria as described in Section 9.4.3) at the main study database lock, which will incorporate all available follow-up of enrolled participants at the time that the last participant dosed has completed the Week 48 study procedures, including the ileocolonoscopy
• To evaluate symptoms such as stool frequency and abdominal pain scores in guselkumab versus placebo after surgery	• Abdominal pain free (abdominal pain [AP] score = 0) at Week 48 • Time-to-recurrence of symptoms, defined as time to attaining an AP mean daily score >1 (and also >1 point higher than baseline) along with stool frequency (SF) mean daily score >3 (and also >3 higher per day than baseline) for 2 consecutive weeks through Week 48
• To evaluate the safety and pharmacokinetics of guselkumab in participants with CD in the postoperative period	• Frequency and type of adverse events (AEs) and serious adverse events (SAEs) • Describe serum guselkumab concentrations over time
• To evaluate the efficacy of guselkumab in limiting steroid use and maintaining remission in the postoperative period	• Steroid free clinical remission at Week 48, defined as CDAI <150 and no corticosteroids within 30 days
Other	
• To evaluate fatigue and other patient reported outcomes in guselkumab versus placebo after surgery	• Change in PROMIS-Fatigue Short Form 7a score over 48 weeks • Change in PROMIS-Fatigue SF 7a at each post baseline visit through Week 152 • Change in PROMIS-29 score, both overall score and individual domain scores at each post baseline visit through Week 152 • Change from baseline in the WPAI at each post baseline visit through Week 152 • Abdominal pain (AP score = 0) at each post baseline visit through Week 152
• To evaluate steroid use and healthcare utilization in participants within the postoperative period	• The number of participants not on corticosteroids and without disease recurrence at each post baseline visit through Week 152 • The number of participants not on corticosteroids and who have not experienced endoscopic or disease recurrence at each post baseline visit through Week 152
• To evaluate histologic status in CD patients after surgery	• Histologic score (as measured by Geboes scale/RHI/GHAS) at Week 48 ileocolonoscopy

Objectives	Endpoints
	• The number of participants with Geboes score of 2.0 or less at Week 48 ileocolonoscopy • The number of participants with Geboes score over 3.1 at Week 48 ileocolonoscopy
• To evaluate the efficacy and safety of open-label guselkumab SC induction and maintenance treatment in the cross over population after postoperative endoscopic or disease recurrence of CD has occurred	• Clinical remission (CDAI < 150) at 24 weeks after initiation of guselkumab SC induction • Clinical response (CDAI decrease of <100 points or CDAI <150) at 24 weeks after initiation of guselkumab SC induction • Endoscopic remission (SES-CD of 3 or less) 24 weeks after guselkumab SC induction • Endoscopic remission (modified Rutgeerts score <i2a) 24 weeks after guselkumab SC induction
• To evaluate the efficacy of guselkumab treatment versus placebo in changes to inflammatory biomarkers after surgery	• The change from baseline in CRP concentration at all postbaseline visits through Week 152 • The change from baseline in fecal calprotectin concentration at all postbaseline visits through Week 152 • Fecal calprotectin recurrence, defined by calprotectin of >200 µg/g with a 100 µg/g increase over baseline
• To evaluate the clinical efficacy of guselkumab treatment	• Disease recurrence (using CDAI/Event-driven definition as described in Section 9.4.3) at Week 152 • Clinical remission (CDAI <150) at each post baseline visit • Time to a flare of abdominal pain
• To evaluate the endoscopic efficacy of guselkumab treatment	• Endoscopic remission (SES-CD of 3 or less) at Week 24, Week 48, Week 152 • Endoscopic recurrence (modified Rutgeerts score >i2a) at Week 24, Week 152

Key: AE = adverse event; AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's disease activity index; CRP = C-reactive protein; GI = gastrointestinal; PROMIS = Patient-Reported Outcomes Measurement Information System; SC = subcutaneous; SAE = serious adverse event; SES-CD = Simple Endoscopic Score - Crohn's disease; SF = stool frequency

Hypothesis

It is hypothesized that guselkumab, when initiated after recent ileocolonic surgical resection for CD, is superior to placebo in reducing the recurrence of CD in adult patients, as measured by endoscopic recurrence prior to or at Week 48.

OVERALL DESIGN

This is a Phase 3, multicenter, randomized, placebo-controlled, prospective double-blind study designed to evaluate the efficacy and safety of SC guselkumab in reducing the recurrence of CD in adult patients who have recently undergone a surgical resection for CD.

The target population consists of participants with CD who have undergone a recent (≤49 days) ileocolonic resection with ileocolonic anastomosis for CD, without evidence of active disease postoperatively. Participants must not have had their qualifying surgery for the purpose of resecting known dysplasia.

Participants will have a baseline CDAI <200 and will be eligible regardless of prior biologic use. Participants who are low risk for recurrent CD (ie, participants whose qualifying surgery was their first in >10 years since their diagnosis of CD and was performed for fibrostenotic stricturing disease involving <10 cm of the intestine) will be excluded. Participants must be able to undergo randomization no later than 49 days after surgery.

NUMBER OF PARTICIPANTS

A target of approximately 370 participants will be enrolled from approximately 150 sites.

INTERVENTION GROUPS AND DURATION

Randomization will occur in a 1:1 ratio with participants receiving either:

- **Arm 1:** Guselkumab CCI at Week 0 and then CCI at Week 8, then every CCI thereafter through Week 144.
- **Arm 2:** Matched placebo CCI at Week 0 and then CCI thereafter through Week 144.

The Week 48 video ileocolonoscopy will be performed between Week 48 and Week 51 and participants with endoscopic recurrence confirmed by a central reader will cross over to open-label treatment with guselkumab CCI induction. An optional video ileocolonoscopy can be performed at Week 24 and cross over may occur at the discretion of the principal investigator for endoscopic recurrence. If participants meet criteria for disease recurrence (defined in Section 9.4.3) after Week 8 they will also cross over to open-label treatment.

Description of Interventions

Participants in the guselkumab cohort will receive guselkumab CCI) provided in a single-use 1 mL prefilled syringe (PFS) assembled with the CCI . Participants will receive CCI CCI at Week 0 and then 1 CCI CCI starting at Week 8. At the discretion of the investigator and participant, and after appropriate and documented training, participants may self-administer study intervention at home (or by a caregiver).

Participants in the placebo cohort will receive placebo (to match guselkumab) 1 mL-injections in a single dose CCI .

Participants who have disease recurrence will cross over to receive open-label guselkumab, regardless of Week 0 treatment assignment (ie, in either the placebo or guselkumab groups). At the cross over visit, they will receive CCI guselkumab, and then receive additional CCI SC doses, 4 and 8 weeks after the cross over visit. The CCI SC doses will be given as CCI of CCI guselkumab (CCI provided as single-use 2 mL PFS assembled with the CCI). These doses may be given at home. After the third 400 mg dose, participants will continue on guselkumab CCI .

Study Assessments

A complete list of efficacy and safety assessments can be found in Section 8. Efficacy, safety, pharmacokinetics (PK), immunogenicity, and biomarkers will be assessed according to the Schedule of Activities. Efficacy assessments include the CDAI, PRO-2 score; endoscopic assessments; inflammatory biomarkers; external perianal fistula assessment; patient reported outcome (PRO) measures; and histologic assessments.

Key safety assessments include AEs, clinical laboratory tests (hematology and chemistry), vital signs, screening physical examination, concomitant medication review, monitoring for hypersensitivity reactions, injection site reactions, suicidal ideation and behavior by the Columbia Suicide Severity Rating Scale (C-SSRS), and early detection of active tuberculosis (TB).

An optional pharmacogenomic blood sample will be collected to allow for pharmacogenomic research (where local regulations permit).

STATISTICAL METHODS

A sample size of 185 participants for each cohort will have >90% power to detect differences between the guselkumab treatment group and placebo group for the primary endpoint, assuming a 2-sided alpha level of 0.05.

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

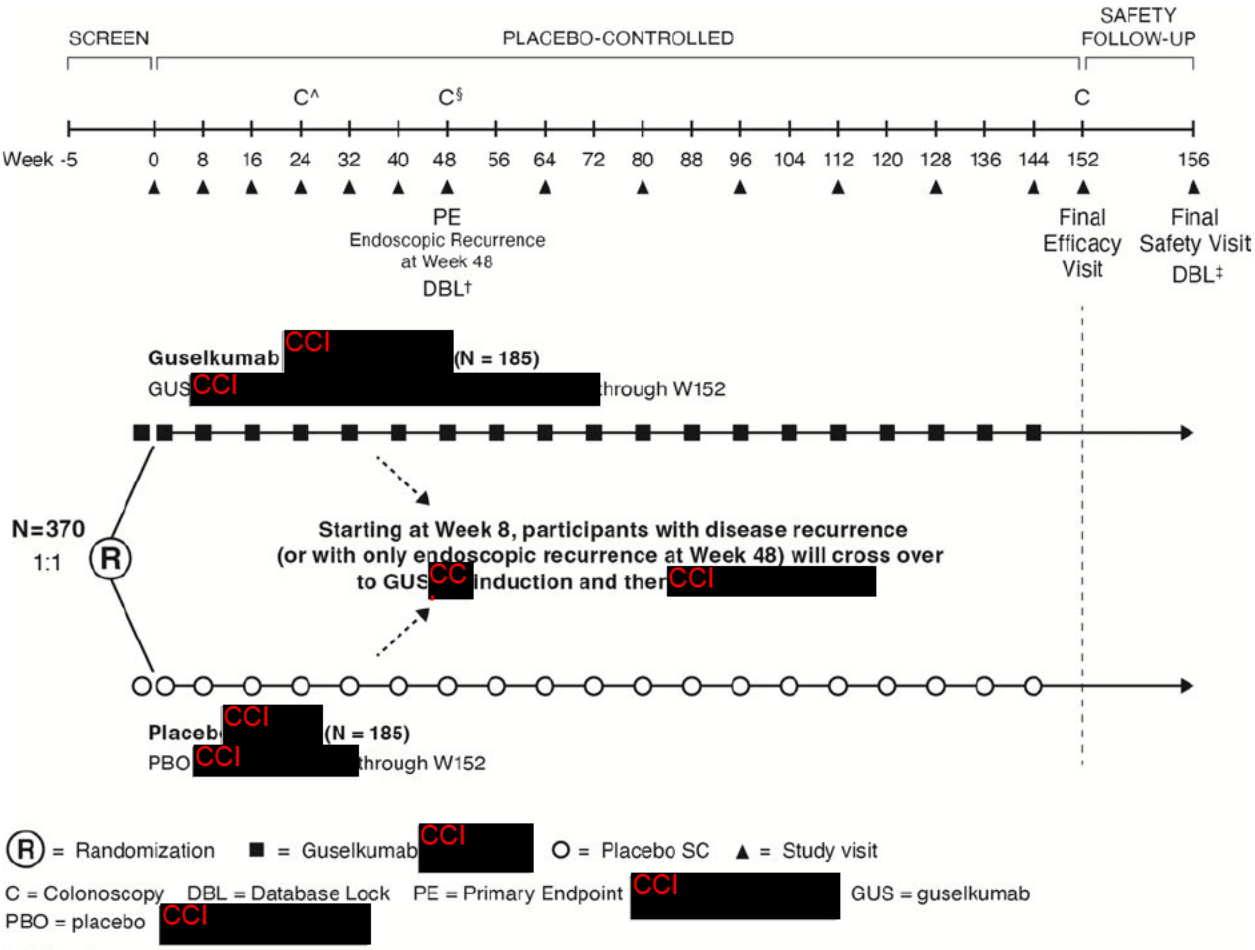
Analyses suitable for categorical data (eg, chi-square tests, Cochran-Mantel-Haenszel chi-square tests, or logistic regression, as appropriate) will be used to compare the proportions of participants achieving selected endpoints (eg, clinical response). In cases of rare events, the Fisher's exact test will be used for treatment comparisons. Continuous response parameters will be compared using an analysis of variance (ANOVA), analysis of covariance (ANCOVA), or a mixed model for repeated measures (MMRM), unless otherwise specified. If the normality assumption is in question, an ANOVA or ANCOVA on the van der Waerden normal scores will be used. For time to event endpoints, survival analysis techniques will be used.

The primary endpoint is endoscopic recurrence prior to or at Week 48 defined by modified Rutgeerts score ≥ i2a in the neo-terminal ileum, anastomotic site, or its equivalent elsewhere in the gastrointestinal tract (eg, colonic ulceration). The primary endpoint will be analyzed based on the estimands defined in Section 9. The overall Type I error rate will be controlled at the significance level of 0.05 (2-sided) for the primary and major secondary endpoints. Hierarchical testing will be performed for primary and secondary endpoints, the ordering of which will be described in the Statistical Analysis Plan. No multiplicity control will be made for other endpoints and nominal p-values will be reported.

For safety analyses, for each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group. The analyses of AEs will be performed for safety measures including but not limited to, AEs, SAEs, infections, and injection site reactions. Descriptive statistics will be calculated for selected laboratory analytes at baseline, observed values and changes from baseline at each scheduled timepoint.

1.2. Schema

Schematic Overview of the Study



^ Optional

§ Week 48 colonoscopy can be performed between Weeks 48 through 51.

† The first DBL will occur when all randomized participants have either completed the Week 48 assessments or terminated study participation prior to the Week 48 visit.

‡ The second DBL will occur when all participants have either completed their final safety visit or have terminated study participation.

* Crossover induction is 3 doses of CCI then CCI Participants will remain blinded to their treatment before recurrence through the end of the study. Subjects with confirmed endoscopic recurrence on the optional Week 24 colonoscopy may cross over to active treatment at the discretion of the PI. Subjects may not cross over after the Week 128 visit.

1.3. Schedule of Activities (SoA)

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Screening and Randomization																			
Informed consent	X																		
Medical history & baseline characteristics	X																		
IGRA	X																		Participants with a negative IGRA test result are eligible to continue with pre-randomization procedures. Participants with a newly identified positive IGRA test result must undergo an evaluation for active or latent TB, or suspected false-positive initial testing, and initiate appropriate treatment if needed (see Section 5.2).

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Chest imaging	X																		A historical chest radiograph or CT scan is acceptable if obtained within 3 months before the Week 0 visit. If unavailable, a chest radiograph must be done during the screening period.
HIV, HBV, HCV testing	X																		Refer to Exclusion criteria 5.2, 21, 22 for further details.
Serum pregnancy test	X																		Must be performed in female participants of childbearing potential.
Confirm Inclusion /Exclusion criteria	X	X																	Eligibility should be reconfirmed at Week 0 PRIOR to randomization.
Dispense CDAI electronic diary and train participants regarding completion	X																		Diary to record CDAI components and concomitant medications. Participant should complete the CDAI electronic diary daily throughout screening.
Randomization		X																	

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Directed physical exam at all visits, with additional full physical exam where noted (F)	X (F)	X	X	X	X	X	X	X	X	X	X	X	X	X	X (F)		X	X	Directed physical exam for abdominal mass and fistulas, (perianal and other) at all visits. Additional full physical exam, including height, where indicated.
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X	X	X	X	X				Only in females of childbearing potential. The Week 0 must be performed prior to randomization, to determine eligibility. At all other on-site visits, perform prior to dispensing study intervention.

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	At screening, the C-SSRS will be the first assessment performed, before any other study procedure. The C-SSRS should be completed after all PRO assessments and before any other tests, procedures, or other consultations to prevent influencing participant perceptions and prior to randomization at Week 0.
Vital signs	X	X			X			X							X		X	X	Includes temperature, pulse/heart rate, respiratory rate, and blood pressure.

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
TB evaluation / other infection assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If TB reactivation or new TB infection is suspected at any time during the study, study intervention must be withheld and an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Record all prescribed and OTC medications as specified in the eCRF, including initiation of any biologic therapy outside of that provided in this study.

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Adverse events are to be recorded beginning after the informed consent form is signed through the end of the study. After a participant's participation in the study has ended, adverse events should be followed as described in Section 8.5.
[redacted] site evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	An injection site reaction is any adverse reaction at an SC study intervention injection site. Injection sites will be evaluated for reactions and any injection site reaction will be recorded as an AE.

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Laboratory Evaluations																			
Hematology and chemistry, CRP	X	X	X	X	X	X	X	X	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. At Week 156, laboratory tests to be performed only if needed to follow up a prior abnormality.
Blood collection for serum guselkumab concentration and/or anti-drug antibodies [e]		X	X	X	X	X		X			X		X		X			X	Blood samples should be collected before the administration of study intervention. Record the actual times of PK sample collections.
Pharmacodynamics and Biomarkers (where local regulations permit)																			
Serum biomarkers		X			X			X			X				X			X	Serum biomarkers will be collected from all participants to assess peripheral proteins related to both Crohn's disease and response to guselkumab.

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Whole blood sample collection for RNA analysis		X			X			X			X								Whole blood for RNA analysis will be collected from all participants to assess the RNA transcriptome related to both Crohn's disease and response to guselkumab.
Ileocolonoscopy biopsy sample collections for exploratory RNA and biopsy-based single cell assessments					X			X							X		X		Refer to the biopsy manual for details on the biopsy sample collection. Biopsy sample at Week 24 is obtained only if optional Week 24 ileocolonoscopy is performed.

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Pharmacogenomics (DNA))																			
Genetic (DNA) evaluation (where local regulations permit)		X																Whole blood will be collected only from participants who consent to participate in the optional DNA analysis. The pharmacogenomic (DNA) sample should be collected at the specified time point; however, if necessary it may be collected later without constituting a protocol deviation.
Efficacy (clinical assessments/CD-related healthcare utilization/PROs)																			
Electronic daily diary by site staff		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	Remind participant to complete electronic daily diary for the length of the study. The daily diary includes patient-reported data for the CDAI (includes PRO-2 components).

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
CDAI assessments		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	For calculation of CDAI. The hematocrit value obtained during screening will be used to calculate CDAI at Week 0. For all other visits, the hematocrit value from the most recent study visit available will be used to calculate the CDAI.
Weight (component of CDAI)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	In kilograms (kg)
Fistula assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Video ileocolonoscopy with biopsy and histology					X[f]			X[f]							X [f]		X	X [f]	Week 24 procedure is optional, at the discretion of the investigator with agreement of the participant and should be performed ± 14 days from the scheduled visits. Week 48 procedure should be performed between Weeks 48 to Week 51. In the event procedure performed on the day of the designated visit or the 7 days prior, CDAI scores should be calculated using the proximate 7 days that were not impacted by the ileocolonoscopy or its preparation. Refer to the biopsy manual for details on the biopsy sample collection.
Stool sample (fecal calprotectin)	X	X			X		X	X		X			X		X		X		Week 0: Not required if sample already collected during screening is within 2 weeks of the Week 0 visit.

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Stool for enteric pathogens																	X		For Flare visits: Stool studies for enteric pathogens must include a stool culture and Clostridium difficile toxin assay. Additional testing, such as ova and parasites or Escherichia coli O157:H7 assessment, may be performed at the investigator's clinical discretion.
WPAI-CD		X	X		X			X		X			X		X			X	
PROMIS-29		X	X		X			X		X			X		X			X	
PROMIS Fatigue 7a		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	X	X	X	Items to be recorded are listed in the healthcare resource utilization worksheet.

Study Procedure	Screening Visit (within 5 weeks prior to Week 0)	Study visits (Week)[a]														Flare visit [a,c]	Early Termination visit [a,d]	Notes
		0	8	16	24	32	40	48	64	80	96	112	128	144 Final dose	152 Final efficacy	156 Final safety [b]			
Study Intervention Administration																		
Administer (or dispense) study intervention		X	X	X	X	X	X	X	X	X	X	X	X	X					At the discretion of the investigator and participant, and after appropriate and documented training, participants may self-administer study intervention at the investigative site or at home. A caregiver may also be trained to administer study intervention. Starting at Week 48 participants will be given study drug to self-administer the intervening dose (eg, Week 56, 72, 88, 104, 120, 136) dose at home.
Record drug accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	Participants will return study intervention packaging (boxes) when administered at home, for drug accountability, including any unadministered syringes.

a: Study visits should occur at the specified times post-Week 0 +/- 10 days. Note that while visits out of this window should be documented as a protocol deviation, performing them out of window is preferable to not performing them at all, unless so much time has passed that it is time for the next visit. All assessments described in this table are to be completed prior to study intervention administration, unless otherwise specified. PRO assessments should be completed first, then C-SSRS and then any other clinical procedures, tests, or consultations.

b: If clinically appropriate and allowed by local regulations, the Week 156 visit can be done by telephone and no labs drawn.

c: If a flare visit coincides with a scheduled visit, procedures for the scheduled visit should be performed, along with any additional procedures required by a flare visit. Flare visit blood tests are not required if performed within 2 weeks of the Flare visit.

d: Early termination visits should ideally take place approximately 12 weeks after last study intervention administration, though if a patient intends to withdraw their consent sooner than this milestone the ET visit should be scheduled as needed to accommodate with the patient's intent.

e: Blood collected from one venipuncture will be divided into multiple aliquots of serum for the measurement of guselkumab concentration, antibodies to guselkumab, and a back-up sample. Details will be provided in the Laboratory Manual.

f: Ileocolonoscopy does not need to be repeated if an ileocolonoscopy for a flare visit occurred within 12 weeks of the visit date, unless patient and investigator wish to, for example due to subsequent change in clinical status.

Key: AE = adverse event; CD = Crohn's disease; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; CT = computed tomography; C-SSRS = Columbia Suicide Severity Rating Scale; eCRF = electronic case report form; ET = Early Termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGRA = interferon gamma release assay; OTC = over the counter; PK = pharmacokinetics; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; CCI ; CCI ; TB = tuberculosis; WPAI = Work Productivity Activity Impairment.

Cross Over (CO) Schedule of Activities (Follow if participant meets cross over criteria)

Study Visits (Week) [a]									
Study Procedure	**CO[b]**	**CO+8 wks**	**CO+16 wks [c]**	**Every 16 wks (up to Week 128) [d]**	**Week 144 - Final Dosing Visit [e]**	**Week 152 - Final Efficacy Visit [f]**	**Week 156 -Final Safety Visit [g]**	**Early Termination Visit**	**Notes**
Directed physical exam, with full physical exam where noted (F)	X	X	X	X	X	X(F)		X	Directed physical exam for abdominal mass and fistulas at all visits.
Urine pregnancy test	X	X	X	X	X	X			Must be performed at on-site visits prior to dispensing study intervention in participants of childbearing potential.
C-SSRS	X	X	X	X	X	X	X	X	The C-SSRS should be completed after all PRO assessments and before any other tests, procedures, or other consultations to prevent influencing participant perceptions. The investigator or trained study site personnel will interview the participant and complete the C SSRS.
Vital signs	X					X		X	Includes temperature, pulse/heart rate, respiratory rate, and blood pressure, obtained prior to and approximately 30 minutes after the SC injection
TB evaluation / other infection assessment	X	X	X	X	X	X	X	X	If TB reactivation or new TB infection is suspected at any time during the study, study intervention must be withheld and an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.
Concomitant therapy	X	X	X	X	X	X	X	X	Record all prescribed and OTC medications as specified in the eCRF, including initiation of any biologic therapy outside of that provided in this study.
Adverse events	X	X	X	X	X	X	X	X	Adverse events are to be recorded beginning after the informed consent form is signed through the end of the study. After a participant's participation in the study has ended, adverse events should be followed as described in Section 8.5.

Study Visits (Week) [a]									
Study Procedure	**CO[b]**	**CO+8 wks**	**CO+16 wks [c]**	**Every 16 wks (up to Week 128) [d]**	**Week 144 - Final Dosing Visit [e]**	**Week 152 - Final Efficacy Visit [f]**	**Week 156 -Final Safety Visit [g]**	**Early Termination Visit**	**Notes**
Injection site evaluation	X	X	X	X	X		X	X	An injection site reaction is any adverse reaction at an SC study intervention injection site. Injection sites will be evaluated for reactions and any injection site reaction will be recorded as an AE.
Hematology and chemistry, CRP	X	X	X	X	X	X	X	X	
Blood collection for serum guselkumab concentration and/or anti-drug antibodies [h]	X		X	X		X		X	Blood samples should be collected before the administration of study intervention. Record the actual times of PK sample collections.
Serum biomarkers	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 including (but not limited to) IL-17A and IL-22.
Complete daily diary	X	X	X	X	X	X		X	Diary information should be completed daily for the length of the study. The daily diary includes patient-reported data for the CDAI (includes PRO-2 components).
CDAI assessment	X	X	X	X	X	X		X	For calculation of CDAI. CDAI: The hematocrit value obtained during screening 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 (component of CDAI)	X	X	X	X	X	X		X	In kilograms (kg)
Fistula assessment	X	X	X	X	X	X		X	

Study Visits (Week) [a]									
Study Procedure	**CO[b]**	**CO+8 wks**	**CO+16 wks [c]**	**Every 16 wks (up to Week 128) [d]**	**Week 144 - Final Dosing Visit [e]**	**Week 152 - Final Efficacy Visit [f]**	**Week 156 -Final Safety Visit [g]**	**Early Termination Visit**	**Notes**
Video ileocolonoscopy with biopsy and histology			X			X			XO+16 [OPTIONAL] May be performed between week 16 and 24. 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. Final efficacy visit ileocolonoscopy does not need to be repeated if the XO+16 ileocolonoscopy occurred within 24 weeks of the visit date
Stool sample (fecal calprotectin)	X		X			X			
WPAI-CD	X		X			X		X	
PROMIS-29	X		X			X		X	
PROMIS Fatigue 7a	X		X			X		X	
Crohn's disease-related hospitalizations and surgeries	X	X	X	X	X	X	X	X	Items to be recorded are listed in the healthcare resource utilization worksheet.
Administer (or dispense) study intervention [i]	X	X	X	X	X				All assessments described in this table are to be completed prior to study intervention administration, unless otherwise specified. PRO assessments should be completed first, and then any other clinical procedures, tests, or consultations. Cross over dosing: GUS 400 mg SC at CO, CO+4 (home dose), CO+8; and then CCI every 8 weeks (every other maintenance dose after the CO+16 visit will be home administration.
Record drug accountability	X	X	X	X	X			X	Participants will return study intervention packaging (cartons) when administered at home, for drug accountability, including any unadministered syringes.

Footnotes:

a: Study visits should occur at the specified times post-cross over +/- 10 days. Note that while visits out of this window should be documented as a protocol deviation, performing them out of window is preferable to not performing them at all. If sufficient time has passed that it is now in-window for the next subsequent visit, it is advised to contact the medical monitor for assistance in how to best manage the situation. All assessments described in this table are to be completed prior to study intervention administration, unless otherwise specified. PRO assessments should be completed first, then C-SSRS and then any other clinical procedures, tests, or consultations.

b: Laboratory assessments do not need to be performed if performed within 2 weeks prior to the CO visit

c: Approximately 16-24 weeks after cross over, it will be determined, based on investigator's judgement, whether treatment with open-label SC guselkumab should be continued or not. It is recommended to include an ileocolonoscopy in this assessment. If a decision is undertaken to discontinue further study agent in the course of this assessment, an early termination visit should subsequently be performed.

d: Additional follow up in cross over arm post Cross over Week 16 to occur every 16 weeks until the last dose of IP given.

e: The final dose of IP should be given at the Final Dosing Visit, which will fall between Week 137 and Week 144 from the original randomization date. The final dose of IP should not be given past Week 144 from the original randomization date.

f: The Final Efficacy Visit will occur 8 weeks after the Final Dosing Visit, between Week 145 and Week 152 from the original randomization date.

g: The Final Safety Visit should occur 4 weeks after the Final Efficacy Visit, between Week 149 and Week 156 from the original randomization date. If allowed by local regulations and if clinically appropriate, the Final Safety Visit can be done by telephone and no safety laboratory blood samples drawn.

h Blood collected from one venipuncture will be divided into multiple aliquots of serum for the measurement of guselkumab concentration, antibodies to guselkumab, and a back-up sample. Details will be provided in the Laboratory Manual.

i Participants who discontinue study drug should have early termination visit as per protocol.

Key: AE = adverse event; CD = Crohn's disease; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; CT = computed tomography; C-SSRS = Columbia Suicide Severity Rating Scale; eCRF = electronic case report form; ET = Early Termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGRA = interferon gamma release assay; OTC = over the counter; PK = pharmacokinetics; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; CCI [redacted]; TB = tuberculosis; WPAI = Work Productivity Activity Impairment.

2. INTRODUCTION

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1 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 the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, thus inhibiting IL-23 specific intracellular signaling and downstream activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

Guselkumab (CNTO1959, TREMFYA®) is currently approved for the treatment of adults with moderate-to-severe plaque psoriasis (in patients who are candidates for systemic therapy or phototherapy) and moderate-to-severe psoriatic arthritis, in the United States (US), European Union (EU), Canada, and several countries in Latin America and the Asia-Pacific region. Guselkumab has also been approved for the treatment of generalized pustular psoriasis, erythrodermic psoriasis, and palmoplantar pustulosis in Japan. In addition, guselkumab is being evaluated in both moderate to severe ulcerative colitis (UC) and Crohn's disease (CD), as well as in several other immune-mediated dermatologic and rheumatologic diseases globally.

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

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

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

2.1. Study Rationale

Crohn's disease (CD) is a chronic debilitating inflammatory disease of the digestive tract with a remitting and relapsing course. Despite the use of immunosuppressants and biologic therapies, approximately 26-47% of all patients with CD will require surgery within 10 years of diagnosis (Peyrin-Biroulet 2010, Frolkis 2013, Tsai 2021). Surgery is not a cure and disease recurrence after surgery is common.

Postoperative Crohn's disease (POCD) can affect all patients with CD regardless of their previous disease severity, and the two types of postoperative recurrences described in the literature - endoscopic recurrence and clinical recurrence - are common. Meta-analyses of placebo-controlled randomized clinical trials in POCD demonstrated that postoperative endoscopic recurrence occurs in 50-58% of placebo-treated patients within 52 weeks (Renna 2008, Pascua 2008). Clinical recurrence at 52 weeks after intestinal resection for CD has been demonstrated in 10-38% of placebo-treated patients in a pooled analysis of randomized controlled trials (Buisson 2012). In the PREVENT trial - the first, large, multicenter placebo-controlled POCD study with a biologic (infliximab) - the placebo clinical recurrence and placebo endoscopic recurrence rates at or before Week 76 were 20% and 60%, respectively (Reguiero 2016).

About 25% of patients with CD who undergo a first resection will need a second surgery within 5 years, and just over one-third will require a second resection within 10 years (Frolkis 2014). Prevention of POCD is paramount because of the morbidity associated with clinical relapse and repeated surgeries, including the risk of short-bowel syndrome.

Despite how common disease recurrence is in the postoperative population, there are no approved treatments for the prevention of POCD. Various pharmacologic interventions have been studied, including antibiotics, mesalamine, immunomodulators, and biologic medications. A network meta-analysis evaluating medical therapy for postoperative prophylaxis in CD suggested that antibiotics, immunomodulators and anti-tumor necrosis factor (TNF)α monotherapy were more effective than placebo in preventing endoscopic recurrence, whereas mesalamine and budesonide were not (Singh 2015). At the primary endpoint at Week 76 in the PREVENT trial, infliximab reduced endoscopic recurrence compared with placebo (30.6% versus 60.0%; absolute risk reduction with infliximab 29.4%; 95% confidence interval [CI]: 18.6%-40.2%; nominal p <0.001), but the reduction in clinical recurrence (the primary endpoint) with infliximab compared with placebo was not statistically significant (Regueiro 2016).

In summary, there is a high unmet need for effective treatment to prevent disease recurrence in patients after surgery. Since the PREVENT trial, there have been no large, randomized trials of newer biologic therapies for prevention of POCD including inhibitors of interleukin-23. The American Gastroenterology Association maintained that "the prevention of postoperative disease recurrence is a high priority given the morbidity associated with clinical and surgical recurrence and the long-term risk of short gut syndrome that may arise from multiple bowel resections" and emphasized the need to determine the role of newer classes of biologics for the prevention of POCD (Nguyen 2017). Likewise, in their recommendations for standardizing clinical trial design in POCD, an international consensus panel stated that "effective medical treatment for prevention of postoperative Crohn's disease is a substantial unmet need." (Hanzel 2021)

2.2. Background

2.2.1. Clinical Development of Guselkumab in Crohn's Disease

The ongoing clinical program for guselkumab in CD, CNTO1959CRD3001 (GALAXI; ClinicalTrials.gov Identifier: NCT03466411; hereafter referred to as CRD3001), is designed to evaluate the safety and efficacy of guselkumab compared with placebo and an active control (ustekinumab). The study is being conducted under a single seamless 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 CD who have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy.

Three studies are included in the CRD3001 protocol: The Phase 2 portion of CRD3001 is a 48-week, Phase 2, dose-ranging study of the efficacy of guselkumab with induction doses of CCI [redacted] administered CCI [redacted] at Weeks 0, 4, and 8, followed by CCI [redacted] doses of CCI [redacted] every CCI [redacted] or CCI [redacted]

CCI which also includes a long-term extension (LTE). The initial 48-week study has undergone database lock and continuing participants are currently in the LTE.

Within CRD3001 there are also 2 ongoing identical 48-week, Phase 3, confirmatory studies, with induction doses of CCI administered at Weeks 0, 4, and 8, followed by maintenance doses of CCI or CCI. Through Week 12, analyses are based on comparisons between each guselkumab group and placebo. The main comparison at Week 48 is guselkumab versus placebo as well, although after Week 12 placebo non-responders are permitted to cross over to receive active treatment. Ustekinumab was included as a reference arm through Week 12, and as an active comparator to guselkumab for the maintenance portion of the trial. Participants who complete the 48-week visit in either the Phase 2 or Phase 3 studies may be eligible to enter the LTE (Weeks 48 to 252) and receive approximately 4 additional years of treatment.

Induction results from the Phase 2 portion of CRD3001 showed that all 3 induction doses of guselkumab met the primary endpoint of change from baseline in Crohn's Disease Activity Index (CDAI) score at Week 12 (Sandborn 2022). No dose-response relationship was identified between the 3 induction doses of guselkumab, and the combined group produced a mean drop of 148-points from baseline CDAI, compared to a 36.2-point drop in the placebo group. Further, the 3 induction groups performed similarly in the major secondary endpoint of endoscopic response at Week 12 (defined by at least 50% improvement from baseline in Simple Endoscopic Score – Crohn's Disease (SES-CD) score or SES-CD score $\leq$2); in the combined guselkumab groups, 35.7% of participants achieved endoscopic response compared to 11.5% of participants in the placebo group.

At Week 12, all participants in the Phase 2 portion of CRD3001 who received guselkumab CCI induction continued on guselkumab CCI or CCI weeks, while placebo responders continued on placebo, placebo non-responders crossed over to active treatment with ustekinumab, and the ustekinumab arm continued CCI CCI dosing through Week 48. Clinical remission at maintenance Week 48 in the combined guselkumab groups was 64.9%, with the group receiving CCI dosing achieving a remission rate of 63.9%. In addition, 44.9% of the participants from the 3 guselkumab groups were in endoscopic response at Week 48.

Safety analysis from the Phase 2 portion of CRD3001 showed that rates for adverse events (AEs), serious adverse events, AEs leading to discontinuation, infections and serious infections were all comparable across treatment arms and overall, guselkumab was well tolerated.

In addition to the CRD3001 program, a single Phase 3 study (GRAVITI or CNTO1959CRD3004; hereafter referred to as CRD3004) is in progress that evaluates guselkumab SC induction for CD, employing a dose regimen of CCI at Weeks 0, 4, and 8.

More detailed information about the clinical development program of guselkumab may be found in the IB.

2.2.2. Rationale for the Use of Guselkumab in Postoperative Crohn's Disease

As reviewed in Section 2.2.1, the Phase 2 portion of the GALAXI trial suggested that guselkumab treatment was both safe and effective for induction and maintenance of remission is patients with moderate to severely active CD. Previously, the PREVENT study examined the proactive use of a biologic, safe and effective for moderate to severely active CD, in the post-operative population.

There are extensive learnings from the PREVENT study, in which 297 participants were randomized to 5 mg/kg of IV infliximab or placebo q8w. As mentioned above, while the primary endpoint of clinical recurrence before or at Week 76 did not meet statistical significance (20% in the placebo group, 12.9% in the infliximab group, p=0.097), the major secondary endpoint of endoscopic recurrence before or at Week 76 was strongly positive in favor of infliximab: 60.0% of the placebo group had an endoscopic recurrence versus 30.6% for the infliximab group (nominal p<0.001).

There are some aspects of guselkumab treatment which may be advantageous compared to infliximab treatment. For example, in PREVENT there was a difference in the persistence of infliximab compared to placebo. Considering that participants did not have active disease at baseline, the infliximab arm had a discontinuation rate of 37% (compared to 26% for placebo). In the infliximab arm, 22% had discontinuations specifically due to AEs (compared to 13% for placebo). These AEs included 9 patients (6.2% of the sample size) with infections (compared to 5 in the placebo group) and also 5 patients (3.4% of the sample size) with infusion-related reactions (compared to none in the placebo group). In comparison, the safety profile of guselkumab is expected to be better than that of infliximab, and to result in fewer discontinuations due to AEs.

While antibodies to infliximab and drug levels were only assessed at baseline and at Week 72 in PREVENT, it was clear that immunogenicity was common in the infliximab arm. Using a drug tolerant assay, 62% of participants in the infliximab arm were found to have anti-drug antibodies. While no therapeutic drug level has been defined for POCD to date, participants with antibodies had a median trough level of 0.58 µg/mL, which is far below what is considered a therapeutic level for moderate to severe CD. In contrast, participants without antibodies had a substantially higher median trough level of 4.63 µg/mL, comparable to the median Week 14 trough level of 4.0 µg/mL in ACCENT-1 which was associated with durable sustained response through Week 54 (Cornillie 2014). Accordingly, participants with antibodies to infliximab had an endoscopic recurrence rate (40%) of nearly twice that of infliximab participants without antibodies (21%) and a higher serum infliximab concentration was associated with a lower endoscopic recurrence. Similarly, of the participants randomized to infliximab who did not develop antibodies, none (0/39) had a clinical recurrence at Week 76 while 10.9% (6/55) of patients with antibodies to infliximab had a clinical recurrence.

In comparison, the incidence of antibodies to guselkumab in CD participants, as part of the Week 48 analysis of the Phase 2 portion of CRD3001, is lower, with an anti-drug antibody rate of 1.4% (3/215) through Week 48. In the larger experience with guselkumab in psoriasis, as described in the USPI, the anti-drug antibody rate is 6% through Week 52 among patients with plaque psoriasis

and 2% through Week 24 among patients with psoriatic arthritis. As described in the Investigator's sta for guselkumab, in pooled Phase 2 and Phase 3 analyses in patients with psoriasis and psoriatic arthritis, 5% (n=145) of patients treated with guselkumab developed antidrug antibodies in up to 52 weeks of treatment. In pooled Phase 3 analyses in patients with psoriasis, a population in which patients were not on immunomodulators, 15% of patients treated with guselkumab developed antibodies in up to 264 weeks exposure; however, only 5% of that group of patients had neutralizing antibodies, which equates to 0.76% of all patients treated with guselkumab.

Despite these limitations, infliximab did result in marked differences in rates of endoscopic recurrence compared with placebo, and had a numerical, but not significant, difference for preventing clinical recurrence. The use of guselkumab has additional potential advantages over that of infliximab as described above. From an administration perspective, guselkumab will be given SC which is generally better tolerated and preferred by patients. Finally, IL-23 blockade may have fewer safety concerns overall compared to traditional TNF inhibition. These analyses of the PREVENT trial and the Phase 2 safety and efficacy data from CRD3001 suggest that guselkumab may be an effective and safe agent for the prevention of POCD.

In the ten years that have passed since the PREVENT trial, endoscopic recurrence has been adopted as the standard endoscopic outcome in many trials of POCD therapy (Rutgeerts 1990, Ewe 1999, Hellers 1999, Lochs 2000, Hanauer 2004, Rutgeerts 2005, Marteau 2006, D'Haens 2008, Reguiero 2016) and these trials demonstrate that endoscopic recurrence in POCD patients is more common than clinical recurrence at the same timepoint, and may be a more objective endpoint than symptoms. With this increase in importance in endoscopic outcomes has come the more common utilization of them as primary or co-primary endpoints in pivotal trials, including that of guselkumab.

Recently, an international group of 19 widely-published experts on the management of POCD (Hanzel 2021) made recommendations regarding clinical trial design. This group, which included experts from the United States as well as Australia, Belgium, Canada, Germany, the Netherlands and Slovenia, found it appropriate to use endoscopic recurrence as the sole primary end point (as opposed to using clinical recurrence or having co-primary end points). This recommendation was based primarily on several advantages of an endoscopic end point, including its association with subsequent clinical recurrence and its objective nature, which is further magnified by the availability of central reading. Among the different endoscopic scoring systems available, the group recommended the modified Rutgeerts score as the most appropriate, a similar recommendation to that of the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) 5 years earlier (Vuitton 2016). In addition, they favored a placebo-controlled trial with one year as appropriate follow up for the primary end point.

While the scientific communities have continued to focus on endoscopic outcomes as a primary endpoint, it is critical to also ensure a clinically meaningful benefit to patients. Clinical remission without disease recurrence is a composite major secondary endpoint that can be assessed for at the 6-month time point and will take both clinical as well as endoscopic data into account using CDAI as well as other clinical features in addition to endoscopic data. This can allow for an outcome that

can capture the importance of clinical remission while providing an opportunity to ensure endoscopic remission at the same time.

2.3. Benefit-risk Assessment

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

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Risks Due to Study Intervention(s)		
Clinical Worsening of CD	The benefit-risk of guselkumab for the treatment of CD patients who have had recent ileal or ileocolonic resection has not been established.	• During the study, participants will be permitted to continue treatment of CD with certain concomitant medications (Section 6.8.1), including corticosteroids (Section 6.8.1.1). • Participants will discontinue study intervention if it is not in their best interest or if they need to initiate protocol prohibited medications including certain biologics (Sections 6.8.2 and 7.1). • Participants with confirmed disease recurrence, endoscopic recurrence prior to or at Week 48, or, at the investigator's discretion, with endoscopic recurrence at Week 24, will receive open-label induction treatment with guselkumab and continue maintenance treatment (Section 6.5.1).
Serious infections and reactivation of latent infections	Available animal and human data suggest that blockade of IL-23 may be associated with an increased infection risk. Infections that have been identified as adverse reactions to guselkumab are listed in the informed consent form.	• Discontinuation of a participant's study intervention must be considered if the participant develops a serious infection. In addition, any serious infection should be discussed with the Medical Monitor or designee, and study intervention should be withheld until the clinical assessment is complete (Section 8.4.8). • Potential overlap period between prior advanced therapies and study therapy is brief (Section 5.1). • Participants with a history of, or ongoing chronic or recurrent infectious disease, including human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C virus (HCV) will be excluded. Similarly, participants with evidence of active or untreated latent TB will be excluded from the study (Section 5.2).

		• Participants who have received a live viral or bacterial vaccine within 12 weeks of baseline will be excluded from the study (Section 5.2). In addition, participants must agree not to receive a live viral or live bacterial vaccine during the study and for 12 weeks after receiving the last dose of study intervention (Section 5.3).
Hypersensitivity reactions, including serious hypersensitivity reactions and anaphylaxis.	Serious hypersensitivity reactions including anaphylaxis have been reported in postmarketing experience with guselkumab	• Participants with known allergy, hypersensitivity, or intolerance to guselkumab will be excluded from the study (Section 5.2). • All participants must be alert for or, when on site, observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, itching, hives) (Section 8.4.7). • Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1).
Malignancy	The preponderance of preclinical data suggests that blockade of endogenous IL-23 would not be detrimental and may in fact be beneficial in tumor immunosurveillance and host protection; however, a risk of malignancy cannot be excluded.	• Those participants who currently have a malignancy or have a history of malignancy within 5 years prior to screening (with exceptions noted in Section 5.2) will be excluded from the study. • Additionally, participants who have a history of lymphoproliferative disease, including lymphoma, a history of monoclonal gammopathy of undetermined significance or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly will be excluded from the study (Section 5.2). • During the conduct of the study, participants will undergo regular clinical monitoring including routine safety laboratory assessments to evaluate any changes in health status that may indicate a possible malignancy. • Participants who develop a malignancy during the study (with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from study intervention (Section 7.1).
Liver injury	An SAE of 'toxic hepatitis' was reported in a participant in the ongoing Phase 2/3 guselkumab CD who received guselkumab [redacted] at Weeks 0, 4, and 8, and [redacted] at Week 12. This event may represent drug induced liver injury	• During the conduct of the study, liver function tests will be monitored at regular intervals in accordance with regulatory guidance (FDA 2009). In addition, the induction doses evaluated in this clinical program will not exceed [redacted]

	(DILI) possibly related to guselkumab (see Section 5.15.3 in the IB). Transaminase increases have been identified as an adverse reaction of guselkumab. In 2 Phase 3 psoriatic arthritis studies, increased ALT and/or AST was observed more frequently in participants treated with guselkumab [redacted] compared to participants treated with guselkumab [redacted] or placebo.	(systemic exposure comparable to guselkumab [redacted] • Participants with marked liver enzyme elevations or symptoms or signs of liver dysfunction (eg, jaundice), should undergo a thorough investigation for possible causes of liver injury (Appendix 7, Section 10.7). A participant must have their study intervention discontinued if the participant has severe liver test abnormalities that are not transient and are not explained by other etiologies (Section 7.1).
Immunosuppression	It is unknown if guselkumab in combination with other immunosuppressives, including short period of overlap between prior biologics that are washing out at the beginning of study, increases the risk of diseases associated with immunosuppression, such as infections or malignancy.	• In order to minimize the theoretical increased risk of infection or malignancy with the combination of guselkumab with immunosuppressive therapy, the baseline dose of oral corticosteroids on study entry is limited to ≤20 mg prednisone or its equivalent per day, or 9 mg/day of budesonide, or 5 mg/day beclomethasone. Participants who enter the study on steroids should initiate, or continue, tapering of corticosteroids for CD without any delay upon study entry at Week 0, unless medically inappropriate. Furthermore, per protocol, participants receiving AZA, 6 MP, or MTX, must discontinue them prior to randomization. Additionally, participants are also excluded from the study if they have received approved biologics for CD, including anti-TNFα therapy (eg, infliximab, etanercept, certolizumab pegol, adalimumab, golimumab), natalizumab, vedolizumab, ustekinumab, or rizankizumab within 6 weeks of baseline, unless the participant has an available drug level of ≤ 1 mcg/mL. Participants are also excluded if they have received cyclosporine, tacrolimus, sirolimus, 6-thioguanine, or mycophenolate mofetil within 4 weeks of baseline or approved or investigational small molecules for IBD (eg, JAK inhibitors [eg, tofacitinib, upadacitinib] or S1P inhibitors [eg, ozanimod] within 4 weeks prior to baseline, or 5 half-lives, whichever is longer). Further detail regarding concomitant medications is provided in Sections 5.1 and 5.2. • During study participation, the use of immunomodulators other than AZA, 6-MP, and MTX (eg, cyclosporine) as well as biologic immunomodulators (eg, TNFα antagonists, vedolizumab) is prohibited.

		Participants initiating these treatments will be discontinued from further study intervention administration (see Section 6.8.2 for further details on prohibited concomitant medications).
Risks Due to Study Procedures		
Risks associated with video ileocolonoscopy including bleeding or intestinal perforation.	These risks are well recognized, but rare. (Arora 2009; Rabeneck 2008)	Trained and experienced endoscopists will be performing the procedure during this study.
Radiation	A chest X-ray will be performed at screening if the participant does not have a chest X-ray or chest CT within 3 months prior to the first administration of study intervention. The exposure from 1 standard chest X-ray is 0.1 mSV, comparable to 10 days of exposure to natural background radiation (Acr.org).	Exposure to radiation through radiographs is kept to a minimum by not requiring a chest Xray be performed at screening if a chest Xray or chest CT is available from within 3 months prior to the first administration of study intervention.

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; AZA = azathioprine; CD = Crohn's disease; CT = computed tomography; HBC = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IBD = inflammatory bowel disease; MP = mercaptopurine; MTX = methotrexate; SC = subcutaneous; TNF = tumor necrosis factor

2.3.2. Benefits for Study Participation

There is no established benefit to participants who will be receiving study intervention with guselkumab. However, given the data from clinical studies of IL-23 antagonists in CD, participants in the study may experience prevention of recurrence of CD postoperatively. The frequent visits and medical care to be provided during the course of this study can also lead to improved disease control. Participants in the study will also contribute to furthering development of this therapy to prevent POCD.

2.3.3. Benefit-risk Assessment for Study Participation

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

Potential risks of guselkumab, including those of infections including serious infections, malignancy, hypersensitivity reactions, and liver injury are being addressed via judicious inclusion/exclusion criteria, frequent study visits to allow for close monitoring of patient safety, guidelines for participant management (including monitoring of clinical laboratory tests and treatment discontinuation criteria), detailed description of allowed and prohibited concomitant medications, and comprehensive medical monitoring of data by the Sponsor/designee during the conduct of the studies.

The underlying risk of postoperative recurrence of CD must be considered, such as poor quality of life, malnutrition, and intestinal strictures or bowel perforations and abscesses that require surgical intervention. Multiple mitigation measures are in place, including full-dose induction and

maintenance treatment of those with confirmed disease recurrence from either the placebo group or the treatment group.

Taking into account the measures taken to minimize risk to participants of this study and the known complications of POCD, the potential risks identified in association with guselkumab are justified by the anticipated benefits that may be afforded to participants who have had surgery for their CD.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of guselkumab treatment versus placebo in preventing endoscopic recurrence of CD in participants after surgery	• Endoscopic recurrence prior to or at Week 48 (as defined by modified Rutgeerts score ≥ i2a in the neo-terminal ileum, anastomotic site, or its equivalent elsewhere in the gastrointestinal (GI) tract [eg colonic ulceration])
Secondary	
• To evaluate clinical remission without disease recurrence in participants treated with guselkumab versus placebo after surgery	• Clinical remission (CDAI < 150) without disease recurrence at Week 48 (as defined in Section 9.4.3)
• To evaluate disease recurrence in participants treated with guselkumab versus placebo after surgery	• Time-to-disease recurrence (as defined by CDAI/event driven criteria as described in Section 9.4.3) at the main study database lock, which will incorporate all available follow-up of enrolled participants at the time that the last participant dosed has completed the Week 48 study procedures, including the ileocolonoscopy
• To evaluate symptoms such as stool frequency and abdominal pain scores in guselkumab versus placebo after surgery	• Abdominal pain free (abdominal pain [AP] score = 0) at Week 48 • Time-to-recurrence of symptoms, defined as time to attaining an AP mean daily score >1 (and also >1 point higher than baseline) along with stool frequency (SF) mean daily score >3 (and also >3 higher per day than baseline) for 2 consecutive weeks through Week 48
• To evaluate the safety and PK of guselkumab in participants with CD in the postoperative period	• Frequency and type of AEs and serious adverse events (SAEs) • Describe serum guselkumab concentrations over time
• The evaluate the efficacy of guselkumab in limiting steroid use and maintaining remission in the postoperative period	• Steroid free clinical remission at Week 48, defined as CDAI <150 and no corticosteroids within 30 days

Objectives	Endpoints
Other	
• To evaluate fatigue and other patient reported outcomes in guselkumab versus placebo after surgery	• Change in Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue Short Form 7a score over 48 weeks • Change in PROMIS-Fatigue SF 7a at each post baseline visit through Week 152 • Change in PROMIS-29 score, both overall score and individual domain scores at each post baseline visit through Week 152 • Change from baseline in the WPAI at each post baseline visit through Week 152 • Abdominal pain (AP score = 0) at each post baseline visit through Week 152
• To evaluate steroid use and healthcare utilization in participants within the postoperative period	• The number of participants not on corticosteroids and without disease recurrence at each post baseline visit through Week 152 • The number of participants not on corticosteroids and who have not experienced endoscopic or disease recurrence at each post baseline visit through Week 152
• To evaluate histologic status in CD patients after surgery	• Histologic score (as measured by Geboes scale/RHI/GHAS) at Week 48 ileocolonoscopy • The number of participants with Geboes score of 2.0 or less at Week 48 ileocolonoscopy • The number of participants with Geboes score over 3.1 at Week 48 ileocolonoscopy
• To evaluate the efficacy and safety of open-label guselkumab SC induction and maintenance treatment in the cross over population after postoperative endoscopic or disease recurrence of CD has occurred	• Clinical remission (CDAI < 150) at 24 weeks after initiation of guselkumab SC induction • Clinical response (CDAI decrease of <100 points or CDAI <150) at 24 weeks after initiation of guselkumab SC induction • Endoscopic remission (SES-CD of 3 or less) at 24 weeks after guselkumab SC induction • Endoscopic remission (modified Rutgeerts score <i2a) at 24 weeks after guselkumab SC induction
• To evaluate the efficacy of guselkumab treatment versus placebo in changes to inflammatory biomarkers after surgery	• The change from baseline in CRP concentration at all postbaseline visits through Week 152 • The change from baseline in fecal calprotectin concentration at all postbaseline visits through Week 152

Objectives	Endpoints
	• Fecal calprotectin recurrence, defined by calprotectin of >200 µg/g with a 100 µg/g increase over baseline
• To evaluate the clinical efficacy of guselkumab treatment	• Disease recurrence (using CDAI/Event-driven definition as described in Section 9.4.3) at Week 152 • Clinical remission (CDAI <150) at each post baseline visit • Time to a flare of abdominal pain
• To evaluate the endoscopic efficacy of guselkumab treatment	• Endoscopic remission (SES-CD of 3 or less) at Week 24, Week 48, Week 152 • Endoscopic recurrence (modified Rutgeerts score >i2a) at Week 24, Week 152

Key: AE = adverse event; AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's disease activity index; CRP = C-reactive protein; GI = gastrointestinal; PROMIS = Patient-Reported Outcomes Measurement Information System; SC = subcutaneous; SAE = serious adverse event; SES-CD = Simple Endoscopic Score - Crohn's disease; SF = stool frequency

ESTIMANDS

Estimands are discussed in Section 9.

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

HYPOTHESIS

It is hypothesized that guselkumab, when initiated after recent ileocolonic surgical resection for CD, is superior to placebo in preventing postoperative recurrence of CD, as measured by endoscopic recurrence prior to or at Week 48.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, multicenter, randomized, placebo-controlled, prospective double-blind study designed to evaluate the efficacy and safety of SC guselkumab in reducing the recurrence of CD in adult patients who have recently undergone a surgical resection for CD. A diagram of the study design is provided in Section 1.2, Schema.

A target of approximately 370 participants will be enrolled from approximately 150 sites. The target population consists of participants with CD who have undergone a recent (≤49 days) ileocolonic resection with ileocolonic anastomosis for CD, without evidence of active disease postoperatively. Participants must not have had their qualifying surgery for the purpose of resecting known dysplasia.

Participants will have a baseline CDAI <200 and will be eligible regardless of prior biologic use. Participants who are low risk for recurrent CD (ie, participants whose qualifying surgery was their

first in >10 years since their diagnosis of CD and was performed for fibrostenotic stricturing disease involving <10 cm of the intestine) will be excluded. Participants must be able to undergo randomization no later than 49 days after surgery. For a full list of entry criteria, refer to Section 5.1.

Randomization will occur in a 1:1 ratio with participants receiving either:

- **Arm 1 (Guselkumab):** Guselkumab [redacted] at Week 0 and then [redacted] at Week 8, then [redacted] thereafter through the end of the total study period.
- **Arm 2 (Placebo):** Matched placebo [redacted] at Week 0 and then [redacted] thereafter through the end of the total study period.

Randomization will be stratified by clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery).

A Week 48 video ileocolonoscopy will be performed between Weeks 48 and 51 and participants with endoscopic recurrence confirmed by a central reader will cross over to open-label treatment with guselkumab SC induction. An optional video ileocolonoscopy can be performed at Week 24 and optional cross over may occur at the discretion of the principal investigator if there is only endoscopic recurrence without disease recurrence (defined in Section 9.4.3). If participants meet criteria for disease recurrence after Week 8 they will also cross over to open-label treatment.

Participants who discontinue study intervention early will return for an early termination visit at least 12 weeks after study intervention discontinuation, which will also serve as their final safety visit. This visit will include a video ileocolonoscopy at the time of discontinuation, except those participants who have already had demonstrated endoscopic recurrence in a study ileocolonoscopy.

Study Length

After the screening period, the total study duration is 156 weeks, with the final dose of study intervention given at Week 144 and the final efficacy visit at Week 152 followed by the final safety visit at Week 156. The end of the study is defined as when all participants have completed the Week 156 visit assessments, or have terminated study participation prior to Week 156 and had their last follow-up assessment (12 weeks after the last dose of study intervention or at early termination visit).

The main study period is defined as when the last randomized participant has completed the Week 48 assessments at which point the main study database lock will occur. Participant follow-up for the main study period may vary depending upon when they enrolled in the trial (estimated to be from 12 to 30 months, based upon an anticipated accrual time of 18 months, but with an upper limit of 36 months [total study treatment duration], should accrual time exceed 18 months).

Endpoints

The primary endpoint is endoscopic recurrence prior to or at Week 48. Video ileocolonoscopy will be performed at the Week 48 visit and centrally read, using a definition of a modified Rutgeerts score of ≥ i2a disease activity to define endoscopic recurrence.

The first secondary endpoint of clinical remission without disease recurrence at Week 48 is defined in Section 9.4.3. Disease recurrence is a composite endpoint defined by a ≥70-point increase in baseline CDAI and a CDAI of ≥200 and evidence of endoscopic recurrence; OR other disease recurrence-defining events as described in Section 9.4.3. The second secondary endpoint of disease recurrence is defined in Section 9.4.3 and will be a time-to-event analysis incorporating all follow-up available for all participants at the time of the main study database lock (from last randomized participant completing Week 48 though data beyond Week 48, where available) specifically including all events of disease recurrence that have occurred through the full follow-up available at the time of the main study database lock. Thus, for this endpoint, participant follow-up may vary depending upon when they enrolled in the trial (estimated to be from 12 to 30 months, based upon an anticipated accrual time of 18 months, but with an upper limit of 36 months [total study treatment duration], should accrual time exceed 18 months).

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Database Locks and Maintenance of the Blind

The first database lock (DBL) is the main study DBL. It will occur when all participants have completed the Week 48 visit assessments, or have terminated study participation prior to Week 48, and will include all assessments performed as of that date (even those beyond Week 48). The final DBL will occur after the last participant completes the final safety visit at Week 156. Additional DBLs may be added between Weeks 48 and 156, as warranted.

The study blind will be maintained for the investigative sites, site monitors, and study participants until after the final participant has completed their Week 156 visit. In the event of an emergency, the investigator may also unblind a participant's treatment if such knowledge would change the participants' clinical care. The sponsor will remain blinded to the original treatment assignments until after the main study DBL has occurred.

RNA and Biomarker Collection

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 and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect RNA to allow the identification of genetic factors that may influence the efficacy, safety, or tolerability of guselkumab and to identify genetic factors associated with Crohn's disease.

Biomarker samples will be collected to evaluate the mechanism of action of guselkumab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the pharmacodynamics of guselkumab and aid in evaluating the intervention-clinical response relationship.

Medical Resource Utilization and Health Economics Data Collection

Treatment of POCD with guselkumab versus placebo may result in lower utilization of CD-related emergency department visits, hospitalizations, and surgeries; therefore, comparison will be done across intervention groups.

4.2.1. Participant Input Into Design

Input into the study design was obtained from a patient engagement research council which was formed to integrate the voice of inflammatory bowel disease (IBD) patients into study development, execution, and dissemination. Participant insights that informed study design include the importance of including Patient Reported Outcomes (PROs) as endpoints and insights regarding patient perceptions of receiving a biologic postoperatively.

The results of the study may be made available to all participants through a plain language summary, a technical summary of results on clinicaltrials.gov and/or clinicaltrialsregister.eu and/or other national registries at the conclusion of the study according to local standards/restrictions.

4.2.2. Study-specific Ethical Design Considerations

Potential participants and/or their legally acceptable representative will be fully informed of the risks and requirements of the study and, during the study, participants and/or their legally acceptable representative will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Written consent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

One ethical concern is that one half of the participants in the study will be randomized to placebo. Currently, there are no treatments with Food and Drug Administration (FDA) or European Medicines Agency (EMA) approval for the indication of reducing the risk of recurrent CD after surgical resection, and it is important to be able to have a placebo comparison in order to establish whether there is meaningful benefit from the study intervention. The use of placebo is also justified because the study population consists of participants with inactive CD at baseline, and participants will be crossed over to active treatment as soon as they meet the criteria for disease recurrence (see Section 9.4.3). A placebo-controlled design minimizes subject and investigator bias in evaluating the efficacy and safety of guselkumab in the selected patient population (FDA Guidance for Industry E10). Additionally, in their recommendations for clinical trial design in postoperative CD, a recent international panel of 19 international expert IBD specialist gastroenterologists recommended that in regulatory trials assessing the effectiveness of a therapy for prevention of postoperative CD recurrence, participants in the control arm should receive placebo (Hanzel 2021).

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross for whole blood donation (approximately 475 mL q8w) as well the allowable blood sample volumes described in the EU guideline on clinical trials conducted with minors (EU 2017).

4.3. Justification for Dose

As reviewed above, in the Phase 2/3 moderate-to-severely active CD (ie, participants must have a baseline CDAI of 220 to 450) CRD3001 studies, participants are receiving IV induction doses at Weeks 0, 4 and 8 (CCI and 2 maintenances doses are being studied, CCI and CCI CCI. In the CRD3004 study, 3 induction doses of CCI at Weeks 0, 4, and 8 are being examined, followed by maintenance doses of either CCI or CCI.

The participant population in the current study is distinct in that they will not have moderate-to-severely active CD (eg, baseline CDAI will be < 200) and will have had the source of disease activity removed as a result of their recent surgery. Therefore, it is hypothesized that full induction dosing is not necessary . Nevertheless, it has been shown that some patients continue to have some lingering mildly elevated fecal calprotectin for up to 3 months postoperatively (Boube 2020), as well as an elevated CRP post-operatively (Iaculli 2016), which may be associated with somewhat higher drug clearance in patients with CD (Boyle 2017, Grinman 2020). Accordingly, in this study, participants will receive a CCI loading dose at Week 0 followed by CCI. The CCI loading dose at Week 0 is considered appropriate in this setting because it will result in higher initial concentrations in comparison to the eventual steady-state concentration from the CCI regimen.

While not specifically powered to detect a difference between maintenance doses, results from the Phase 2 portion of the GALAXI trial did not appear to show a dose response relationship in the doses studied. For example, the clinical remission rate at Week 48 was similar in the highest dose (CCI followed by CCI) to the remission rate of the lowest tested dose (CCI followed by CCI) at 57.4% and 63.9% respectively. Of note, the

proposed maintenance dose of this study, CCI [redacted], is the same as the currently approved regimen for guselkumab for the treatment of moderate-to-severe plaque psoriasis. Since psoriasis is a chronic immune mediated disease requiring long-term therapy to maintain disease control, the 2 pivotal Phase 3 studies (CNTO1959PSO3001 and CNTO1959PSO3002) included long-term extensions through a total of up to 5 years. The analyses of pooled data support the conclusion that guselkumab is well tolerated through 5 years of treatment, and the safety profile remains consistent when compared to Week 48 data, at the approved dose regimen of CCI [redacted] administered CC [redacted] at Weeks 0, 4, and then CCI [redacted] in adult participants with moderate to severe plaque psoriasis.

When infliximab was previously studied in this patient population in the PREVENT trial, the standard induction dosing of 5 mg/kg at Weeks 0, 2, and 6 was also not utilized. Instead, participants were immediately started on the 5 mg/kg IV q8w established maintenance regimen. While this study did not show significance for clinical recurrence at the Week 76 primary endpoint, it showed clear separation in rates of endoscopic recurrence versus placebo and in the time-to-event analysis for clinical recurrence, with the greatest separation seen in the first 6 months, supporting that it is appropriate to forgo a full induction regimen in this patient population.

In the event a participant experiences confirmed disease recurrence, endoscopic recurrence at Week 48, or, at the investigator's discretion for endoscopic recurrence at the optional Week 24 ileocolonoscopy, they will cross over to receive open-label treatment with guselkumab using the regimen under study for moderately-severely active CD in the ongoing Phase 3 study CNTO1959CRD3004. As these patients will, per protocol, have a CDAI that is ≥220 (or at a minimum is very close, at 201-219) and/or confirmed endoscopic activity, giving induction dosing of CCI [redacted] for 3 doses is appropriate to treat this level of ongoing inflammatory and disease activity from CD that has recurred such that it is now in the moderately-to-severely active category.

4.4. End of Study Definition

The end of study is considered as the Week 156 visit for the last participant in the study. The final data from the study site will be provided to the sponsor (or designee) after completion of the final participant Week 156 assessments at that study site, in the time frame specified in the Clinical Trial Agreement.

Participant Study Completion Definition

A participant will be considered to have completed the study if the participant has completed assessments at the Week 156 visit (including participants who crossed over).

Participants who prematurely discontinue study intervention for any reason before completion of the Week 144 study intervention administration can be considered to have completed the study if they have completed an early termination visit which should occur approximately 12 weeks after the last dose of study agent. This scenario includes participants who crossed over to open-label treatment and subsequently did not respond, precluding further continuation in the study.

5. STUDY POPULATION

Screening for eligible participants will be performed within 5 weeks before administration of the study intervention.

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

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

The target population is male or female participants (minimum age 18) with a diagnosis of CD who have a qualifying surgery (eg, ileocolonic resection) a maximum of 49 days before randomization. Participants will be excluded if they have a short segment of bowel affected (ie, less than 10 cm) for fibrostenotic disease and they had their first surgery more than 10 years after diagnosis of CD. There is no requirement that participants have failed prior biologics.

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristic

2. Have a documented diagnosis of CD confirmed by endoscopic, histologic, and/or radiologic studies prior to resection or by tissue obtained at resection.

3. Have undergone an ileocolonic surgical resection (ie, an intestinal resection with an ileocolonic anastomosis) for CD prior to the baseline visit with the following criteria:

    - Have no known active CD anywhere in the gastrointestinal (GI) tract, including the findings at surgery,
    - Be able to undergo randomization no later than 49 days after surgery, and at least 10 days after surgery (or 8 days after resumption of bowel activity, eg, in case of postoperative ileus),
    - Ileocolonic resection was not for the purpose of removing known dysplasia,
    - If ileocolonic resection occurs > 10 years since the diagnosis of CD and only fibrostenotic stricturing is present, then length of stricture must be > 10 cm

4. Have a baseline CDAI < 200.

Concomitant or previous medical therapies received

5. Meets the following requirements for prior or current medications for CD. The following medications are permitted provided that doses meeting the requirements listed below are stable or have been discontinued within the timeframes prior to baseline specified below:

   - Oral corticosteroids at a prednisone-equivalent dose at or below 20 mg/day, or 9 mg/day of budesonide. Participants on corticosteroids should initiate/continue tapering after baseline, per the recommended schedule (see Section 6.8.1.1).

   - Conventional immunomodulators (ie, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) must be discontinued prior to randomization.

Screening Laboratory Tests

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

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

   b. White blood cells $\geq 3.0 \times 10^3/\mu L$ (SI: $\geq 3.0 \times 10^9/L$)

   c. Neutrophils $\geq 1.5 \times 10^3/\mu L$ (SI: $\geq 1.5 \times 10^9/L$)

   d. Platelets $\geq 100 \times 10^3/\mu L$ (SI: $\geq 100 \times 10^9/L$)

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

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

   g. Total bilirubin ≤1.5 × ULN (isolated bilirubin ≥1.5 × ULN is allowed for those participants with known Gilbert's syndrome).

Sex and Contraceptive/Barrier Requirements

7. Male or female (according to their reproductive organs and functions assigned by chromosomal complement), to guide the criteria below.

8. A woman of childbearing potential must have a negative highly sensitive serum (beta human chorionic gonadotropin [B-hCG]) test result during screening and a negative urine pregnancy test at week 0, prior to randomization.

9. Before randomization, a woman must be

    a. Not of childbearing potential

    b. Of childbearing potential and

        i. If heterosexually active, practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 12 weeks after last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention; 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.

10. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 12 weeks after the last administration of study intervention.

11. During the study and for at least 12 weeks after the last administration of study intervention, a male participant:

    - Who is sexually active with a female of childbearing potential must agree to use a barrier method of contraception (ie, condom with spermicidal foam/gel/film/cream/suppository or female condom/occlusive cap [diaphragm or cervical/vault caps] with spermicidal foal/gel/film/cream/suppository).

    - Who is sexually active with a pregnant female must use a condom.

    - Must agree not to donate sperm for the purpose of reproduction or plan to father a child.

Informed Consent

12. Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

13. Be willing and able to adhere to all specified requirements in this protocol, including but not limited to completion of assessments (which includes an ileocolonoscopy at one year

or upon concern for clinical flare), adherence to visit schedule, multiple blood draws, and compliance with the lifestyle restrictions.

5.2. Exclusion Criteria

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

Medical Conditions

1. Has complications of CD, such as symptomatic strictures or stenoses, short bowel syndrome, a draining (ie, functioning) stoma or ostomy, 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.

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.

3. Have had any active perianal disease within 3 months of screening (except skin tags) or have had any draining fistula within 3 months of screening unless the fistula was removed at the index surgery.

4. Had, in association with their most recent intra-abdominal surgery, postoperative complications such as, but not limited to, postoperative intraabdominal abscess, wound dehiscence, anastomotic leak, the need for a second operation, or have evidence of macroscopically active CD which was not resected at the time of surgery or had active CD in regions beyond the site of surgery in the GI tract within 1 year of the time of enrollment.

5. Evidence of a herpes zoster infection within 8 weeks before the first dose of study intervention.

6. Meet **ANY** of the following TB screening criteria:

   Note: Interferon gamma release assay (IGRA) testing includes either QuantiFERON-TB® or T-SPOT® TB.

   a. Have a history of active TB or show signs or symptoms suggestive of active TB upon medical history and/or physical examination at screening.

   b. Have a history of untreated latent TB prior to screening. An exception is made for participants who are currently receiving treatment or will initiate treatment for latent TB prior to first administration of study intervention.
   Note: For participants with a history of treated latent TB there must be documentation of appropriate treatment prior to the first administration of

study intervention. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation. IGRA testing is not required at screening for participants with a history of treated latent TB or ongoing treatment for latent TB.

c. Have had recent close contact with a person with active TB. An exception is made if such participants are referred to a physician specializing in TB to determine if treatment is warranted or not. This evaluation must be adequately documented and, if treatment is recommended, the participant must be receiving appropriate treatment prior to the first administration of study intervention.

d. Have a positive IGRA test result within 2 months prior to the first administration of study intervention. An exception is made for participants who:

- have a history of adequately treated latent TB described above.
- have a newly identified positive IGRA test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study intervention.
- have a false-positive IGRA test as determined by the following:
    - A suspected false-positive initial IGRA test must be repeated. If repeat testing is **NOT** positive, the participant must be referred to a physician specializing in TB to determine if the initial test can be considered a false-positive. This evaluation must be adequately documented prior to the first 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.

e. Have a chest radiograph or chest computed tomography within 3 months prior to the first administration of study intervention that shows abnormalities suggestive of active or inactive TB.

7. Has or has had any other clinically significant infection (eg, hepatitis, sepsis, pneumonia, or pyelonephritis, enteric infection), within 8 weeks before the first dose of study intervention. Treated and resolved infections, not considered clinically significant at the discretion of the investigator need not be exclusionary (ie, acute upper respiratory tract infection, uncomplicated urinary tract infection, and clinically resolved infections related to the participant's Crohn's-related surgical resection).

8. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, sinopulmonary infections, bronchiectasis, recurrent renal/urinary tract infections (eg, pyelonephritis, cystitis), latent or active granulomatous infection (including histoplasmosis or coccidioidomycosis), an open, draining, or infected skin wound, or an ulcer, or active enteric infections (eg, Clostridium difficile that is untreated and unresolved, without subsequent negative testing). Has current signs or symptoms

of a clinically significant infection. Ongoing infections not considered clinically significant at the discretion of the investigator need not be exclusionary (ie, acute upper respiratory tract infection, uncomplicated urinary tract infection).

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

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

11. Has a history of severe, progressive, or uncontrolled renal, genitourinary, hematologic, endocrine, cardiac, vascular, pulmonary, rheumatologic, neurologic, psychiatric, or metabolic disturbances, or signs and symptoms thereof.

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

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

14. History of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria within 1 year before screening.

15. Has unstable suicidal ideation or suicidal behavior in the last 6 months that may be defined as a 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.

16. Has known allergy, hypersensitivity, or intolerance to guselkumab or its excipients (refer to the guselkumab IB).

Prior/Concomitant Therapy

17. Has received any of the following prescribed medications or therapies within the specified period prior to baseline:

    - If previously receiving antibiotics as a primary treatment for CD, must have been stopped for at least 2 weeks.
    - If previously receiving parenteral or enteral nutrition as a primary treatment for CD, must have been stopped for at least 2 weeks.
    - IV corticosteroids received within 2 weeks.
    - Approved biologics for CD, including anti-TNFα therapy (eg, infliximab, etanercept, certolizumab pegol, adalimumab, golimumab), natalizumab, vedolizumab, ustekinumab, or rizankizumab received within 6 weeks of baseline. If the participant has an available drug level of $\leq$ 1 mcg/mL, they can be randomized despite receiving a biologic within 6 weeks of baseline.
    - Investigational immunomodulatory biologic agents for CD received within 6 weeks of baseline, or 4 half-lives, whichever is longer.
    - Cyclosporine, tacrolimus, sirolimus, 6-thioguanine, or mycophenolate mofetil received within 4 weeks of baseline.
    - Approved or investigational small molecules for IBD (eg, JAK inhibitors [eg, tofacitinib, upadacitinib] or S1P inhibitors [eg, ozanimod], 4 weeks prior to baseline, or 5 half-lives, whichever is longer).

18. Bacille Calmette-Guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 4 weeks prior to baseline, or plans to receive such vaccines during the study.

Prior/Concurrent Clinical Study Experience

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

Infections or Predisposition to Infections

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

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

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

  OR

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

22. Tests positive for hepatitis B virus (HBV) infection (see Appendix 6 [Section 10.6]).

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

23. During the 6 weeks prior to baseline, have had **ANY** of (a) confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Coronavirus Disease 2019 [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:
  - 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

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

Note on COVID-19-related exclusion:

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

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

Other Exclusions

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

25. 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.

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

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening, prior to randomization at the baseline visit (Week 0). If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study.

5.3. Lifestyle Considerations

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

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

2. It is recommended that participants are up-to-date on appropriate vaccinations prior to screening per routine local medical guidelines. For study participants who received locally-approved (including emergency use-authorized) COVID-19 vaccines recently prior to study entry, consider study eligibility and follow applicable local vaccine labelling, guidelines, and standards of care for participants receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 5.2).

3. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements, agrees not to get pregnant or father children while enrolled in this study or within 12 weeks after the last dose of study intervention).

4. Must not receive guselkumab outside of this protocol or participate in any other clinical study with an investigational agent while in this study and must terminate study participation if they do. A participant who intends to participate in any other clinical

study with an investigational agent should undergo an early termination visit before he or she terminates study participation.

5. 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.

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

7. Participants who require treatment for latent TB must complete the appropriate course of TB therapy.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness. When available, the investigator may generate screening and enrollment logs directly from interactive web response system (IWRS).

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened on 1 occasion only after consultation with the Sponsor or designee (eg, study responsible physician, scientists). Rescreened participants must be assigned new participant numbers, undergo the informed consent process, and then start a new screening phase.

Previous TB evaluation results (including the IGRA and Chest x-ray), if done within the specified allowed time, are not required to be repeated.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

Study intervention administration (see Table 1) must be captured in the source documents and the electronic case report form (eCRF). Study site personnel will instruct participants and/or caregiver on how to perform self[CCI] and store study intervention for at-home use as indicated for this protocol. When multiple [CCI] are administered at a visit, each [CCI] of study intervention should be given at a different location of the body.

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

Detailed instructions on the administration of study intervention will be provided in the Site Investigational Product Procedures Manual.

For a definition of study intervention overdose, refer to Section 6.7. Guidelines for study intervention affected by the COVID-19 pandemic are provided in Section 10.8.

Table 1: Description of Interventions

Intervention Name	Guselkumab	Placebo	Open-label guselkumab
Dose Formulation	Active guselkumab 100 mg/mL provided in a single-use 1mL prefilled syringe (PFS) assembled with the [redacted]	Matching placebo 1 mL in a single dose [redacted]	Induction: Active guselkumab [redacted] provided in a single-use 2 mL [redacted] Maintenance: Active guselkumab [redacted] in a single-use 1 mL [redacted]
Unit Dose Strength(s)	[redacted]	Placebo	[redacted]
Dosage Level(s) and Frequency	[redacted] at Week 0 and then [redacted] at Week 8 and then [redacted]	Placebo at Week 0, Week 8 and then [redacted]	[redacted] cross over visit and then every 4 [redacted] Then, [redacted]
Route of Administration	Subcutaneous	Subcutaneous	Subcutaneous
Dosing instructions	Participants will receive [redacted] at Week 0 and then [redacted] starting at Week 8. At the discretion of the investigator and participant, and after appropriate and documented training, participants may self-administer study intervention at home (or by a caregiver).		After Week 8, participants who meet criteria for cross over will receive first dose of [redacted] at cross over visit. This will be given as two [redacted] Participant will then get [redacted] doses (again, [redacted]) 4 weeks and 8 weeks after cross over visitAfter the third [redacted] dose, participants will continue on guselkumab [redacted] until the end of the study period.
Use	☐Experimental	Placebo comparator	Other: Cross over to open-label induction
Investigational Medicinal Product (IMP)	Yes	Yes	Yes
Non-Investigational Medicinal Product (NIMP)	No	No	No
Storage	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	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	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

	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.	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.	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.
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements.)	See individual kits	See individual kits	See individual kits

6.2. Preparation/Handling/Storage/Accountability

Combination Products

For this protocol, the term combination product refers to the single integral drug-device combination.

The Sponsor-manufactured combination product for use in this study is the pre-filled syringe (PFS) assembled in an CCI Additional details on the CCI are provided in the guselkumab Investigator Brochure.

All combination product deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the study as product quality complaints (PQC, see Section 10.4.6).

Preparation/Handling/Storage

For CCI administration, guselkumab will be supplied as a CCI sterile liquid in a single-dose PFS assembled in a CCI in doses of 1 mL and 2 mL. For CCI administration, placebo will be supplied as a 1 mL sterile liquid in a single-dose CCI All study intervention must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C).

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

Study drug may be administered at the study site or at home by the trained participant or their caregiver (without a study visit) and will be routinely done beginning at Week 56. Study personnel will instruct participants on how to transport, store, and administer study intervention for at-home use as indicated for this protocol.

The study intervention may be delivered directly to the participants from the site by a courier, if needed. Each courier will adhere to privacy requirements approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). The capability to utilize these direct-to-patient shipments will be assessed by the sponsor to ensure that it is allowable per local regulations.

Refer to the study Site Investigational Product and Procedures Manual for additional guidance on study intervention preparation, handling, and storage

Accountability

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

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

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

The dispensing of study drug to the participant, and the return of study drug from the participant, must be documented on the drug accountability form. Participants must be instructed to return all original containers, whether empty or containing study drug.

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 individuals participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the Sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Site Investigational Product and Procedures Manual.

Since, once they are trained, participants may potentially be self-administering study drug at home, they will receive detailed instructions for study drug storage and disposal of used syringes and handling of unused study material. Participants will receive a sharps container to dispose of used syringes. Participants will be instructed to return the sharps container and/or unused cartons with syringes. Participants will record study drug administrations with time and date information in their participant diary.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. At Week 0, participants will be randomly assigned to 1 of 2 intervention groups in a 1:1 ratio (see Section 4.1) based on a

computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery). The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant.

Blinding

To maintain the study blind, the study intervention container will have a label containing the study name, study intervention number, and reference number. The study intervention number will be entered in the eCRF when the study intervention is dispensed. Each active study intervention and its matching placebo will be identical in appearance and will be packaged in identical containers. All participants will receive the same device(s), which could be either active or matching placebo at 8-week intervals to maintain treatment blinding.

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

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

At the Week 48 DBL (main study DBL), data will be unblinded for analysis to the sponsor only. Treatment assignment will remain blinded to the study sites and participants until the last participant completes the Week 156 evaluations.

Under normal circumstances, the investigator blind should not be broken until the Week 156 DBL is completed, unless specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant. In such case, the investigator may in an emergency determine the identity of the intervention by contacting the IWRS. It is recommended that the investigator contacts the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and/or in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant’s source documents in a secure manner.

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

6.4. Study Intervention Compliance

When participants have self- (or caregiver-) administration of study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed via the return of boxes that contained study drug and will then be documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

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

When study intervention is self-administered by participants (or caregivers) at home, participants will record all study intervention administrations on a diary card.

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

Compliance with the treatment schedule is strongly encouraged. It is understood that treatment may be interrupted for health-related or safety reasons. Therefore, if for any reason a participant cannot receive a dose of study intervention at the scheduled visit, the participant must make every effort to still come in for the scheduled assessments for that visit. In general, the dose should be administered within approximately 2 weeks of that scheduled visit. The participant should then resume the normal study schedule relative to the baseline visit (Week 0). In the case when a participant does not come into the investigational site for a scheduled visit, the site will follow-up with that participant. Due diligence could include telephone calls, certified letters, and email requests. Measures taken to obtain follow-up information must be documented.

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.

All post-baseline visits up to and including Week 56 will have a visit window of ± 10 days counting from Week 0 as Day 1. If a study visit occurs outside this window, the Sponsor should be consulted about how the participant should resume his or her normal dose schedule.

Information regarding study intervention administrations that are administered outside of the scheduled windows or missed will be recorded. Participant charts and worksheets may be reviewed and compared with the data entries on the eCRFs to ensure accuracy.

6.5. Dose Modification

The dose level of study treatments will not be adjusted.

6.5.1. Open Label / Cross over Treatment

Starting after the Week 8 visit, if disease recurrence is confirmed and the definition as described in Section 9.4.3 is satisfied, participants will cross over to open-label treatment with guselkumab. Similarly, participants who are determined to have endoscopic recurrence by central read on the Week 48 or flare visit ileocolonoscopy will also cross over to open-label treatment; for the optional Week 24 ileocolonoscopy, if the central reader confirms endoscopic recurrence (modified Rutgeerts score of i2a or greater), cross over may be done at the discretion of the principal investigator with the participant's agreement. If a participant does not cross over at Week 24 for endoscopic recurrence but, within the following 16 weeks, develops an increase in CDAI $\geq$ 70 or meets the corticosteroid-related disease recurrence criteria (see Section 9.4.3), then the participant may cross over without the need for a repeat ileocolonoscopy.

As discussed in Section 8, at the cross over visit, participants, regardless of the treatment arm to which they were randomized, will receive guselkumab CCI for 3 doses, followed by maintenance guselkumab CCI. This regimen matches the regimen under study in the ongoing Phase 3 study, CRD3004. The CCI induction will be open-label and the participant and investigator will remain blinded to original randomized treatment assignment. Participants will not be allowed to cross over after the Week 128 visit and, while awaiting their confirmatory ileocolonoscopy, regularly scheduled study intervention may be held.

In the event a participant meets CDAI criteria for recurrence, but endoscopic recurrence is not confirmed on ileocolonoscopy, participants will continue on assigned study intervention, and will not cross over to open-label treatment with guselkumab. At investigator discretion, a repeat evaluation, to include an ileocolonoscopy, could be performed as early as the next scheduled visit. It is recommended that such repeat assessment be undertaken only if/when there are clinical reasons to warrant such re-assessment, eg, there is worsening of symptoms and/or an increase in objective measures of inflammation such as C-reactive protein (CRP) or fecal calprotectin (and clinical criteria for recurrence must still be satisfied). In addition, if a confirmatory ileocolonoscopy was of poor quality or otherwise unreadable such that confirmatory endoscopic recurrence could not be determined, an ileocolonoscopy is recommended to be repeated as soon as feasible.

As it takes time for endoscopic disease to resolve, participants who cross over to open-label guselkumab should then be re-assessed with an ileocolonoscopy approximately 16 to 24 weeks later. At that time, it will be determined, based on investigator judgement, whether treatment with open-label SC guselkumab should be continued or not. It is recommended to include an ileocolonoscopy in this assessment.

6.6. Continued Access to Study Intervention After the End of the Study

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

Local regulations on continued access will always take precedence. Plans for continued access stated in this protocol may change if new information on the benefit-risk profile of guselkumab becomes available during the study or program.

6.7. Treatment of Overdose

For this study, any single dose of guselkumab greater than the highest dose planned (eg 400 mg for the cross over group) will be considered an overdose. The Sponsor does not recommend specific treatment for an overdose. As discussed in Section 10.4.4, overdose is a special reporting situation such that the event requires expedited reporting.

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

- Contact the Medical Monitor (or designee) immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor (or designee), whether study intervention should be interrupted.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose of the overdosing in the eCRF.

6.8. Concomitant Therapy

Concomitant therapies must be recorded throughout the study from signing of consent to the last study visit.

All concomitant therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) must be recorded in the eCRF. Recorded information will include the name of the medication, start and stop dates, and its reason for use.

6.8.1. Concomitant Conventional CD Medications

Standard immunomodulators (MTX, AZA, and 6-MP) or IV/oral corticosteroids should not be initiated (or increased in dose) unless medically necessary as rescue therapy as this will impact the efficacy analyses in this study and will be considered treatment failure (see the SAP for full treatment failure criteria). If initiated as rescue therapy, these treatments should be discontinued or tapered off as soon as medically tolerable and appropriate; however, participants can (and should) continue to receive study intervention and attend all study visits despite initiation (or increasing dose) of any of these CD related medications, except for those described as prohibited medications below (see Section 6.8.2).

6.8.1.1. Oral Corticosteroids

It is recognized that some participants will have been steroid dependent prior to their surgery and may be unable to safely complete tapering of their steroid therapy prior to randomization. However, as participants enter the study without residual active CD, participants who enter the study on steroids should initiate, or continue, tapering of corticosteroids for CD without any delay upon study entry at Week 0, unless medically inappropriate. Corticosteroid tapering should follow the below-recommended schedule (Table 2), without exceeding the prescribed magnitude or rate

of tapering unless due to medical necessity (eg, participant experiencing corticosteroid-related side effects).

If a participant experiences worsening in his/her disease activity while tapering corticosteroids, further dose decreases may be suspended, and the oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator, to attempt to return to response. For participants whose corticosteroid taper is interrupted on this basis, investigators should resume tapering as soon as possible thereafter.

Table 2: Recommended Tapering Schedule for Oral Corticosteroids	
Recommended Tapering Schedule for Oral Corticosteroids (Other than Budesonide)	
Dose > 15 mg/day prednisone or equivalent	Taper daily dose by 5 mg/week until receiving 10 mg/day, then continue tapering at 2.5 mg/week until 0 mg/day
Dose 11 to 15 mg/day prednisone or equivalent	Taper daily dose to 10 mg/day for 1 week, then continue at 2.5 mg/week until 0 mg/day
Dose ≤ 10 mg/day prednisone or equivalent:	Taper daily dose by 2.5 mg/week until 0 mg/day
Recommended Tapering Schedule for Oral Budesonide	
Participants receiving budesonide should have their daily dose tapered by 3 mg every 3 weeks until 0 mg/day.	

If medically necessary (due to worsening disease or symptoms), participants may initiate oral corticosteroids if needed to manage their disease, but these should be discontinued and/or tapered off, as described above, as soon as clinically possible. The initiation of a physician-prescribed corticosteroid, or an increase in the dose of steroids already being taken (by greater than 5 mg/day), for over one week for the treatment of CD warrants further evaluation for clinical recurrence as described in Section 9.4.3.

6.8.2. Prohibited Concomitant Medications

In contrast to the concomitant medications described above, initiation of any of the following medications is prohibited (until the last study intervention administration at Week 144) and if initiated, should result in discontinuation from further study intervention, although such participants should not terminate study participation (unless enrolling in an interventional CD study or initiating a commercial anti-TNF, anti-IL-12 or 23, anti-IL 23 or anti-integrin biologic- as described further below), and are encouraged to complete all visits through the next 12 weeks, at which point the mandatory early termination visit should be performed.

- Immunomodulator agents other than AZA, 6-MP, or MTX (including but not limited to 6-thioguanine, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, tofacitinib and other JAK inhibitors)

Note: As discussed in Section 6.8.1, AZA, 6-MP, MTX and corticosteroids may be initiated if medically necessary for rescue therapy, so their initiation does NOT necessitate discontinuation of study intervention.

- Immunosuppressant biologic agents, including but not limited to commercial TNF-antagonists (eg, infliximab, adalimumab, certolizumab), IL 12-23 inhibitors (ie, ustekinumab), IL-23 inhibitors (eg, risankizumab), integrin inhibitors (eg, natalizumab, vedolizumab), and abatacept

- Experimental or investigational CD medications

Note: Until the study treatment period is completed (ie, Week 152), participants must not receive commercial guselkumab outside of the protocol or participate in any other CD clinical study with an investigational agent while in this study. Further, participants must discontinue any further study intervention and also terminate study participation in these circumstances, with performance of the early termination visit prior to initiating these drugs. If the decision or realization that this is about to occur coincides with a scheduled visit, then the early termination visit should be performed in place of the scheduled visit, with the scheduling and performance of the follow-up ileocolonoscopy occurring as soon as possible. The rationale for handling initiation of these agents in this way is that subsequent efficacy and safety data in the context of the study would be uninterpretable.

As protection of human research participants is paramount, it is recognized that initiating these prohibited therapies may rarely be required due to medical necessity. However, initiation of the above prohibited medications prior to Week 152 should be documented as a deviation from the study protocol (unless study intervention has already been discontinued or completed), and participants must be discontinued from receiving further study intervention once these agents are started.

6.8.3. Vaccinations (including COVID-19)

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study treatment should be discontinued if:

- The investigator or the medical monitor believes that for safety reasons (eg, an AE) it is in the best interest of the participant to stop treatment.

- The participant becomes pregnant or plans a pregnancy within the study period or within 12 weeks after the last study intervention administration.
- The participant meets **ANY** of the following TB related conditions:
  - A diagnosis of active TB is made.
  - A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.
  - A participant undergoing evaluation has chest imaging with evidence of current active TB and/or a positive IGRA test result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study intervention and continued to completion.
  - A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The participant has a serious adverse reaction that is related to an CCI 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. In general, discontinuation of study intervention administration must be considered for participants who develop non-serious, but severe CCI site reactions.
- The participant develops a malignancy including squamous cell skin cancer. Consideration may be given to allow participants to continue to receive study intervention if they develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease.
- The initiation of the following protocol-prohibited medications at any time during the study as listed in Section 6.8.2.
- A serious opportunistic infection occurs.
- The participant (or the participant's representative) withdraws consent (or assent) for further administration of study intervention.
- The participant has CD-related surgeries that will preclude the future ability to assess efficacy through the CDAI. Surgeries that are thought to represent a lack of efficacy of study intervention should be considered for discontinuation at the discretion of the Investigator other than minor procedures (eg, placement of a seton or cutaneous drainage of an abscess).
- The participant has severe liver test abnormalities that are not transient and are not explained by other etiologies; see Section 10.7 for definitions of abnormal values.
- 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.

- A participant who has crossed over to receive open-label treatment with guselkumab and is assessed not to have subsequently attained improvement, in the investigator's judgement (recommended to be initially assessed approximately 16-24 weeks after initiating open-label guselkumab treatment).

Participants who discontinue study intervention (for the reasons above) before the end of planned study treatment (Week 144), should not terminate their study participation (unless enrolling in an investigational advanced therapy CD study or initiating commercial guselkumab prior to cross over to open-label treatment, as described further below). Instead, participants discontinuing study intervention are encouraged to complete study visits through the next 12 weeks, at which time an early termination visit (see SoA, Section 1.3) must be performed. Should the early termination visit be due within 4 weeks of a regularly scheduled visit, it is appropriate to perform the procedures specified for the early termination visit at the appointed time in place of the regular scheduled visit.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up (see Section 7.3)
- Withdrawal of consent for study participation (distinct from desire to/withdrawal of consent to receive further study intervention)
- Death
- Sponsor decision (eg, participating in any other interventional clinical study with an investigational agent or initiating commercial guselkumab treatment prior to cross over to open-label guselkumab treatment)

When a participant withdraws or is withdrawn/terminated prior to study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. These participants should complete the safety and efficacy evaluations specified for the early termination visit in the SoA (Section 1.3). If participants refuse to remain in the study to perform the early termination visit 12 weeks after last study intervention administration, the participant's desire to withdraw their consent for further study participation should be accommodated by performing the early termination visit as soon as necessary/possible. Thus, if possible, the early termination visit should be moved up and performed prior to when the participant might withdraw their consent. If/when a participant decides to withdraw their consent to participate in the study, then no additional assessments are allowed, or can be performed.

Withdrawal of Consent

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

If the participant also chooses to withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations), 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.

7.3. Lost to Follow up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of efficacy, safety, and other (ie, PK, immunogenicity, pharmacodynamics (PD), biomarker, pharmacogenomic, medical resource utilization, and health economic) measurements applicable to this study.

All PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses. Refer to the PRO completion guidelines for instructions on the administration of PROs.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PROs, C-SSRS, blood sample collection, urine pregnancy test if required, then study intervention administration.

PK (urine and blood) and PD (fecal calprotectin and CRP) assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints

if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The total blood volume to be collected from each participant will be no more than approximately 250 mL. However, additional repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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

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 serum 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 11) and must continue taking such precautions for 12 weeks after receiving the last administration of study intervention. The method(s) of contraception used by each participant must be documented.

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 Week 0.

Participants must undergo testing for TB (Section 8.4.9.1) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. A participant’s eligibility according to TB screening criteria is described in Section 5.2, Exclusion Criteria.

Week 0 Visit

Prior to entering the study, the participant must be evaluated for eligibility.

An assessment of all previous laboratory 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 prior to randomization.

Post-baseline Visits

Study visits should occur at the week indicated ± 10 days. Note that while out of window visits should be recorded as protocol deviations, it is preferable to perform visits and procedures out of window than not perform them at all. One exception may be if sufficient time has passed that it is now in-window for the next subsequent visit, in which case it is advised to contact the medical monitor for assistance in how to best manage the situation.

Study agent administration should not occur when a participant is experiencing a clinically important, active infection, an example of an appropriate reason to deviate from protocol-specified windows (which should then be documented appropriately).

The participant will be instructed to complete the CDAI daily diary through Week 152. For all visits where a score needs to be calculated in real-time, the most recent hematocrit value available will be used when calculating the CDAI score.

Flare Visit

During the study, participants who are suspected to be having a flare of disease activity (eg, example, an increase in the PRO-2 [as described in Section 8.1.2] score of at least 50 points over a 7-day period compared to baseline, or suspicion of a new fistula or abscess) can present for further evaluation at the flare visit (see SoA). This visit may include an endoscopy if it is determined that participant has a both a CDAI score of over 200 and an increase of at least 70 points over baseline.

Participants in clinical flare should undergo endoscopy, unless it can be determined without endoscopy that they have met criteria for disease recurrence (see Section 9.4.3).

Cross Over Visit

After Week 8, if a determination has been made that the participant has had a disease recurrence (by meeting the criteria outlined in Section 9.4.3 and confirmed by the central reader of i2a or greater disease when applicable) a cross over visit should be scheduled. Participants who have endoscopic recurrence confirmed by the central reader at the scheduled Week 48 ileocolonoscopy or on a flare visit ileocolonoscopy will be scheduled for a cross over visit. In addition, participants who are determined by the central reader to have endoscopic recurrence at the Week 24 (but do not have disease recurrence) can also schedule a cross over visit at the discretion of the principal investigator.

Procedures to be performed at the cross over visits are outlined in the Cross Over SoA (Section 1.3). Participants will receive their first dose of open-label guselkumab 400 mg SC at the cross over visit. Participants will then get a second CCI dose4 weeks after the cross over visit which will be self-administered at home. The third CCI dose will be given 8 weeks after the

cross over visit at a scheduled post-cross over visit. After the three CCI induction doses, participants will receive open-label guselkumab CCI. The first open-label CCI dose will be given at a scheduled visit. Subsequent study visits will occur every 16 weeks during which the CCI dose will be administered, with every other dose administered at home. The final dose will be given at the Final Dosing Visit, which will fall between Week 137 and Week 144 from the original randomization date. The Final Efficacy Visit will occur 8 weeks after the Final Dosing Visit, and will therefore fall between Weeks 145 and 152 from the original randomization date. The Final Safety Visit should occur 4 weeks after the Final Efficacy Visit (12 weeks after last dose of study agent), and will therefore fall between Weeks 149 and Weeks 156 from the original randomization date. If allowed by local regulation and if clinically appropriate, the Final Safety Visit can be done by telephone and no safety laboratory blood samples drawn. The study assessments for the Final Dosing Visit, Final Efficacy Visit, and Final Safety Visit will match the Week 144, Week 152 and Week 156 assessments in the original SoA, respectively.

Home Health Care and Telehealth Visits

Telehealth visits (conducted via phone or video conference) may be implemented by or with approval from the sponsor and per clinical judgement of the investigator for certain circumstances when warranted where feasible and permissible by local policy, regulations (as applicable) and for participants for whom there is no safety concern.

The nature of study procedures which may be performed with home health care and telehealth visits as circumstances necessitate will be defined by the Sponsor (see Section 10.8 for more details).

Sample Collection and Handling

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

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IB)
- Investigational Product Procedures Manual (IPPM)
- Instructions for Use (IFU) for at home administration of guselkumab/placebo
- Central laboratory manual
- eCRF completion instructions

- Patient recruitment materials
- ICF
- Home dosing study medication diary
- IWRS manual
- Biopsy manual
- Electronic patient-reported outcome equipment, questionnaires and quick reference guide
- Endoscopy kit
- Imaging manual
- Laboratory manual
- Laboratory kits
- Source documents as applicable

8.1. Efficacy Assessments

Efficacy assessments 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 modified Rutgeerts score and SES-CD
- Histologic assessments based on the Global Histology Activity Score (GHAS), Robarts histopathology index (RHI), and Geboes score
- Inflammatory PD markers, including CRP and fecal calprotectin
- Fistula assessment
- PRO measures to assess health-related quality of life and work productivity outcomes including PROMIS-29, PROMIS Fatigue-7a, Work Productivity and Activity Index for Crohn's Disease (WPAI-CD)

8.1.1. CDAI

The CDAI (Crohn's Disease Activity Index) will be assessed by collecting information on 8 different Crohn's disease-related variables (Best, 1976): 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 (Appendix 9). The abdominal mass is assessed through physical examination. Total number of liquid or very soft stools, AP/cramping, use of antidiarrheal drug(s) and/or opiates, and general well-being are recorded by the participant on an electronic home diary or diary card on a daily basis.

8.1.2. PRO-2: Unweighted Mean Daily CDAI Components of the Total Number of Liquid or Very Soft Stools and the AP

The PRO-2 includes the CDAI components of the total number of liquid or very soft stools and the AP score.

8.1.3. Endoscopic Assessments of the Intestinal Mucosa

Endoscopic assessments of the intestinal mucosa will be evaluated during ileocolonoscopy in all participants. A video ileocolonoscopic examination will be performed at the time points specified in the Schedule of Activities (Section 1.3). Video endoscopies will be assessed by a central facility that will be blinded to treatment group and visit. If the video ileocolonoscopy is inconclusive (eg the recording fails, poor preparation obscures the ability to identify recurrence), then it is recommended to repeat the procedure as soon as feasible, if the participant is willing. The modified Rutgeerts score (Table 3) will be used to evaluate endoscopic recurrence.

The Rutgeerts score is widely accepted as a clinical and research tool and is commonly utilized in clinical practice as well. It is used to assess endoscopic severity and predict the risk of clinical postoperative recurrence based on early endoscopic findings in the neo-terminal ileum and anastomosis after ileocolonic resection (Rutgeerts 1984, Rutgeerts 1990). Ileal lesions are scored at ileocolonoscopy and characterized as i0 (no lesions) through i4 (diffuse inflammation with large ulcers, nodules or narrowing). In the 1990 study by Rutgeerts et al, the Rutgeerts score (see Section 8.1) was found to be the most important predictor of symptomatic recurrence of CD (p=0.0001). Furthermore, 80% of patients with a score of i0 or i1 had no progression of endoscopic disease activity at 3 years, whereas 92% of patients with i3 or i4 lesions had progression of endoscopic disease at 3 years. The outcomes of patients with i2 lesions have been heterogenous, therefore, a modified Rutgeerts score was proposed to divide the i2 category into lesions at the ileocolonic anastomosis (i2a) and > 5 aphthous ulcers in the neo-terminal ileum with normal mucosa in between (i2b). However, recent studies did not show a difference in clinical recurrence amongst patients with Rutgeerts scores of i2a versus i2b (Bayart 2016, Rivière 2019).

Endoscopic recurrence defined as a Rutgeerts score $\geq$ i2 (modified Rutgeerts $\geq$ i2a) has been adopted as the standard endoscopic outcome in most trials of POCD therapy (D'Haens 2008, Hanauer 2004, Hellers 1999, Reguiero 2016). The International Organization for the Study of Inflammatory Bowel Disease performed a technical review and then a 2-round vote among 14 IBD specialists using the Delphi method, and all agreed on a Rutgeerts' score of i0-i1 as the definition of postoperative endoscopic remission (Vuitton 2016). Additionally, in their recommendations for clinical trial design in POCD, an international panel of IBD experts recommended the modified Rutgeerts score as an appropriate measure of postoperative endoscopic CD activity in regulatory clinical trials (Hanzel 2021). Endoscopic recurrence has also been shown to be a strong predictor of subsequent clinical recurrence. In a meta-analysis of randomized controlled trials, the relative risk for clinical recurrence among patients who experienced endoscopic recurrence was 10.77 (95% CI 4.08-28.40). An accompanying meta-analysis of 11 cohort studies showed an even higher relative risk of 21.33 (95% CI 9.55-47.66). In addition, a single cohort study in the analysis showed a linear relationship between Rutgeerts score and clinical recurrence risk (Ble 2021).

While the study is ongoing, the modified Rutgeerts score as interpreted by the central reader will be used to determine whether endoscopic recurrence has occurred. As discussed in Section 6.5.1, cross over to open-label induction with guselkumab is permissible, at the discretion of the principal investigator, if endoscopic recurrence is confirmed on optional Week 24 ileocolonoscopy, and is mandatory after confirmed endoscopic recurrence on Week 48 ileocolonoscopy or after confirmed disease recurrence. If a participant does not cross over at Week 24 for endoscopic recurrence but within the following 16 weeks develops a CDAI in ≥ 70 or meets the corticosteroid-related disease recurrence criteria (see Section 9.4.3), then the participant may cross over without the need for a repeat ileocolonoscopy. Results of the video ileocolonoscopies read by the central reader will also be the basis for the primary and secondary analyses of disease and endoscopic recurrence.

Table 3: Modified Rutgeerts Score

Score	Endoscopic Findings
i0	No lesions
i1	< 5 aphthous lesions
i2	> 5 aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis (ie, < 1 cm in length)
i2a	Lesions confined to the ileocolonic anastomosis (including anastomotic stenosis)
i2b	More than 5 aphthous ulcers or larger lesions, with normal mucosa in-between, in the neoterminal ileum (with or without anastomotic lesions)
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Large ulcers with diffuse mucosal inflammation or nodules or stenosis in the neoterminal ileum

Ileocolonoscopies will also be read by central reader(s) using the SES-CD for scientific/exploratory purposes. 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.

8.1.4. Histologic Assessments Based on Global Histologic Disease Activity (GHAS), Geboes Score, and Robarts Histopathology Index (RHI)

Histologic assessments will be performed using biopsy samples collected during video ileocolonoscopy (see endoscopy manual for biopsy details). Histologic assessments will be conducted by a central reader who is blinded to treatment groups and visit. The GHAS, Geboes score, and Robarts Histopathology Index will be used to evaluate histologic improvements and healing (Geboes 2000; Mosli 2017; D'Haens 1999).

8.1.5. Inflammatory PD markers: CRP and Fecal Calprotectin

Inflammatory pharmacodynamic markers will be evaluated using blood samples as indicated by the Schedule of Activities (Section 1.3).

CRP has been demonstrated to be useful as a marker of inflammation in patients with IBD. In CD, elevated CRP concentrations have been associated with severe clinical activity, elevated sedimentation rate, and active disease as detected by ileocolonoscopy. 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. 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.

8.1.6. External Perianal Fistula Assessment

Fistula assessment will be performed in all participants on an ongoing basis throughout the duration of the study. All participants will be assessed for fistulas at baseline. For participants with perianal disease, fistula closure will be assessed during the study. 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).

8.2. Patient-reported Outcomes

The PRO instrument will be provided in the local language in accordance with local guidelines.

Details regarding the PROs will be available for regulators and for IRB/IEC submissions and will be provided separately in a companion manual with the instruments that will be submitted with the protocol.

The PRO and AE data will not be reconciled with each other.

8.2.1. Patient-reported Outcomes Measurement Information System (PROMIS)-29

The Patient-Reported Outcomes Measurement Information System (PROMIS)-29 is a validated general health profile instrument that is not disease-specific (Hayes 2018). 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 an activities). They assess all domains over the past seven days except for Physical Function which has no timeframe specified. PROMIS-29 also includes an overall average pain intensity 0-10 numeric rating scale. The raw score of each domain is converted into a standardized score with a mean of 50 and a standard deviation (SD) of 10 (T-Score). The standardized T-score is reported as the final score for each participant. Pain Intensity is presented as raw responses (0-10). Norm-based scores have been calculated for each domain on the PROMIS measures, with a score of 50 representing the

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

8.2.2. PROMIS Fatigue-7a

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, selfcare, and exercise) (Ameringer 2016). PROMIS Fatigue Short Form 7a has a recall period of past 7 days. Compared to the fatigue scale of PROMIS-29, PROMIS Fatigue Short Form 7a provides additional information to evaluate severity of fatigue. The raw total score is converted into a standardized score with a mean of 50 and a SD of 10 (T-Score). The standardized T-score is reported as the final score for each participant.

8.2.3. Work Productivity and Activity Index for Crohn's disease (WPAI-CD)

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 CD (Reilly 2008). The WPAI-CD consists of 6 questions to determine employment status, hours missed from work due to CD, hours missed from work for other reasons, hours worked, the degree to which CD affected work productivity while at work, and the degree to which CD affected activities outside of work. Higher scores indicate greater impairment.

8.3. Healthcare Resource Utilization Data

CD-related hospitalizations, surgeries, emergency room visits, medication use, and physician visits will be used to evaluate healthcare resource utilization, which are important considerations when assessing ideal therapy selection in CD patients.

8.4. Safety Assessments

Safety evaluations will include the assessment of AEs, clinical laboratory tests (hematology and chemistry), vital signs, screening physical examination, concomitant medication review, and monitoring for hypersensitivity reactions, CCI site reactions, suicidal ideation and behavior by the C-SSRS, and early detection of active TB.

Evaluations of safety and tolerability will occur at time points specified in the SoA (Section 1.3).

Adverse events will be reported and followed by the investigator as specified in Section 8.5, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

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

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.4.1. Physical Examinations

A complete, detailed physical examination, including height and weight, will be performed as per local practice standards for eligibility assessment. While assessment of the participants for safety and efficacy requires a full physical examination at screening and at Week 152, a directed physical exam for abdominal mass and fistulas, (perianal and other) will be performed at all visits. Participants will be instructed to remove shoes and outdoor apparel and gear prior to measurements for height and weight.

Physical examination data will not be included in the study database as such; abnormal physical examination findings are to be reported as AEs.

8.4.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, and blood pressure will be assessed at the Week 0, 48, and 152 visits. Vital signs should be recorded before and approximately 30 minutes after the study intervention CCI during the main treatment period through Week 48, or if the participant reports symptoms.

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 CCI 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.

Vital signs data, which are considered source data, are not to be entered into the study database or analyzed. Abnormal vital signs are to be recorded as AEs.

8.4.3. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Appendix 2: Clinical Laboratory Tests. 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.

8.4.4. Pregnancy Testing

Pregnancy testing will consist of a serum pregnancy test at screening and urine testing at on-site study visits. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, or if a participant suspects pregnancy, to establish the absence of pregnancy at any time during the participation in the study.

8.4.5. Suicidal Ideation and Behavior Risk Monitoring

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 and will be generally conducted on the electronic clinical outcomes assessment (eCOA) device provided to the site. The C-SSRS will be provided in the local languages in accordance with local guidelines.

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 Week 0 and all other site visits through the end of the study.

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. The investigator or trained study-site personnel will interview the participant in a private place and complete the C-SSRS.

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 intervention should be considered for any participant who reports Suicidal Ideation with Intention to Act ("Ideation level 4"), Suicidal Ideation with Specific Plan and Intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a 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 (Section 7.1).

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. The completed C-SSRS and AE data will not be reconciled with each other.

8.4.6. CCI Site Reactions

A study intervention CCI site reaction is any adverse reaction at a SC study intervention CCI site. The CCI sites will be evaluated for reactions at on-site visits and any CCI site reaction will be recorded as an AE.

8.4.7. Hypersensitivity Reactions

Before any administration of study intervention at the study site, appropriately trained personnel and medications (eg, antihistamines, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. All participants must be alert for or, when on site, observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritus, angioedema, wheezing, dyspnea, or hypotension). If a mild or moderate hypersensitivity reaction is observed, acetaminophen, nonsteroidal anti-inflammatory drugs, and/or diphenhydramine may be administered. Participants who experience serious adverse reactions related to an infusion must strongly be considered to be discontinued from further study intervention administrations.

In the case of a severe hypersensitivity reaction (eg, anaphylaxis), SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures are essential and must be available at the study site where the infusions are being administered.

Participants who experience reactions suggestive of serum sickness (resulting in symptoms such as myalgia and/or arthralgia with fever and/or rash that are not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an infusion 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 headache.

8.4.8. Infections

Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits. Study intervention administration should not be given to a participant with a clinically significant, active infection. If a participant develops a serious infection, discontinuation of study intervention should be considered.

8.4.9. Tuberculosis Evaluations

8.4.9.1. Initial Tuberculosis Evaluation

Participant medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest imaging results and responses to tuberculin skin or other TB testing. Investigators have the option to use the tuberculin skin test in addition to IGRA testing to screen for latent TB if preferred by local health authorities, or if they believe based on their judgment that both tests are clinically indicated to evaluate a participant at high risk for latent TB.

Participants with a negative IGRA test result are eligible to continue with pre-randomization procedures. Participants with a newly identified positive IGRA test result must undergo an evaluation for active or latent TB, or suspected false-positive initial testing, and initiate appropriate treatment if needed. 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.

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

8.4.9.2. Ongoing Tuberculosis Evaluation

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

– "Have you had a new cough of > 14 days' duration or a change in a chronic cough?"

– "Have you had any of the following symptoms:

  Persistent fever?

Unintentional weight loss?

Night sweats?"

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

If the evaluation raises suspicion for TB infection or the participant has had a close contact exposure to TB, study intervention must be withheld and an immediate and thorough investigation must be undertaken, including consultation with a physician specializing in TB to determine if treatment is warranted prior to any further study intervention. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol.

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

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

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

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

For study intervention that meets the definition of a combination product, malfunctions or deficiencies of a device constituent will be reported as a PQC.

Further details on AEs, SAEs, and PQCs can be found in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious Adverse Events

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

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

A **possible Hy's law Case** is defined by the occurrence of ALT/AST ≥3 x ULN, alkaline phosphatase (ALP) <2 x ULN together with total bilirubin ≥2 x ULN or International Normalized Ratio (INR) >1.5 (if measured) (see Appendix 10.7). Any possible Hy's Law case is considered an important medical event and must be reported to the sponsor in an expedited manner, even before all other possible causes of liver injury have been excluded. A confirmed Hy's law case must be reported as a SAE.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.5.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

Solicited AEs are predefined as CCI site reactions and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

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

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

Adverse events and the special reporting situation of pregnancy, will be followed by the investigator as specified in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.5.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated 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 suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an 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.

8.5.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy for female participants who become pregnant, or where the pregnancy was the result of male participant and his partner, and any postnatal sequelae in the infant will be requested.

8.5.6. Adverse 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 8.5.3 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.

8.6. Pharmacokinetics

8.6.1. Evaluations

Venous blood samples of sufficient volume will be collected for measurement of serum concentrations of guselkumab.

Each serum sample will be divided into 3 aliquots (1 each for PK, anti-guselkumab antibodies to guselkumab, and a back-up). Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

8.6.2. Analytical Procedures

Pharmacokinetics

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

8.6.3. Pharmacokinetic Parameters and Evaluations

Parameters

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

Pharmacokinetic/Pharmacodynamic Evaluations

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

8.7. Genetics and Pharmacogenomics

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

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.

Whole blood samples of approximately 6 mL will be collected for genetic analyses as specified in the SoA (Section 1.3).

8.8. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab treatment and/or Crohn's disease. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, whole blood, and ileocolonic biopsy samples, and ileocolonic video biopsy collected as specified in the SoA (Section 1.3), where local regulations permit. Digital images of biopsy histology slides and endoscopy videos may be used to support exploratory research to develop artificial intelligence algorithms to aide in the evaluation of mucosal improvement in Crohn's disease.

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 treatment.
2. To understand CD pathogenesis.
3. To understand why an individual participant may respond differently to guselkumab.
4. To understand the impact of treatment with guselkumab on intestinal inflammation.
5. To develop diagnostic tests to identify CD populations, and IBD patients in general, that may be responsive or nonresponsive to treatment with guselkumab.

Stopping Analysis

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. 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 CD. Transcriptome studies may be conducted using RNA sequencing, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each blood sample. This will enable the evaluation of

changes in transcriptome profiles that may correlate with biologic response relating to CD or the action of guselkumab.

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

Mucosal biopsy samples will be collected from all participants during ileocolonoscopy at the times specified in the SoA for histologic assessment, RNA expression analysis, and single cell isolation.

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

8.8.3. Serum-based Biomarkers

Blood samples for serum-based biomarker analyses will be collected from all participants where local regulations permit. Assays to be performed may include proteins associated with proinflammatory and anti-inflammatory effects, the recruitment and proliferation of cells associated with inflammation and repair, and markers associated with tissue injury or repair. These analyses will include but will not be limited to IL-17A and IL-22.

8.9. Immunogenicity Assessments

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

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

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

Analytical Procedures

The detection and characterization of antibodies to guselkumab will be performed using a validated assay method by or under the supervision of the sponsor. Samples may be stored up to 15 years (or according to local regulations) following the last participant’s last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to guselkumab.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

The primary hypothesis is that guselkumab is superior to placebo in preventing endoscopic recurrence prior to or at Week 48.

9.2. Sample Size Determination

A sample size of 370 participants (185 participants assigned to guselkumab and 185 assigned to placebo) will allow to have at least 90% power to detect 20% differences between guselkumab (30%) and placebo (50%) for endoscopic recurrence rate (primary endpoint) prior to or at Week 48, assuming a 2-sided alpha level of 0.05.

This also will allow at least 90% power to detect 17% differences between guselkumab (37%) and placebo (20%) for clinical remission without disease recurrence at Week 48, assuming a 2-sided alpha level of 0.05. This also will allow 90% power to detect 10% differences between guselkumab (10%) and placebo (20%) for disease recurrence at the main study database lock, all available follow-up of all participants will be used to examine disease recurrence at the time of the database lock.

Endoscopic Recurrence

Assumptions for endoscopic recurrence prior to or at Week 48 were based on previous studies, as described in Table 4.

Table 4: Endoscopic Recurrence, Placebo Group

Reference	Endoscopic Recurrence definition	Sample Size	Placebo rate	Timepoint
Regueiro 2016	Rutgeerts $\geq$ i2	150	60%	76 weeks
Yamamoto 2007	Rutgeerts $\geq$ i2	20	70%	52 weeks
Marteau 2006	Rutgeerts $\geq$ i2	47	64%	24 weeks
Rutgeerts 2005	Rutgeerts $\geq$ i2	33	78.8%	52 weeks
Hanauer 2004	Rutgeerts $\geq$ i2	40	64%	104 weeks
Lochs 2000	Rutgeerts $\geq$ i2	166	50%	72 weeks
Ewe 1999	Rutgeerts $\geq$ i2	40	70%	52 weeks
Hellers 1999	Rutgeerts $\geq$ i2	66	58%	52 weeks

Based on these data above, the endoscopic recurrence rates are assumed to be 50% for placebo and 30% for guselkumab.

To accommodate other potential scenarios, power was calculated based on different assumptions as listed in Table 5.

Table 5: Power to Detect a Treatment Effect Based on Different Scenarios in Endoscopic Recurrence

Event rate at Week 48 for endoscopic recurrence in placebo group	Event rate at Week 48 for endoscopic recurrence in guselkumab group	Difference to be detected	Power
50%	30%	20%	97.7%
50%	25%	25%	99.9%
50%	35%	15%	83.3%
45%	25%	20%	98.3%
40%	20%	20%	98.9%
60%	30%	30%	>99.9%

Clinical Remission without Disease Recurrence

Based on data from PREVENT (20% for placebo, and 36.7 for Infliximab), the rates of clinical remission without disease recurrence are assumed to be 20% for placebo and 37% for guselkumab.

To accommodate other potential scenarios, power was calculated based on different assumptions as listed in Table 6:

Table 6: Power to Detect a Treatment Effect Based on Different Scenarios in Clinical Remission without Disease Recurrence

Event rate at Week 48 for clinical remission without disease recurrence in placebo group	Event rate at Week 48 for clinical remission without disease recurrence in guselkumab group	Difference to be detected	Power
20%	35%	15%	90.0%
20%	**36%**	**16%**	**93.1%**
20%	**37%**	**17%**	**95.4%**

Disease Recurrence

Assumptions for disease recurrence were based on previous studies, as described in Table 7

Table 7: Disease Recurrence, Placebo Group

Reference	Disease Recurrence definition	Sample Size	Placebo rate	Timepoint
Regueiro 2016	CDAI ≥ 200 and 70 point increase	150	20%	76 weeks
Ng 2009	Symptoms related to CD associated with endo, lab or radiologic findings	99	28%	52 weeks
Yamamoto 2007	CDAI ≥ 150	20	35%	52 weeks
Rutgeerts 2005	CDAI > 250 or need for rescue medical therapy	40	37.5%	54 weeks
Prantera 2002	CDAI >150, confirmed by endoscopy	22	10.5%	52 weeks
Lochs 2000	CDAI >250 or CDAI > 200 with a 60 point increase	166	31.4%	72 weeks
Hellers 1999	CDAI > 200	66	31%	52 weeks
Ewe 1999	CDAI > 200, rise of 60 points	40	28%	52 weeks
Olaison 1992	CDAI > 150 or HBI ≥4	42	37%	52 weeks

For this endpoint, all follow-up data available at the primary DBL, including beyond one year when available, will be used. Based on this, as well as these data above, the disease recurrence rates are assumed to be 20% for placebo and 10% for guselkumab.

To accommodate other potential scenarios, power was calculated based on different assumptions as listed in Table 8.

Table 8: Power to Detect a Treatment Effect Based on Different Scenarios in Disease Recurrence

Event rate at Week 48 for disease recurrence in placebo group	Event rate at Week 48 for disease recurrence in guselkumab group	Difference to be detected	Power
20%	10%	10%	90.0%
	8%	12%	98.5%
25%	15%	10%	80.9%
	10%	15%	99.7%
30%	15%	15%	98.5%

Accrual time used here is 18 months, total time used here is 30 months. It is expected median follow-up time available at the time of, and thus incorporated in, the main database lock is approximately 18 months. Assuming non-uniform accrual pattern: 25% of participants will be enrolled in the first 6 months, 35% of participants will be enrolled in the next 6 months, and 40% will be enrolled in the last 6 months. Assuming dropout rate is 15% annually. Average duration of follow-up is expected to be approximately 20 months.

9.3. Participant Analysis Sets

For purposes of analysis, the following populations are defined in Table 9.

Table 9: Description of Analysis Populations

Population	Description
Full Analysis Set	All randomized participants
Safety Analysis Set	All randomized participants who received at least 1 dose of study intervention
PK Analysis Set	All randomized participants who received at least 1 dose of study intervention and have at least 1 valid blood sample drawn post-baseline for PK analysis
Immunogenicity Analysis Set	All randomized participants who received at least 1 dose of study intervention and have appropriate samples for anti-drug antibody detection

9.4. Statistical Analyses

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

9.4.1. General Considerations

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. The SAP will include a more technical and detailed description of the statistical analyses described in this section.

Descriptive statistics (eg, mean, median, standard deviation [SD], interquartile [IQ] range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphical data displays (eg, line plots) may also be used to summarize data. If significant imbalances were found between treatment groups, additional analyses may be conducted to adjust for the baseline difference. The Kaplan-Meier method will be used to summarize data for time-to-event variables.

The overall Type I error rate will be controlled at the significance level of 0.05 (2-sided). Hierarchical testing will be performed for primary and secondary endpoints, the ordering of which will be described in the SAP.

9.4.2. Primary Endpoint

The primary endpoint is endoscopic recurrence prior to or at Week 48 as defined by modified Rutgeerts score ≥ i2a in the neo-terminal ileum, anastomotic site, or its equivalent elsewhere in the GI tract (eg, colonic ulceration).

Estimands and Estimators

Primary Estimand of Endoscopic Recurrence prior to or at Week 48

Treatment by Week 48:

Experimental: Guselkumab CCI [redacted] at Week 0 and then CCI [redacted] at Week 8, then CCI [redacted] thereafter through the end of the total study period.

Control: Matched placebo CCI at Weeks 0 and 8 and then CCI thereafter through the end of the total study period.

i. Population:

Participants with recent (<49 days) qualifying surgery and no evidence of active Crohn's disease postoperatively.

ii. Variable (endpoint):

A binary recurrence variable (recurrence/no recurrence) where recurrence is defined as Endoscopic Recurrence prior to or at Week 48 (as defined by modified Rutgeerts score greater than or equal to i2a) or experiencing intercurrent events (ICEs) 1-4 presented below.

iii. Intercurrent events (ICEs) and corresponding strategies:

The following are the ICEs considered for this study:

1) A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)
2) A prohibited change in CD medication
3) Discontinuation of study intervention due to lack of efficacy or an AE of worsening CD
4) Cross over to open-label guselkumab
5) Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)
6) Discontinuation of study intervention due to reasons other than those in ICE 3 or 5

Intercurrent events in categories 1-4 will be handled by the composite strategy. The composite strategy assesses the treatment effects not only based on the variable measurements, but also based on ICEs. This estimand acknowledges that having an ICE in categories 1-4 is an unfavorable outcome. For participants experiencing ICEs in category 5 and 6, the treatment policy strategy will be used and considers the occurrence of ICE category 5 and 6 is irrelevant in defining the treatment effect and so observed values of the variable will be used, if available, regardless of the occurrence of ICE category 5 and 6.

iv. Population-level summary:

– Difference in proportions of the binary recurrence variable of endoscopic recurrence, as described above, between guselkumab group and the placebo group.

Estimators

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

To compare the guselkumab versus placebo group for the primary endpoint, the Cochran Mantel Haenszel chi-square test (2-sided) will be used. The study will be considered successful if the test of the primary endpoint is positive at the 0.05 significance level.

After accounting for the ICE strategies, missing data will be imputed by multiple imputation. To examine the robustness of the primary endpoint analyses, sensitivity analyses using alternative missing data handling rules (eg, treat missing as endoscopic recurrence) will be performed. Details will be specified in the SAP.

In addition, subgroup analyses of the primary endpoint will be performed based on demographic and baseline disease characteristics, and baseline and previous use of medications for CD.

9.4.3. Secondary Endpoints

The first secondary endpoint is clinical remission without disease recurrence at Week 48. The analyses of this endpoint will be performed after the test of the primary endpoint.

- Clinical remission without disease recurrence is a composite endpoint defined by the following:
    - CDAI < 150 at Week 48 and
    - No endoscopic recurrence as defined by Rutgeerts score < i2 by Week 48 and
    - Have not experienced a disease recurrence as defined below

The second secondary endpoint is time to disease recurrence. The analyses of this endpoint will be performed after the test of the primary endpoint and the first secondary endpoint.

- Disease Recurrence is a composite endpoint defined by the following:
    - A ≥ 70-point increase from baseline in CDAI score at beyond 8 weeks after randomization; and a CDAI score of ≥ 200 **and** evidence of endoscopic recurrence. Endoscopic recurrence is defined as a modified Rutgeerts score of ≥ i2a at the anastomotic site or its equivalent elsewhere in the GI tract, unless a stool test for C. difficile toxin or other enteric pathogen is positive;
        - In event of a positive test for enteric pathogen including C. difficile toxin, the underlying infection should be treated and if ileocolonoscopy has not yet been performed, it should only be done when the infection has resolved, and if disease recurrence threshold is still met
    - OR initiation of a physician-prescribed corticosteroids, or an increase in the dose of steroids already being taken (by greater than 5 mg/day), for over one week for the treatment of CD **and** evidence of endoscopic recurrence as described above, unless a stool test for C. difficile toxin or other enteric pathogen is positive
    - OR a new draining external fistula
    - OR the reopening and draining of a previously existing external fistula
    - OR developing a new internal fistula
    - OR developing a new perianal abscess

- OR developing a new intra-abdominal abscess more than three months after the date of the index surgery

Participants who have confirmed endoscopic recurrence without disease recurrence at Week 24 or Week 48 and cross over to open-label guselkumab treatment will be censored at cross over for the time to disease recurrence endpoint.

Estimands and Estimators

Estimand of Clinical Remission without Disease Recurrence at Week 48

Treatment:
Experimental: Guselkumab CCI at Week 0 and then CCI at Week 8, then CCI thereafter through the end of the total study period.

Control: Matched placebo CCI at Weeks 0 and 8 and then CCI thereafter through the end of the total study period.

i. Population: Participants with recent (<49 days) qualifying surgery and no evidence of active Crohn's disease postoperatively.

ii. Variable (endpoint):
A binary variable of clinical remission without disease recurrence at Week 48 (as defined by Rutgeerts score smaller than i2 and CDAI < 150 without disease recurrence) or experiencing ICEs 1-4 presented below.

iii. ICEs and corresponding strategies:
The following are the ICEs considered for this study:
1) A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)
2) A prohibited change in CD medication
3) Discontinuation of study intervention due to lack of efficacy or an AE of worsening CD
4) Cross over to open-label guselkumab
5) Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)
6) Discontinuation of study intervention due to reasons other than those in ICE 3 or 4

Intercurrent events in categories 1-4 will be handled by the composite strategy. The composite strategy assesses the treatment effects not only based on the variable measurements, but also based on ICEs. This estimand acknowledges that having an ICE in categories 1-4 is an unfavorable outcome. For participants experiencing ICEs in category 5 and 6, the treatment policy strategy will be used and considers the occurrence of ICE category 5 and 6 is irrelevant in defining the treatment effect and so observed values of the variable will be used, if available, regardless of the occurrence of ICE category 5 and 6.

iv. Population-level summary: Difference in proportions of the binary variable of clinical remission without disease recurrence, as described above, between guselkumab group and the placebo group.

Estimators

The analysis of the first secondary endpoint will be based on the Full Analysis Set. Participants will be analyzed according to the intervention group to which they were randomized regardless of the study intervention they actually received.

To compare the guselkumab versus placebo group for the first secondary endpoint, the CMH chi-square test (2-sided) will be used.

After accounting for the ICE strategies, missing data will be imputed by multiple imputation.

Estimand of Disease Recurrence

Treatment:

Experimental: Guselkumab CCI at Week 0 and then CCI at Week 8, then CCI thereafter through the end of the total study period.

Control: Matched placebo CCI at Weeks 0 and 8 and then CCI thereafter through the end of the total study period.

i. Population: Participants with recent (<49 days) qualifying surgery and no evidence of active Crohn's disease postoperatively.
ii. Variable (endpoint): The time to disease recurrence (as defined above) or experiencing ICE 1-3 presented below.
iii. ICEs and corresponding strategies:
   1) A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)
   2) A prohibited change in CD medication
   3) Discontinuation of study intervention due to lack of efficacy or an AE of worsening CD
   4) Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)
   5) Discontinuation of study intervention due to - reasons other than those in ICE 3 or 4

Intercurrent events in categories 1 to 3 will be handled by the composite strategy. This estimand acknowledges that having an ICE in categories 1 to 3 is an unfavorable outcome. For participants experiencing ICEs in category 4 and 5, the treatment policy strategy will be used and considers the occurrence of ICE category 4 and 5 is irrelevant in defining the treatment effect and so observed values of the variable will be used, if available, regardless of the occurrence of ICE category 4 and 5.

iv. Population-level summary: Difference in the time to disease recurrence (as defined above) or experiencing ICE 1-3 presented above between guselkumab group and the placebo group.

Estimators

The analyses will be based on the Full Analysis Set. Participants will be analyzed according to the intervention group to which they were randomized regardless of the study intervention they actually received.

The log-rank test will be used to compare disease recurrence distribution between the two treatment groups. The Kaplan-Meier method will be used to estimate the distribution of disease recurrence for each treatment. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals are to be estimated using Cox regression model with treatment and stratification factors. Participants who have not achieved disease recurrence during the main study period at the database lock will be censored at the last visit. Participants without any post-baseline follow-up will be censored at randomization.

The other secondary endpoints include:

- Abdominal pain free (abdominal pain [AP] score = 0) at Week 48
- Time-to-recurrence of symptoms
- Steroid-free clinical remission at Week 48

These endpoints will be analyzed in a similar way as endoscopic recurrence (binary endpoint) or time to disease recurrence (time to event endpoint). Type I error will be controlled over the primary and secondary endpoints hierarchically. Further details will be included in SAP.

9.4.4. Other/Exploratory Endpoints

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

Other endpoints include:

- Change in PROMIS-Fatigue Short Form 7a score over 48 weeks
- Abdominal pain (AP score = 0) at each post baseline visit through Week 152
- Time to a flare of abdominal pain
- Clinical remission (CDAI <150) at each post baseline visit
- Change in PROMIS-Fatigue SF 7a at each post baseline visit through Week 152
- Change in PROMIS-29 score, both overall score and individual domain scores at each post baseline visit through Week 152
- Change from baseline in the WPAI at each post baseline visit through Week 152
- The number of participants not on corticosteroids and without disease recurrence at each post baseline visit through Week 152
- The number of participants not on corticosteroids and without endoscopic or disease recurrence at each post baseline visit through Week 152
- Endoscopic recurrence prior to or at Week 24
- Histologic score (as measured by Geboes scale/RHI/GHAS) at Week 48 ileocolonoscopy
- The number of participants with Geboes score over 3.1 at Week 48 ileocolonoscopy

- The number of participants with Geboes score of 2.0 or less at Week 48 ileocolonoscopy
- Clinical remission (CDAI <150) at Week 24 after initiation of guselkumab SC induction
- Clinical response (CDAI decrease of <100 points or CDAI <150) 24 weeks after initiation of guselkumab SC induction
- Disease recurrence (using definition described in Section 9.4.3) at Week 152
- Fecal calprotectin recurrence, defined by calprotectin of >200 µg/g with a 100 µg/g increase over baseline
- The change from baseline in fecal calprotectin concentration at all postbaseline visits through Week 152
- The change from baseline in CRP concentration at all postbaseline visits through Week 152

An additional exploratory analysis for risk factors of endoscopic and disease recurrence will be performed. A sensitivity analysis of the primary endpoint will be performed using a Rutgeerts score of > i3 as the definition for endoscopic recurrence.

9.4.5. Safety Analyses

All safety analyses will be based on the Safety Analysis Set. For the safety analyses, participants will be analyzed according to the study intervention they actually received regardless of the study intervention they were randomized to.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Any AE occurring at or after the initial administration of study intervention is considered to be treatment emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

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 AE or a SAE.

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

- Frequency and type of AEs.
- Frequency and type of SAEs.
- Frequency and type of related AEs as assessed by the investigator.
- Frequency and type of AEs leading to discontinuation of study intervention.
- Frequency and type of infections, including serious infections.
- Frequency and type of injection site reactions.

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.

9.4.6. Other Analyses

9.4.6.1. Pharmacokinetic Analyses

The analyses are based on the PK Analysis Set.

Descriptive statistics of the serum guselkumab 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 may be used to evaluate guselkumab PK parameters. The influence of important covariates on the population PK parameter estimates may be evaluated. If performed, details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate 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 SAP.

9.4.6.2. Pharmacogenomic Analyses

DNA samples will be analyzed for identification of genetic factors that may be associated with clinical response. This research may consist of the analysis of 1 or more candidate genes or assessment of single nucleic polymorphisms in relation to guselkumab intervention and/or Crohn's disease.

9.4.6.3. 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 intervention group where local regulations permit. Associations between baseline levels and changes from baseline in select biomarkers 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, and ileocolonic biopsy analyses will be reported in separate technical reports.

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.

9.4.6.4. Immunogenicity Analyses

The analyses are based on the Immunogenicity Analysis Set.

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

A listing of participants who are positive for antibodies to guselkumab will be provided. The maximum titers of antibodies to guselkumab will be provided for participants who are positive for antibodies to guselkumab.

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

9.4.6.5. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum guselkumab concentrations and efficacy measures will be analyzed graphically. If any visual trend is observed, additional analysis may be conducted if deemed necessary.

9.5. Interim Analysis

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

Abbreviation	Definition
6-MP	6-mercaptopurine
AE	adverse event
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ALT	alanine transferase
AP	abdominal pain
AST	aspartate transaminase
AZA	Azathioprine
BCG	Bacille Calmette-Guérin
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
DBL	database lock
eCRF	electronic case report form
ET	early termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GHAS	Global Histology Activity Index
GI	Gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator Brochure
IBD	inflammatory bowel disease
ICE	intercurrent event
ICF	informed consent form
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IGRA	interferon gamma release assay
IL	Interleukin
INR	International Normalized Ratio
IQ	Interquartile
IRB	Institutional Review Board
C [redacted]	[redacted]
IWRS	interactive web response system
LTE	long-term extension
mAb	monoclonal antibody
MMRM	mixed model for repeated measures
MTX	Methotrexate
OTC	over the counter
PCC	Protocol Clarification Communication
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic(s)

POCD	postoperative Crohn's disease
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PROMIS	Patient-Reported Outcomes Measurement System
CCI	[redacted]
RHI	Robarts histopathology index
SAE	serious adverse event
SAP	Statistical Analysis Plan
C	[redacted]
SD	standard deviation
SES-CD	Simple Endoscopic Score – Crohn's Disease
SF	stool frequency
SI	International Units
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
WPAI	Work Productivity Activity Index

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory.

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose [nonfasting]
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)</td><td>Total bilirubin
Alkaline phosphatase
Calcium
Phosphate
Albumin
Total protein
Magnesium</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Appendix 7: Liver Safety.

Potential Hy's Law case (ALT or AST ≥3 x ULN and Tbili ≥2 x ULN) reporting requirements are defined in Section 8.5.1.</td></tr>
<tr><td>Other Screening Tests</td><td colspan="3">• Serum (at screening) and urine Pregnancy Testing (for women of childbearing potential only)
• Serology (at screening; HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody, hepatitis B surface antibody [antiHBs], hepatitis B core antibody total [anti-HBc])
• TB evaluation (QuantiFERON-Gold)</td></tr>
</table>

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country- or territory-specific requirements.

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

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers, Clinical Trial Managers, and/or Contract Research Organizations who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

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

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree

on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

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

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.2.

10.3.2. Financial Disclosure

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

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

10.3.3. Informed Consent Process Form

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

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

participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. 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 physician may also recontact the participant for the purpose of obtaining consent to collect information about his or her survival status.

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

If the participant or legally acceptable representative is unable to read or write, an impartial witness must be present for the entire informed consent process (which includes reading and explaining all written information) and must personally date and sign the ICF after the oral consent of the participant or legally acceptable representative is obtained.

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

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

Participants who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative.

10.3.4. 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 (or his or her legally acceptable representative) includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete, or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory PD, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. 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. Samples will only be used to understand guselkumab, to understand CD, to understand differential intervention responders, and to develop tests/assays related to guselkumab and CD. The research may begin at any time during the study or during 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.

10.3.6. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or 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 the goals of this study and will not use it for other purposes without the sponsor's prior written consent.

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

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

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

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

of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.7. 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, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

The sponsor may review the 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.

10.3.8. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the eCRF. All eCRF 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.

The study data will be transcribed by study site personnel from the source documents onto an electronic eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms must be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.3.9. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents must be identifiable. Given that PROs are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

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

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

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

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

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

10.3.10. Monitoring

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

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor may compare the data entered into the eCRF 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 eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

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

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

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

10.3.11. On-site Audits

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

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

10.3.12. Record Retention

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

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

10.3.13. Study and Site Start and Closure

The first subject screened is considered the first act of recruitment and the study start date.

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

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.5.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

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

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it 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 must be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

10.4.2. Attribution Definitions

Assessment of Causality

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

Related

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

Not Related

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

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

10.4.3. Severity Criteria

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

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

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

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

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

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention (see Section 6.7)
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

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

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the 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 AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

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

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number

- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

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

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

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

The cause of death of a participant in a study within 12 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

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

10.4.6. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

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

Procedures

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

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

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.5. Appendix 5: Contraceptive Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.5.5, Pregnancy and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as >45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle-stimulating hormone [FSH] level >40 IU/L). If there is a question about menopausal status in women on hormone replacement therapy (HRT), the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  - Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.
  - Has congenital abnormalities resulting in sterility.

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

If reproductive status is questionable, additional evaluation should be considered.

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

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

Examples of Contraceptives

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
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception 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).

10.6. Appendix 6: 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 (antiHBc+) 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.

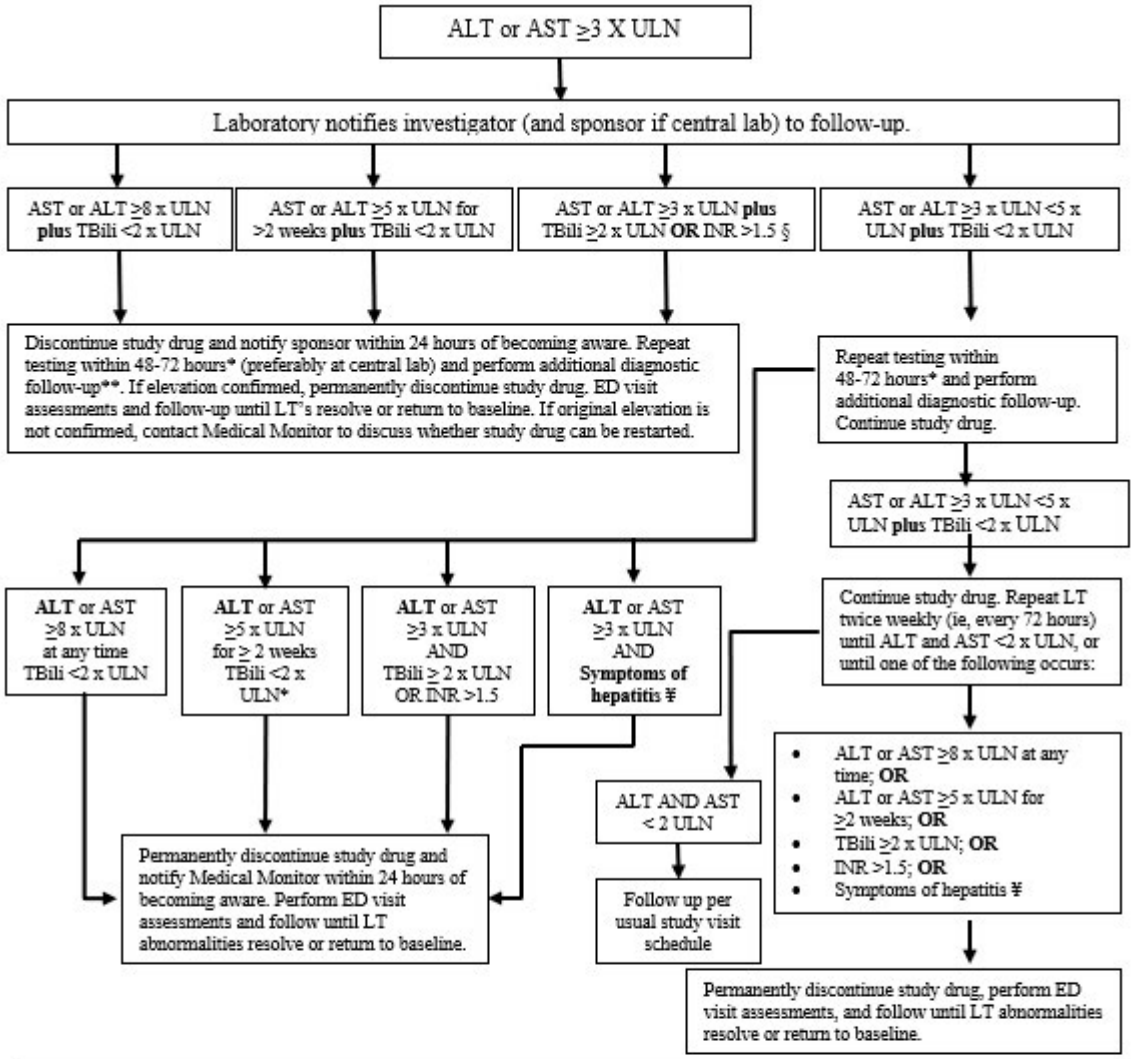
These eligibility criteria based on HBV test results are also represented in table below. For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines.

Eligibility Based on Hepatitis B Virus (HBV) Test Results			
Hepatitis B Test Result			STATUS
Hepatitis B surface antigen (HBs-Ag)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	
negative	negative	negative	ELIGIBLE
negative	(+)	negative	
negative	(+)	(+)	
(+)	negative *or* (+)	negative *or* (+)	**NOT ELIGIBLE**
negative	negative	(+)	Requires 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 this protocol.

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

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



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

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

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

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

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

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

- **ALL STUDIES SHOULD BE REPORTED WITH APPROPRIATE SOURCE DOCUMENTATION.**
- **THE STUDY MEDICAL MONITOR SHOULD BE NOTIFIED WHEN THE ABNORMALITIES ARE DETECTED AND PROVIDED WITH AN UPDATE OF THE CONTINUED MONITORING RESULTS OF THE DIAGNOSTIC WORK-UP.**
- **CONSULT MEDICAL MONITOR FOR ANY QUESTIONS ON WORK -UP RECOMMENDATIONS, INCLUDING WHEN OPTIONAL TEST MAY BE INDICATED.**
- **A HEPATOLOGIST CONSULTATION SHOULD BE CONSIDERED IF CLINICALLY INDICATED FOR THE DIAGNOSIS AND MANAGEMENT OF POTENTIAL DILI.**

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

1. Obtain detailed history of present illness (abnormal LTs) including (if not already obtained at baseline) height, weight, body mass index. Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure, occupational exposure to hepatotoxins, diabetes mellitus, gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other medications including acetaminophen, nonsteroidal anti-inflammatory drugs, over-the-counter herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical exam, obtain vital signs and body mass index, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy).
2. Imaging is strongly recommended to exclude other liver injury causes, particularly if TBili or ALP is >2 x ULN, or when clinically indicated based on medical history (eg, to exclude non-alcoholic hepatic steatosis). Imaging is mandatory if subject meets criteria for study intervention discontinuation according to the liver tests algorithm. Liver ultrasound is the recommended initial imaging modality with consideration of further imaging (eg, CT, MRI, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation).
3. If TBili is ≥2 x ULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia.

4. Complete blood count with WBC, eosinophil, and platelet count (to further scrutinize potential immune-mediated mechanism of injury)
5. INR, and total protein and albumin (compute globulin fraction) should also be documented (to further scrutinize potential severity of the liver damage). If INR is abnormal, prothrombin time, partial thromboplastin time should be obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.
6. If initial LTs and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin (Ig)M, anti-hepatitis A virus total, HBsAg, anti-HBs, anti-HBc total, anti-HBc IgM, anti-HCV, anti-hepatitis E virus IgM (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus, and cytomegalovirus screen.
   - If participant is immunosuppressed, test for HCV RNA and hepatitis E virus RNA by polymerase chain reaction.
   - If HBsAg or anti-HBc IgM or anti-HBc IgG positive, also get HBV DNA to detect active Hepatitis B, especially in patients who are immunosuppressed.
   - If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.

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

7. Based on potential baseline confounders of the disease target population consider (optionally): gamma-glutamyl transferase (to confirm the liver origin of elevated ALP levels), serum creatine phosphokinase (to confirm the liver origin of elevated AST levels], lactate dehydrogenase (to help exclude hemolysis), glutamate dehydrogenase (if muscle injury is suspected or if muscle disease is target population).
8. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including antinuclear antibody, anti-liver kidney microsomal antibody type 1, anti-liver-kidney microsomal antibodies, anti-smooth muscle antibodies (to screen for additional immune-related etiologies), erythrocyte sedimentation rate, and CRP (to screen for potential systemic inflammatory causes).
9. If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions below), then gamma-glutamyl transferase, anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/total iron binding capacity and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If patient is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient is sick enough

to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.

Patterns of DILI Based on Elevations of Liver Tests

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

10. A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

    A liver biopsy may be considered:

    - if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.
    - if peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak ALP has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
    - in cases of DILI where continued use or re-exposure to the implicated agent is expected.
    - if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

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

10.8. Appendix 8: Study Conduct During a Natural Disaster/Major Disruption/ Pandemic

It is recognized that the COVID-19 pandemic 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, 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 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 travel to the study site is considered to be dangerous, 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 COVID-19 pandemic, scheduled visits cannot be conducted in person at the study site, they 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. 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 CRF.

If the participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing study assessments, and follow-up. Modifications made to the study conduct as a result of the infection 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 pandemic. Therefore, temporary measures may be implemented if considered appropriate by the Sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
  - remote (eg, by phone/telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures eg, those related to safety monitoring/efficacy evaluation/study intervention storage and administration (including training where pertinent)

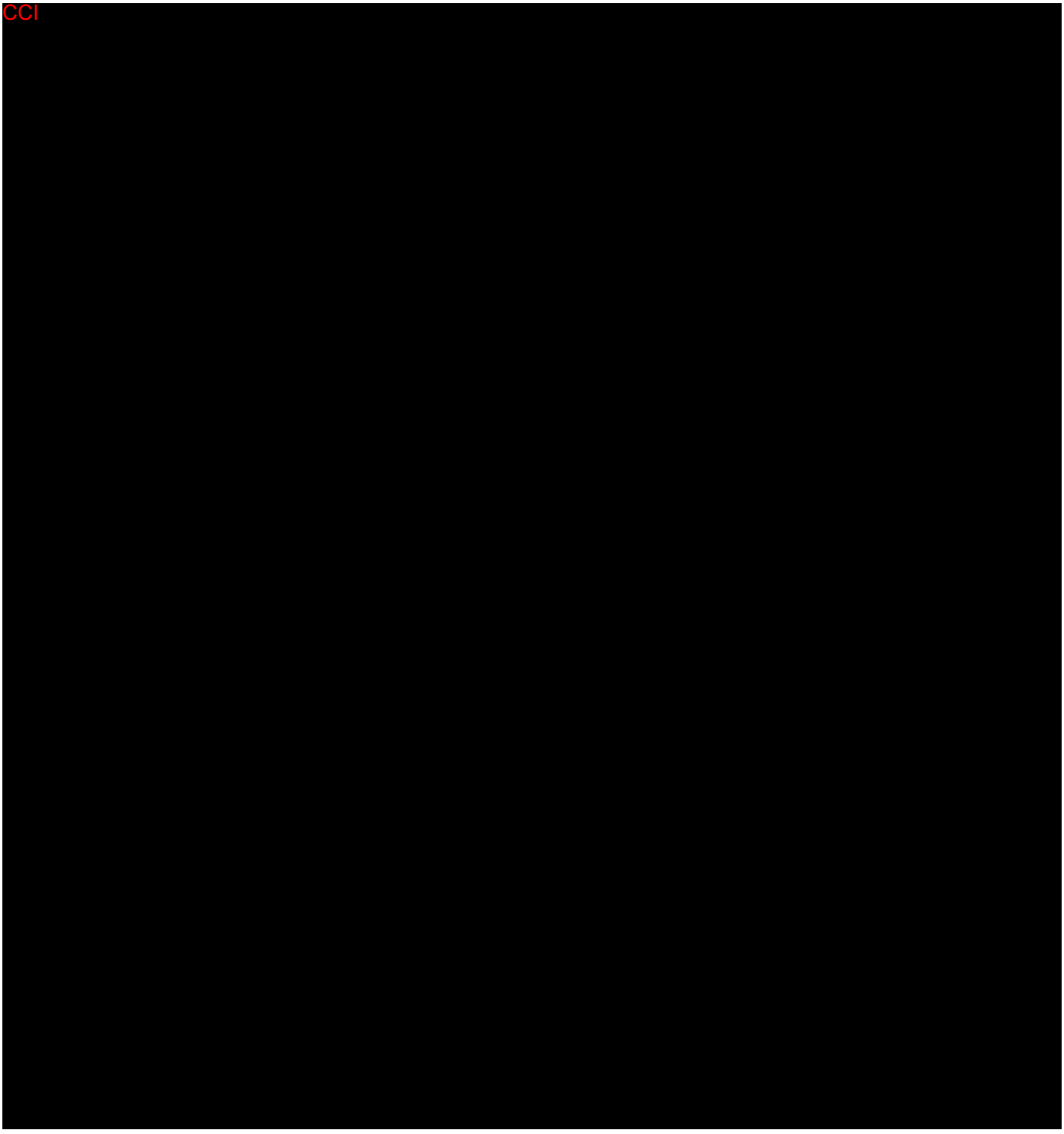
  - procurement of study intervention by patients (or designee) or shipment of study intervention from the study site directly to patients for at-home administration (including the potential for patient self-administration of study intervention)
  - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.
  - other relevant study data elements impacted by the pandemic should also be documented as "COVID-19-related" in eCRFs and/or other study systems, as directed by detailed Sponsor guidance. These may include missed/delayed/modified study visits or assessments/dosing, and instances where temporary measures such as those above are implemented.
  - The study intervention may be delivered directly to the participants from a courier, if necessary, as permitted by local requirements and/or regulations if approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) (see Section 6.1). Details regarding delivery are provided in the study manual. The participant has the ability to opt-in or opt-out of using this service throughout the duration of the trial according to the protocol Schedule of Activities (SoA).
- 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).

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.

10.9. Appendix 9: Clinical Disease Activity Index

CCI



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INVESTIGATOR AGREEMENT

CNTO1959 (guselkumab) Clinical Protocol CNTO1959CRD3007 Amendment 1

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:

[redacted]

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