Janssen Pharmaceutical K.K.*

Clinical Protocol

Protocol Title

A Phase 3, Open-label, Multicenter Study to Evaluate the Safety and Efficacy of Guselkumab in Participants With Moderately to Severely Active Crohn's Disease

Protocol CNTO1959CRD3003; Phase 3
AMENDMENT 1

CNTO1959 (guselkumab)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

Status: Approved
Date: 11 December 2020
Prepared by: Janssen Pharmaceutical K.K.
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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	11 December 2020
Original Protocol	6 March 2020

Amendment 1 (11 December 2020)

Overall Rationale for the Amendment: To revise the inclusion criteria around SES-CD scores in align with the amendment of GALAXI program.

Section Number, Name	Description of Change	Brief Rationale
1.1, Synopsis 4.1, overall design	Participants who have a concurrent or history of SB disease activity confirmed by radiography, imaging and/or endoscopy may be eligible to participate in the substudy for additional SB assessment by device-assisted enteroscopy.	To clarify the imaging data are acceptable to confirm a concurrent or history of SB disease.
1.3, Table 1	The Note for Chest radiograph item was edited: Chest radiograph (posterior-anterior and lateral views) must ~~may~~ be obtained within 12 weeks before the Week 0 visit.	To clarify that the time frame for obtaining this screening activity is required, and not optional.
	The Note for Stool studies item was edited: Stool studies for enteric pathogens may be performed at screening at either the central or a local laboratory and must include a stool culture and *Clostridium difficile* toxin assay. Although stool studies may be processed at either the central or local laboratory, the central laboratory is preferred when available. Stool studies must have been performed within 4 months before Week 0. Additional testing, such as ova and parasites or *Escherichia coli* O157:H7 assessment, may be performed at the investigator's clinical discretion.	To clarify that central laboratory processing is preferred and to confirm the timing of screening stool studies.
1.3, Table 2	"Review medical history" row added to the SoA for Week 0 to Week 48.	Added as a double-check at Week 0 before participant randomization.
1.3, Table 2, 3 8.2.6, Tuberculosis Evaluation(s)	If TB is suspected at any time during the study, a chest radiograph or chest CT, and QuantiFERON-TB or T-SPOT test should be performed.	To clarify that chest CT is also acceptable for the test method to assess TB during the study
1.3, Table 2, 4	The required timing of the endoscopy was clarified, and it should be scheduled as close as possible to the designated visit	Clarification
1.3, Table 2	Delete the following footnote. a. If a participant discontinues study intervention prior to the Week 12 visit, the participant should complete the evaluations as detailed under the Study Intervention Discontinuation (SID) visit at the time of SID. In addition, the participant should	All tests specified at Week 12 is no longer necessary for a participant who discontinues study intervention prior to the Week 12 visit if SID and FES are performed as per protocol.

Section Number, Name	Description of Change	Brief Rationale
	return for the Week 12 visit and complete all evaluations specified at Week 12 (except the endoscopy if already completed at the SID visit) and have a final efficacy and safety (FES) visit approximately 12 weeks after their last study intervention administration. See Table 4 for additional details .	
1.3, Table 3	Weight measurement was added at q4w visit timing in the LTE.	To have sufficient data to precisely calculate CDAI in the LTE
	Stool samples required for ~~last efficacy visit~~ q48w visit must be obtained before the start of the bowel preparation	To clarify the timing of stool sample collection
5.1, Inclusion Criteria	Have endoscopic evidence of active ileocolonic CD as assessed by central endoscopy reading at the screening endoscopy (~~Schedule of Activities~~SoA, Table 14), defined as a screening SES-CD score ≥~~3~~6 (or ≥4 for participants with isolated ileal disease), based on the presence of ulceration in ~~any~~at least 1 of the 5 ileocolonic segments, resulting in the following specified ulceration component scores: a. a minimum score of 1 for the component of "size of ulcers" AND b. a minimum score of 1 for the component of "ulcerated surface". OR Have endoscopic evidence of active SB CD as assessed by central endoscopy reading at the screening device assisted enteroscopy (~~Schedule of Activities~~SoA, Table 14), defined as a screening modified SES-CD score ≥5, based on the presence of ulceration in any 1 of the 3 segments including terminal ileum, proximal ileum and jejunum.	Inclusion criteria for endoscopic evidence in Guselkumab Crohn's disease phase 3 study (GALAXI 2/3) have been revised based on foreign Health Authority feedback and Phase 2 (GALAXI 1) results. The inclusion criteria for this study should be aligned accordingly in order to make the study population of this study consistent with GALAXI program. Typos for table reference is also corrected.
	Have screening laboratory test results within the following parameters, and if 1 or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted during the approximately 8~~5~~-week screening period	To align with designated screening period allowance
5.2, Exclusion Criteria	Exclusion Criterion 3: "Requiring general anesthesia" was removed as an example of other major surgery: 3. Has had any kind of bowel resection within 6 months, or any other intra-abdominal or other major surgery ~~(eg, requiring general anesthesia)~~ within 12 weeks, before baseline.	The example was removed to prevent confusion because general anesthesia may be administered for less invasive surgeries that would not be exclusionary.
	Exclusion Criterion 6.d.4: Clarification was added for other immunomodulatory biologic agents:	Clarification

Section Number, Name	Description of Change	Brief Rationale
	6. Has received any of the following prescribed medications or therapies within the specified period: …d. Biologic agents: …4) Other immunomodulatory biologic agents, including approved and investigational biologic agents, received within 12 weeks of baseline or within 5 half-lives of baseline, whichever is longer.	
	Exclusion Criterion 6.e: A clarification was added to the EC regarding investigational interventions: e. Any investigational intervention received within 4 weeks of baseline or within 5 half-lives of baseline, whichever is longer. (Refer to Exclusion Criterion 6.d.4 for investigational biologic agents.)	Clarification
6.5.1, Concomitant Medications	A phrase was deleted from the following subsection: **Week 12 and through Week 48** From Week 12 through Week 48 of each study, participants may transiently use (ie, for <4 weeks) increased doses of corticosteroids for reasons other than ~~loss of response to~~ treatment for Crohn's disease (eg, stress doses of corticosteroids for surgery, asthma, adrenocortical insufficiency).	Clarification
8, Study assessments and procedures	electrocardiogram (ECG) and vital signs (blood pressure, pulse rate, respiratory rate, and ~~axillary~~ body temperature) should be performed first	Amended to allow other models of body temperature measurements in addition to axillary
8.2.11, Columbia-Suicide Severity Rating Scale (C-SSRS)	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	To clarify the C-SSRS should be performed before any other study procedure
10.2, Appendix 2: Clinical Laboratory Tests	FSH was added	Omitted from the previous version
10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	Following section was deleted: ~~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 Crohn's~~	No additional sample retention is currently planned for future research

Section Number, Name	Description of Change	Brief Rationale
	~~disease, to understand differential intervention responders, and to develop tests/assays related to guselkumab and Crohn's disease. The research may begin at any time during the study or the poststudy storage period.~~ ~~Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2, Withdrawal From the Study).~~	
10.4, Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Following sentence was deleted: ~~· Unexpected therapeutic or clinical benefit from use of a sponsor study intervention~~	This is not intended to be reported in a clinical study
10.6, Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments	Added a sentence to the first paragraph of text in the Appendix (below the algorithm): A hepatologist consultation should be considered if clinically indicated for the diagnosis and management of potential DILI.	Added at the request of a Health Authority, to ensure that investigators will perform appropriate follow-up in the evaluation and management of cases of potential drug-induced liver injury.
Throughout the protocol	Minor grammatical, formatting, and/or spelling changes were made.	Minor errors were noted.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3, Open-label, Multicenter Study to Evaluate the Safety and Efficacy of Guselkumab in Participants With Moderately to Severely Active Crohn's Disease

Guselkumab (CNTO 1959) is a fully human immunoglobulin G (IgG)1 lambda monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

OBJECTIVES AND HYPOTHESIS

Primary Objective

- To evaluate the safety of guselkumab in participants with Crohn's disease (CD)

Secondary Objectives

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

Exploratory Objective

- To assess the efficacy of guselkumab on small bowel (SB) lesions

Hypothesis

The primary objective is to evaluate the safety of guselkumab in participants with CD. No hypothesis testing will be performed in this study.

OVERALL DESIGN

This is a Phase 3, open-label, multicenter study to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active CD who have demonstrated an inadequate response or failed to tolerate the previous conventional therapy (ie, 6-mercaptopurine [6-MP], azathioprine [AZA], or corticosteroids [CON-failure. Refer to Section 10.7 Appendix 7]) or biologic therapy (ie, TNFα antagonists or vedolizumab [BIO-failure. Refer to Section 10.8 Appendix 8]).

Participants will receive following guselkumab treatment in an open-label fashion;

- Weeks 0, 4, and 8: Guselkumab 200 mg intravenous (IV) administration (induction)
- Every 4 weeks (q4w) after Week 8 until the end of the study: Guselkumab 200 mg subcutaneous (SC) administration (maintenance)

The study will be conducted in 3 phases: a maximum 8-week screening phase, a 48-week treatment phase followed by long-term extension (LTE) phase, and a posttreatment follow up visit (12 weeks after the participant's last dose of study intervention to collect any adverse events since the last study visit). The duration of individual participation will be approximately 68 weeks if a participant ends the study participation at the end of treatment phase and does not enter the LTE.

At-home self-administration can begin after the Week 48 visit at the discretion of the investigator and participant, and upon completion of at least 3 training sessions starting from Week 48. All participants who

are willing to perform at-home self-administration will be requested to record at-home administration medication diary.

Long-term extension will be continued until the time when guselkumab is approved for CD indication in Japan and marketed guselkumab becomes available at the study site (up to around 3 years at maximum in addition to a 48-week treatment phase depending on the timing of approval of guselkumab for CD in Japan) or discontinuation of the clinical development of guselkumab for CD, and all participants who will be continuing the treatment at the time of marketing approval of guselkumab for CD or discontinuation of the clinical development of guselkumab for CD will be asked to come to the study site, and complete their safety and efficacy assessments.

Participants who have a concurrent or history of SB disease activity confirmed by radiography, imaging and/or endoscopy may be eligible to participate in the substudy for additional SB assessment by device-assisted enteroscopy.

Key safety assessments will include the monitoring of adverse events (AEs), vital sign measurements, and clinical laboratory tests including inflammatory biomarkers. Key efficacy assessments include Crohn's Disease Activity Index (CDAI) and its components, endoscopic assessments by either ileocolonoscopy or device-assisted enteroscopy (if a participant agrees to perform additional SB assessment).

NUMBER OF PARTICIPANTS

The study will target to enroll a total of approximately 25 participants.

INTERVENTION GROUPS AND DURATION

Participants will receive guselkumab 200 mg IV induction doses at Weeks 0, 4, and 8 (total of 3 IV doses), followed by guselkumab 200 mg SC maintenance doses as q4w starting at Week 12 through Week 44.

During LTE, participants will continue to receive the same study intervention regimen that they were receiving at the end of maintenance, with the first dose in the LTE being administered at Week 48.

EFFICACY EVALUATIONS

Efficacy evaluations will include the following:

- CDAI including patient-reported outcome (PRO)-2 score (the unweighted CDAI components of the total number of liquid or very soft stools and the abdominal pain [AP] score)
- Endoscopic assessments of the intestinal mucosa based on the presence and absence of mucosal ulcerations and the simple endoscopic score for Crohn's Disease (SES-CD) and/or modified SES-CD

PHARMACOKINETIC EVALUATIONS

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

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Inflammatory PD markers (CRP and fecal calprotectin) will be evaluated to assess the disease activities of CD for the participants throughout the study. Biomarker data may be used to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab treatment.

IMMUNOGENICITY EVALUATIONS

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

SAFETY EVALUATIONS

Safety evaluations conducted at each study visit will include the assessment of adverse events (AEs, at the visit and those occurring between evaluation visits), a tuberculosis evaluation and other infection assessments, clinical laboratory blood tests (complete blood count and serum chemistries), vital signs (as defined in the Schedule of Activities [SoA]), suicidality assessment, concomitant medication review, and observations for injection-site reactions, reactions temporally associated with an infusion, and/or allergic reactions.

STATISTICAL METHODS

There will be 3 analysis plans supporting this protocol: one for the analysis based on Week 24 database lock (including efficacy and safety analysis through Week 24), second one for the analysis based on Week 48 database lock (including full data through Week 48 except LTE), and last one for the analysis based on the entire study result including LTE.

No statistical hypothesis testing based on any endpoint is planned in this study, thus the sample size was not calculated based on statistical considerations. The objective of the study is to assess the safety of guselkumab in the Japanese patients with moderately to severely active CD together with CNTO1959CRD3001 study, and the sample size was chosen to achieve this objective and provide additional safety information as much as possible.

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

Safety Analysis

Safety analyses will include summaries of AEs, vital signs, and laboratory parameters. These analyses will be based on participants who received at least 1 dose of guselkumab.

Efficacy analysis

Efficacy analyses will be based on the Full Analysis Set, which is defined as all enrolled participants who had at least 1 dose of guselkumab in the study.

Efficacy analysis for SB assessment will only be performed among the participants who have assessment data at both baseline and Week 48 (or at the end of LTE period).

Pharmacokinetic Analysis

Pharmacokinetic analysis will be performed based on the population which includes all participants who received at least 1 dose of guselkumab and have at least 1 observed postdose PK data. Descriptive statistics of the serum guselkumab concentrations will be calculated at each sampling time point. These concentrations will be summarized over time.

Immunogenicity analysis

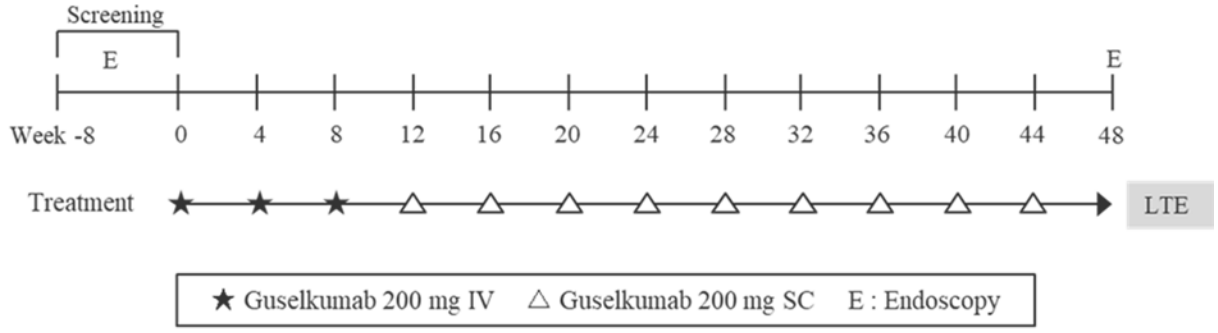
The incidence and titers of antibodies to guselkumab will be summarized for all participants who received at least 1 dose of guselkumab and have at least 1 observed postdose immunogenicity data. The incidence of neutralizing antibodies to guselkumab will be summarized for participants who are positive for antibodies to guselkumab and have samples evaluable for neutralizing antibodies to guselkumab.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum guselkumab concentrations and biomarker and/or efficacy measures may be analysed graphically.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Table 1: SoA – Screening Activities

Study Procedures	SCR (-8 wks)	Notes
Administrative		
Informed consent	X	
Inclusion/exclusion criteria	X	
Medical history and demographics including small bowel disease status	X	
ECG	X	
Chest radiograph/Chest CT	X	Chest radiograph (posterior-anterior and lateral views) or chest CT must be obtained within 12 weeks before the Week 0 visit.
QuantiFERON-TB or T-SPOT test	X	All participants will undergo QuantiFERON-TB or T-SPOT testing. The QuantiFERON-TB and T-SPOT tests are not required at screening for participants with a history of latent TB, if active TB has been ruled out, and if appropriate treatment has been initiated/completed (as described in Inclusion Criterion 8 [Section 5.1]).
Stool studies to evaluate for enteric pathogens	X	Stool studies for enteric pathogens may be performed at screening at either the central or a local laboratory and must include a stool culture and *Clostridium difficile* toxin assay. Although stool studies may be processed at either the central or local laboratory, the central laboratory is preferred when available. Stool studies must have been performed within 4 months before Week 0. Additional testing, such as ova and parasites or *Escherichia coli* O157:H7 assessment, may be performed at the investigator's clinical discretion.
HBV, HCV, and HIV testing	X	
Provide participant diary (CDAI) and training	X	Provide participants with the take-home diary and provide training on diary completion. A minimum of 7 days of CDAI/PRO-2 data during the screening period is required to calculate the CDAI/PRO-2 score at baseline (Week 0).
Schedule video ileocolonoscopy or device-assisted enteroscopy	X	During the initial screening visit the video endoscopy should be scheduled, if feasible.
Safety Assessments		
Adverse events	X	The reporting of adverse events should begin after the informed consent is signed and should continue for the duration of the screening period.
Physical examination	X	
Weight and height	X	
Vital signs	X	Temperature, pulse/heart rate, respiratory rate, and blood pressure
Urine pregnancy test	X	
C-SSRS	X	At the screening visit, the C-SSRS should be completed as the first assessment after signing informed consent and before any other tests, procedures, or other consultations to prevent influencing participant perceptions.
Efficacy Assessments		
Video ileocolonoscopy or device-assisted enteroscopy	X	To prevent interfering with the collection of CDAI/PRO-2 data for the Week 0 visit, the screening endoscopy will be performed at least 8 days before but no more than approximately 3 weeks before the Week 0 visit.
Clinical Laboratory Assessments		
Hematology and Chemistry including CRP	X	

Table 1: SoA – Screening Activities

Study Procedures	SCR (-8 wks)	Notes
Stool sample (fecal calprotectin)	X	If stool samples are collected around the time of the screening endoscopy, they must be collected before the start of the bowel preparation.
Ongoing Participant Review		
Concomitant therapy	X	Concomitant therapies should be documented after signing informed consent and should continue for the duration of the screening period.

Abbreviations: CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computerized tomography; ECG=electrocardiogram; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PRO=patient-reported outcome(s); SCR=screening; TB=tuberculosis; wks=weeks.

Table 2: SoA – Week 0 to Week 48

Week:	0	4	8	12	16	20	24	28	32	36	40	44	48[a,b]	Notes
Study Procedures[c,d]														
Administrative														
Inclusion/exclusion criteria	X													
Study Intervention Administration														
Review medical history	X													
Administer study intervention	X	X	X	X	X	X	X	X	X	X	X	X		All assessments described in this table are to be completed prior to study intervention administration, unless otherwise specified. C-SSRS should be completed first, and then any other clinical procedures, tests, or consultations.
Safety Assessments														
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X		Includes temperature, pulse/heart rate, respiratory rate, and blood pressure. Must be obtained: • before each IV infusion, approximately every 30 minutes during the infusion, and for 1 hour at approximately 30-minute intervals after completion of the final infusion • prior to and approximately 30 minutes after the final SC injection
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	Must be performed before every study intervention administration in female participants of childbearing potential.
TB evaluation/other infection assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	If TB is suspected at any time during the study, a chest radiograph or chest CT, and QuantiFERON-TB or T-SPOT test should be performed.
Injection-site evaluation				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.
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	For visits between Week 0 and Week 48, the C-SSRS should be completed first before any other tests, procedures, or other consultations to prevent influencing participant perceptions.

Table 2: SoA – Week 0 to Week 48

Week:	0	4	8	12	16	20	24	28	32	36	40	44	48[a,b]	Notes
Study Procedures[c,d]														
Efficacy Assessments														
Collect and review participant CDAI diary	X	X	X	X	X	X	X	X	X	X	X	X	X	Diary information should be completed daily and participants should bring their diaries to each visit. The daily diary includes patient-reported data for the CDAI (includes PRO-2 components). 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	X	X	X	X	X	X	X	X	X	X	X	X	X	Weight measurement is used to support CDAI assessments and safety.
Video ileocolonoscopy or device-assisted enteroscopy													X	To prevent interfering with the collection of CDAI/PRO-2 data, the video endoscopy must be performed at least 8 days before the designated visit (but as close as possible to the designated visit) or at the designated visit (ie, Week 48). If performed on the day of the designated visit, the 7 days before the initiation of the endoscopy preparation should be utilized to calculate CDAI/PRO-2 scores for these visits.
Clinical Laboratory Assessments														
Hematology and chemistry including CRP[e]	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.
Stool sample (fecal calprotectin)	X	X	X	X			X						X	Week 0: Not required if sample already collected within 2 weeks of the Week 0 visit. Week 48: Stool samples required for this visit must be obtained before the start of the bowel preparation for the video endoscopy if it is also scheduled for the visit.
Pharmacokinetics and Immunogenicity														
Guselkumab serum concentration	X	X	X	X	X	X	X		X		X		X	Blood samples should be collected before the administration of study intervention. The actual times of PK sample collections should be recorded. Week 0, Week 4, and Week 8: At these study visits with IV dosing, blood samples for PK analysis should be collected before the start of and approximately 60 minutes after completion of the final infusion.

Table 2: SoA – Week 0 to Week 48

Week:	0	4	8	12	16	20	24	28	32	36	40	44	48[a,b]	Notes
Study Procedures[c,d]														
Assessment for antibody to guselkumab	X	X	X	X			X		X		X		X	Blood samples should be collected before the administration of study intervention. The actual times of sample collections should be recorded.
Ongoing Participant Review														
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	
Crohn's disease-related hospitalizations and surgeries	X	X	X	X	X	X	X	X	X	X	X	X	X	Hospitalization for Week 48 endoscopy is not included in this category.

Abbreviations: AE=adverse event; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computerized tomography; IV=intravenous; PK=pharmacokinetic(s); PRO= patient-reported outcome(s); SC=subcutaneous; TB=tuberculosis.

Footnotes:

a. If a participant discontinues study intervention prior to the Week 48 visit, the participant should complete the evaluations as detailed under the Study Intervention Discontinuation (SID) visit at the time of SID. In addition, the participant should return for a Final Efficacy and Safety (FES) visit approximately 12 weeks after their last study intervention administration. See Table 4 for additional details.

b. Participants who are entering the long-term extension (LTE) at Week 48 should complete the Week 48 activities in this table (Table 2) and then refer to Table 3 for Week 48 study intervention administration activities. Participants who do not enter the LTE at Week 48 should complete a FES visit approximately 12 weeks after their last study intervention administration. See Table 4 for additional details.

c. Visit window should be ±7 days for each visit.

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

e. 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 at least every 3 months or shorter.

Table 3: SoA – Week 48 until the end of study of Long-Term Extension for eligible participants who have completed Week 48

	Week 48[a]	q4w visit	q8w visit[b]	q16w visit[c]	q48w visit[d]	Notes
Study Procedures[e,f]						
Study Intervention Administration						
Administer study intervention	X	X	X	X	X	All assessments described in this table are to be completed prior to study intervention administration, unless otherwise specified. The C-SSRS assessments should be completed first and then any other clinical procedures, tests, or consultations.
Instruction and training for self-administration	X	X	X	X	X	At-home self-administration can begin anytime at the discretion of the investigator and participant, and upon completion of designated training.
Safety Assessments						
Adverse events		X	X	X	X	Study participants who are trained to self-inject study intervention at home will be trained to perform self-evaluation for injection-site reactions and reporting of adverse events after administering the study intervention at home.
Physical examination	X				X	
Vital signs[g]	X	X	X	X	X	Includes temperature, pulse/heart rate, respiratory rate, and blood pressure. Must be obtained prior to and approximately 30 minutes after the final SC injection. For study participants receiving study intervention administration at the study site, vital signs will be assessed during the visit. For study participants who are trained to self-inject study intervention at home, vital signs will only be assessed at the study site when these participants receive study intervention at the study site.
Urine pregnancy test[g]		X	X	X	X	Must be performed prior to each study intervention administration in female participants of childbearing potential.
TB evaluation / other infection assessment		X	X	X	X	If TB is suspected at any time during the study, a chest radiograph or chest CT and a QuantiFERON-TB test or T-SPOT test should be performed.
Injection-site evaluation	X	X	X	X	X	An injection-site reaction is any adverse reaction at any SC study intervention injection site. Injection sites will be evaluated for reactions and any injection-site reaction will be recorded as an AE.
C-SSRS			X	X	X	The C-SSRS should be completed first before any other tests, procedures, or other consultations to prevent influencing participant perceptions.
Efficacy Assessments						
Collect and review diary cards (CDAI)[g]		X	X	X	X	Diary information should be completed daily and participants should bring their diaries to each visit. The daily diary includes patient-reported data for the CDAI. The most recent hematocrit value obtained will be used to calculate the CDAI.
Collect and review participant at-home administration medication diary			X			
Weight (for CDAI)[g]		X	X	X	X	Weight measurement is used to support the CDAI assessments and safety.

Table 3: SoA – Week 48 until the end of study of Long-Term Extension for eligible participants who have completed Week 48

	Week 48[a]	q4w visit	q8w visit[b]	q16w visit[c]	q48w visit[d]	Notes
Study Procedures[e,f]						
Video ileocolonoscopy or device-assisted endoscopy					X	Video endoscopy can be performed at discretion of the investigator at q48w visit but should be performed at SID visit at the end of the study. If video endoscopy were performed within 48 weeks before the SID visit, the test is not necessary to be repeated.
Clinical Laboratory Assessments						
Hematology and Chemistry including CRP[h]				X	X	Hematology: The most recent hematocrit value obtained will be used to calculate the CDAI.
Stool sample (fecal calprotectin)				X	X	Stool samples required for q48w visit must be obtained before the start of the bowel preparation for the video endoscopy if it is scheduled for the visit.
Pharmacokinetics/Immunogenicity						
Guselkumab serum concentration				X	X	Blood samples should be collected before the administration of study intervention. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of sample collections. Guselkumab serum concentration will be collected q16w from Week 48 until the end of the study.
Assessment for antibody to guselkumab				X	X	Blood samples should be collected before the administration of study intervention. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of sample collections.
Ongoing Participant Review						
Concomitant therapy		X	X	X	X	
Crohn's disease-related hospitalizations and surgeries		X	X	X	X	Hospitalization for endoscopy every 48 weeks (if performed) and/or at the end of study is not included in this category.

Abbreviations: AE=adverse event; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein;C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computerized tomography; q4w=every 4 weeks; q8w=every 8 weeks; q16w=every 16 weeks; q48w=every 48 weeks; SC=subcutaneous; SID=study intervention discontinuation; TB=tuberculosis;

Footnotes:

a. Week 48 study procedures outlined in the SoA for Week 0 to Week 48 (Table 2) must be performed prior to study intervention administration. In participants who are considered appropriate for self-administration at home after being trained, at-home administration can begin after the Week 48 visit.
b. The q8w visits include scheduled visits at Weeks 56, 72, 88, 104, 120, and 136.
c. The q16w visits include scheduled visits at Weeks 64, 80, 112, and 128.
d. The q48w visits occur at Week 96 and Week 144.
e. The visit window should be ±7 days for each visit.
f. All assessments are to be completed prior to study intervention administration, unless otherwise specified. The C-SSRS should be completed first then any other clinical procedures, tests, or consultations.
g. After Week 48, these evaluations will be collected only during on-site visits.
h. 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 at least every 3 months or shorter.

Table 4: SoA – Study Intervention Discontinuation (SID) Visit and the Final Efficacy and Safety (FES) Follow-Up Visit

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

	SID[a]	FES[b]	Additional Visit Required	Notes
Participant terminates study participation at any time during the study	X			Evaluations for SID should be completed prior to participant terminating study participation
Participant discontinues study intervention after Week 0 and up to the Week 48 visit	X	X		
Participant completes the 48-week study but does not enter the LTE at Week 48		X	Week 48 (see Table 2)	
Participant discontinues study intervention after Week 48 until the end of study	X	X		Video endoscopy should be performed at SID visit at the end of the study. If video endoscopy were performed within 48 weeks before the SID visit, the test is not necessary to be repeated.

Abbreviations: FES=final efficacy and safety (follow-up visit); LTE=long-term extension; SID=study intervention discontinuation (visit)

Footnotes:
a. The SID visit should be completed at the time of SID.
b. The FES visit should be completed approximately 12 weeks after the last study intervention administration.

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

Period:	SID	FES	Notes
Study Procedures			
Safety Assessments			
Adverse events	X	X	
Physical examination	X	X	
Vital signs	X	X	Include: temperature, pulse/heart rate, respiratory rate, and blood pressure.
Urine pregnancy test	X	X	Must be performed in female participants of childbearing potential.
TB evaluation/ other infection assessment	X	X	If TB is suspected at any time during the study, a chest radiograph or chest CT, and QuantiFERON-TB or T-SPOT test should be performed.
C-SSRS	X	X	The C-SSRS should be completed first before any other tests, procedures, or other consultations to prevent influencing participant perceptions.
Efficacy Assessments			
Collect and review participant diary (CDAI)	X	X	For the FES, daily diary information should be collected for each of the 14 days before the visit. The daily diary includes patient-reported data for the CDAI (includes PRO-2 components). The most recent hematocrit value obtained will be used to calculate the CDAI.
Weight	X	X	Weight measurement is used to support CDAI assessments and safety.
Video ileocolonoscopy or device assisted enteroscopy	X		To prevent interfering with the collection of CDAI data, the endoscopy must be performed at least 8 days before the designated visit (but as close as possible to the designated visit) or at the designated visit. If performed on the day of the designated visit, the 7 days before the initiation of the endoscopy preparation should be utilized to calculate CDAI scores. Video endoscopy should be performed at SID visit at the end of the study. If video endoscopy were performed within 48 weeks before the SID visit, the test is not necessary to be repeated.
Clinical Laboratory Assessments			
Hematology and Chemistry including CRP	X	X	
Stool sample (fecal calprotectin)	X		Stool samples required for this visit must be obtained before the start of the bowel preparation for the video endoscopy if it is also scheduled for the visit.
Pharmacokinetics/ Immunogenicity			
Guselkumab serum concentration	X	X	All reasonable attempts should be made to collect samples and record the actual times of PK sample collections.
Assessment for antibody to guselkumab	X	X	All reasonable attempts should be made to collect samples and record the actual times of sample collections.
Ongoing Participant Review			
Concomitant therapy	X	X	
Crohn's disease-related hospitalizations and surgeries	X	X	Hospitalization for endoscopy at the SID visit is not included in this category.

Abbreviations: CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computerized tomography; FES=final efficacy and safety (follow-up visit); PK=pharmacokinetic(s); PRO= patient-reported outcome(s); SID=study intervention discontinuation; TB=tuberculosis.

2. INTRODUCTION

Guselkumab (CNTO 1959) is a fully human immunoglobulin G (IgG)1 lambda monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biologic activity of IL-23 in all in vitro assays examined.

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

Guselkumab is currently being developed for other diseases including treatment of patients with PsA (globally), hidradenitis suppurativa (HS), familial adenomatous polyposis (FAP), Crohn's disease (CD), and ulcerative colitis (UC). Phase 3 studies in PsA, a Phase 2/3 program in CD, and a Phase 2b/3 program in UC are ongoing globally.

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure (IB)[5] for guselkumab.

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

The term "sponsor" used throughout this document refers to the entities listed in the 'Protocol Supplementary Information', which will be provided as a separate document.

2.1. Study Rationale

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

Sponsor is currently conducting the clinical development program to evaluate the safety and efficacy of guselkumab compared with placebo and an active control (ustekinumab): 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 (Program name: GALAXI, Study number: CNTO1959CRD3001).

Under the protocol, there are 3 separate studies: a 48-week Phase 2 dose-finding study (ie, GALAXI 1) and 2 identical 48-week Phase 3 confirmatory studies (ie, GALAXI 2 and GALAXI 3). Participants who complete the 48-week Phase 2 or Phase 3 studies may be eligible to enter the long-term extension (LTE [Week 48 to Week 156]) and receive approximately 2 years of additional treatment. The overall Phase 2/3 development program will enroll approximately 2,000

participants with a total duration for each participant of up to approximately 3 years. For Phase 2 study, interim analysis has been completed and the study is still ongoing as per protocol. The Phase 3 studies have been initiated using the following dose regimens that were selected based on the interim analysis of Phase 2 study:

- Guselkumab Regimen 1 – Induction: 200 mg IV at Weeks 0, 4, and 8; followed by Maintenance: 200 mg SC every 4 weeks (q4w; ie, at Weeks 12, 16, 20, 24, 28, 32, 36, 40, and 44)
- Guselkumab Regimen 2 – Induction: 200 mg IV at Weeks 0, 4, and 8; followed by Maintenance: 100 mg SC every 8 weeks (q8w; ie, at Weeks 16, 24, 32, and 40)

Based on the preclinical evidence and clinical experience targeting IL-23 in CD, guselkumab could be a potential therapeutic option for patients with CD who have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy.

Since CD is a chronic inflammatory disease requiring long-term therapy, the safety, especially under long-term treatments, in addition to the efficacy would be the critical factor. The primary objective of the study is to assess the safety of guselkumab in patients with CD in Japan. Although the safety of guselkumab in patients with CD will also be assessed in GALAXI program comparing to the entire study results and available data of guselkumab for other diseases, this study is planned to complement the existing safety database by enrolling additional participants exposed to guselkumab in Japan.

In addition to the secondary objectives to assess the efficacy, PK, and immunogenicity of guselkumab in participants with CD, an exploratory objective of this study is to assess the efficacy of guselkumab on small bowel (SB) disease. Crohn's disease is categorized with the part of intestinal lesion into 3 types: the ileal-type, colonic-type, and ileocolonic-type[6,16] and it is known that more ileal-type of CD were identified in Asian countries compared to Western countries.[17] Recent research revealed that patients who achieved the SB improvement had lower rate of relapse, hospitalization, and Crohn's related surgery compared with those who had not.[13] The research also found that antitumor necrosis factor (TNF) therapy might not be as effective in SB lesions as in colonic lesions, therefore there would be a high unmet need for effective treatment for SB lesions in patients with CD.[13] While no clinical efficacy data of either guselkumab or other anti-IL-23 antibodies on the SB lesions are available to date, there are some case reports to support the potential clinical efficacy of ustekinumab, an anti-IL-12/23 antibody on SB lesions as well as stenosis.[9,18] Of note, it is reported that the several major leukocytes inducing the tissue inflammation related to the IL-17/23 pathway such as cluster of differentiation (CD)103+CD11b+ dendritic cells (DCs) and T helper 17 (Th17) cells are specially localized in the small intestine rather than in colon in the mouse intestine.[7] These scientific backgrounds and evidences are considered to provide a rationale to investigate the effect of guselkumab on SB lesions.

2.2. Background

Nonclinical Studies

A comprehensive overview of the nonclinical development program for guselkumab to support the initiation of the study has been completed and the information is available in Section 3 of the latest version of the guselkumab IB.[5]

Details regarding the proposed dose regimen and dose rationale are described in Section 6.1 and Section 4.3. Guselkumab dosing regimens of induction and maintenance to be tested in this study are within the range of dosing regimens investigated in the GALAXI program.

Clinical Studies

Guselkumab has been approved for the treatment of adults with moderate to severe plaque psoriasis (PsO) in the United States, EU, Canada, Japan and a number of other countries worldwide. In addition, guselkumab has been approved for the treatment of psoriatic arthritis (PsA), generalized pustular psoriasis, erythrodermic psoriasis, and PPP in Japan.

Guselkumab is currently being developed in other diseases including for the treatment of patients with PsA (globally), HS, FAP, CD and UC. Global phase 3 development programs are ongoing as Phase 3 studies in PsA, a Phase 2/3 program in CD and a Phase 2b/3 program in UC.

This section provides a summary of the sponsor's assessment of how the overall clinical experience with guselkumab across various indications supports the investigation of guselkumab in CD. Details about these guselkumab clinical development programs across various indications are provided in Section 4 of the latest version of the guselkumab IB.[5]

Through the cutoff date of 12 July 2019, an estimated 203 healthy subjects, 3,454 subjects with PsO, 109 subjects with RA, 1,136 subjects with PsA, 182 subjects with PPP, 151 subjects with CD, 149 subjects with HS, 29 subjects with UC, and 3 subjects with FAP have been exposed to guselkumab. Overall, an estimated 5,416 subjects have been exposed to guselkumab in the clinical development program.

The largest clinical experience to date with guselkumab has been in plaque psoriasis. The safety profile of guselkumab in subjects with moderate to severe plaque psoriasis is based on data from the Phase 2 study CNTO1959PSO2001 and Phase 3 studies CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSO3003, CNTO1959PSO3006, and CNTO1959PSO3009. Of the 2,711 guselkumab-treated subjects, 2,255 subjects were exposed for at least 1 year, 1,516 subjects were exposed for at least 2 years, and 692 subjects and were exposed for 3 years. Long-term extensions of 2 of the studies (CNTO1959PSO3001 and CNTO1959PSO3002) are ongoing and will continue through up to 5 years of follow-up.

For CD program, interim analysis of phase 2 of CNTO1959CRD3001 study has been completed and the study is still ongoing as per protocol. The phase 3 of CNTO1959CRD3001 studies have been initiated after interim analysis of phase 2 part of the study.

CNTO1959CRD1002 was conducted as a Phase 1, randomized, double-blind, placebo-controlled study to assess safety, tolerability, and PK of guselkumab after single IV administrations up to 1,200 mg of guselkumab in Japanese healthy male subjects. No new safety concerns were observed in this study. When the PK of guselkumab following a single IV dose was compared between non-Japanese healthy subjects (CNTO1959PSO1001 Study, Part1) and Japanese healthy subjects (CNTO1959CRD1002 Study), the distribution range of weight-corrected clearance (CL) and volume of distribution at the terminal phase (V_z) mostly overlapped between Japanese and non-Japanese, while uncorrected CL and V_z were slightly lower in Japanese subjects. There was no substantial difference in PK characteristics in terms of elimination/distribution between races (Japanese and non-Japanese) when guselkumab is given in IV formulation. Furthermore, when guselkumab is given in SC formulation as a single dose or multiple dose (SD:10-300 mg, MD: 100 mg at Weeks 0, 4, and q8w thereafter) in Japanese and non-Japanese patients with psoriasis, there was no substantial difference between Japanese and non-Japanese in terms of serum guselkumab concentration or PK parameters (CNTO1959PSO1001 part2, CNTO1959PSO1002, CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSO3004 and CNTO1959PSO3005 study).

2.3. Benefit-Risk Assessment

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

2.3.1. Risks of Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Clinical worsening of CD	The benefit-risk of guselkumab in the treatment of moderately to severely active CD has not been established.	• During the study, participants will be permitted to continue treatment of CD with certain concomitant medications (Section 6.5). • Participants will discontinue study intervention if it is not in their best interest or if they need to initiate protocol-prohibited medications including certain biologics (Section 6.5.2 and Section 7.1). • Disease activities will continuously be evaluated throughout the study with Crohn's Disease Activity Index (CDAI) diary as well as inflammatory biomarkers such as CRP and fecal calprotectin.
Potential Risks Due to Study Intervention Guselkumab		
Serious infections and reactivation of latent infections	Available animal and human data suggest that blockade of IL-23 may be associated with an increased infection risk.	• Participants with a history of, or ongoing, chronic or recurrent infectious disease, including HIV, Hepatitis B or

		C, will be excluded from the study. Similarly, participants with evidence of active or untreated latent TB will be excluded from the study (Section 5.2). • Participants who have received a live viral or bacterial vaccination within 12 weeks of baseline will be excluded from the study. In addition, participants must agree not to receive a live viral or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention (Section 5.2). • Participants will be instructed to seek medical attention if they develop signs or symptoms suggestive of an infection, and investigators are instructed in the protocol to monitor for signs or symptoms of infections, including tuberculosis (Section 8.2.5 and Section 8.2.6). • Discontinuation of a participant's study intervention must be strongly considered if the participant develops a serious infection, including but not limited to sepsis or pneumonia. In addition, any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete (Section 7.1).
Hypersensitivity reactions, including serious hypersensitivity reactions.	Serious hypersensitivity reactions including anaphylaxis have been reported in postmarketing experience with guselkumab in psoriasis patients.	• Participants with known allergy, hypersensitivity, or intolerance to guselkumab or its excipients will be excluded from the study. • Sites are instructed that before any administration of study intervention, appropriately trained personnel and medications (eg, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. In addition, all participants must be observed carefully for signs and symptoms of a hypersensitivity

		reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension) (Section 8.2.8). • Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1).
Malignancy	The preponderance of preclinical data suggests that blockade of endogenous IL-23 would not be detrimental and may in fact be beneficial in tumor immunosurveillance and host protection; however, a risk of malignancy cannot be excluded.	• Those participants who currently have a malignancy or have a history of malignancy within 5 years prior to screening (with exceptions noted in Section 5.2) will be excluded from the study. Additionally, participants who have a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly will be excluded from the study (Section 5.2). • During the conduct of the study, participants will undergo regular clinical monitoring including routine safety labs to assess for any changes in health status that may indicate a possible malignancy. • Participants who develop a malignancy during the study (with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from study intervention (Section 7.1).
Liver injury	A serious adverse event (SAE) of 'toxic hepatitis' was reported in the ongoing Phase 2/3 guselkumab CD program in a participant who received guselkumab 1200 mg IV at Weeks 0, 4, and 8, and 200 mg SC at Week 12. Based on the hepatocellular pattern of injury, temporal relationship of the event to guselkumab exposure, and the exclusion of alternative etiologies, this event may represent drug-	• During the conduct of the study, liver function tests will be monitored at regular intervals in accordance with regulatory guidance.[4] In addition, the induction doses evaluated in this clinical program will be lower and will not exceed 200 mg IV. • Participants with marked liver enzyme elevations or symptoms or signs of liver dysfunction (eg, jaundice),

	induced liver injury possibly related to guselkumab.	should undergo a thorough investigation for possible causes of liver injury. 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 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 ≤40 mg prednisone or its equivalent per day which must be tapered from Week 12. Furthermore, participants receiving azathioprine (AZA) or 6-mercaptopurine (6-MP) must have been taking them for ≥12 weeks and been on a stable dose for at least 4 weeks before baseline. Additionally, participants are also excluded from the study if they have received cyclosporine, mycophenolate mofetil, tacrolimus, or sirolimus within 8 weeks, anti-TNF therapy within 8 weeks, vedolizumab within 16 weeks, or ustekinumab within 16 weeks prior to the first dose of study intervention. Further detail regarding concomitant medications is provided in Section 5.1 and Section 5.2. • During study participation, the use of immunomodulators other than AZA or 6-MP (eg, cyclosporine) as well as biologic immunomodulators (eg, anti-TNFs, vedolizumab) is prohibited. Participants initiating these treatments will be discontinued from further study intervention administration.
Risks Due to Study Procedures		
Risks associated with the endoscopy procedure including	These risks are well recognized, but are rare.[1,11] Risk of increase in	• Trained and experienced endoscopists will be

bleeding, colonic perforation, serum amylase elevation and pancreatitis	serum amylase elevation or pancreatitis are reported for device assisted enteroscopy.[12]	performing the procedure during this study. • Risk of increase in serum amylase elevation or pancreatitis may not be relevant to this study because the scope is not planned to be inserted through the mouth.

2.3.2. Benefits of Study Participation

The efficacy and safety of guselkumab in the treatment of CD has not been established. The well-established scientific and clinical rationale for IL-23 blockade in the treatment of CD supports the clinical evaluation of guselkumab in this disease population.

2.3.3. Benefit-Risk Assessment for Study Participation

Based on the available data and the proposed safety measures described in Section 2.3.1, the sponsor contends that the benefit-risk of the selected dose regimens of guselkumab to be investigated in this protocol is acceptable.

3. OBJECTIVES AND HYPOTHESIS

Primary Objective

- To evaluate the safety of guselkumab in participants with CD

Secondary Objectives

- To evaluate the efficacy of guselkumab in participants with CD
- To evaluate the PK, immunogenicity, and pharmacodynamics (PD) of guselkumab, including changes in C-reactive protein (CRP) and fecal calprotectin

Exploratory Objective

- To assess the efficacy of guselkumab on SB lesions

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

HYPOTHESIS

The primary objective is to evaluate the safety of guselkumab in participants with CD. No hypothesis testing will be performed in this study.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, open-label, multicenter study to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active CD who have demonstrated an inadequate response or failed to tolerate the previous conventional therapy (ie, 6-mercaptopurine [6-MP], azathioprine [AZA], or corticosteroids [CON-failure. Refer to Section 10.7 Appendix 7]) or

biologic therapy (ie, TNFα antagonists, vedolizumab) [BIO-failure. Refer to Section 10.8 Appendix 8].

Participants will receive following guselkumab treatment in an open-label fashion;

- Weeks 0, 4, and 8: Guselkumab 200 mg IV administration (induction)
- Every 4 weeks after Week 8 until the end of the study: Guselkumab 200 mg SC administration (maintenance)

The study will be conducted in 3 phases: a maximum 8-week screening phase, a 48-week treatment phase followed by LTE phase, and a posttreatment follow up visit (12 weeks after the participant's last dose of study intervention to collect any adverse events since the last study visit). The duration of individual participation will be approximately 68 weeks if a participant ends the study participation at the end of treatment phase and does not enter the LTE.

At-home self-administration can begin after the Week 48 visit at the discretion of the investigator and participant, and upon completion of at least 3 training sessions starting from Week 48. All participants who are willing to perform at-home self-administration will be requested to record at-home administration medication diary and will continue to have study visits and assessments at the investigative sites approximately q8w through the end of the study, as outlined in Section 1.3. Details of instruction of at-home administration will be described in a separate document (Training guide for Investigators for Use of Prefilled syringe).

Long-term extension will be continued until the time when guselkumab is approved for CD indication in Japan and marketed guselkumab becomes available at the study site (up to around 3 years at maximum in addition to a 48-week treatment phase depending on the timing of approval of guselkumab for CD in Japan) or discontinuation of the clinical development of guselkumab for CD, and all participants who will be continuing the treatment at the time of marketing approval of guselkumab for CD or discontinuation of the clinical development of guselkumab for CD will be asked to come to the study site, and complete their safety and efficacy assessments.

Participants who have a concurrent or history of SB disease activity confirmed by radiography, imaging and/or endoscopy may be eligible to participate in the substudy for additional SB assessment by device-assisted enteroscopy.

Key safety assessments will include the monitoring of adverse events, vital sign measurements, and clinical laboratory tests including inflammatory biomarkers. Key efficacy assessments include Crohn's Disease Activity Index (CDAI) and its components, endoscopic assessments by either ileocolonoscopy or device-assisted enteroscopy (if a participant agrees to perform additional SB assessment; refer to Section 8.1, Efficacy Assessments).

There will be 3 database locks planned for this study to assess the safety and efficacy data of guselkumab in Japanese participants with CD:

- The first database lock will be at Week 24 after all participants have either completed the Week 24 or terminated study participation prior to Week 24.

- The second database lock will be at Week 48 after all participants have either completed the Week 48 or terminated study participation prior to Week 48.
- The final database lock will be planned at the end of study period including LTE.

A target of 25 participants will be enrolled in this study.

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

4.2. Scientific Rationale for Study Design

The primary objective of the study is to assess the safety of guselkumab in patients with CD in Japan. Although the safety of guselkumab in patients with CD will also be assessed in GALAXI program, this study is planned to complement the existing safety database for CD by enrolling additional participants exposed to guselkumab in Japan.

4.2.1. Study-Specific Ethical Design Considerations

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

The total blood volume of approximately 210 mL will be collected through Week 48, and additional blood sampling of up to approximately 90 mL per year will be required if a participant is willing to enter LTE phase. This amount of blood sampling is considered to be acceptable with reference to the blood donation rule by the Japanese Red Cross Society.

4.3. Justification for Dose

The induction dose selected for this study (200 mg IV at Weeks 0, 4 and 8) is identical to what is selected for phase 3 part of CNTO1959CRD3001 study based on the interim analysis result of phase 2 part of CNTO1959CRD3001 study and will be used to confirm the induction safety of guselkumab in participants with moderately and severely active CD. The maintenance dose selected for this study (200 mg SC q4w) is the highest dosing regimen to be tested in the phase 3 part of CNTO1959CRD3001 study to accumulate the safety data with potential highest maintenance dosing regimen. Of note, guselkumab 200 mg q4w regimen is also being tested in the phase 2 part of CNTO1959CRD3001 study.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the SoA for the last participant in the study. All participants who will be continuing the treatment at the time of marketing approval of guselkumab for CD will be asked to come to the study site and complete their safety and efficacy assessment. The final data from the study site will be sent to the sponsor

(or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Be man or woman (according to their reproductive organs and functions assigned by chromosomal complement) ≥18 years of age.

2. Have CD or fistulizing CD of at least 3 months duration (defined as a minimum of 12 weeks), with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography, histology, and/or endoscopy.

3. Have clinically active CD, defined as:

    a. Mean daily stool frequency (SF) count >3, based on the unweighted CDAI component of the number of liquid or very soft stools

    OR

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

4. Criterion modified per Amendment 1.

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

    a. a minimum score of 1 for the component of “size of ulcers”

    AND

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

    OR

Have endoscopic evidence of active SB CD as assessed by central endoscopy reading at the screening device assisted enteroscopy (SoA, Table 1), defined as a screening modified SES-CD score ≥5, based on the presence of ulceration in any 1 of the 3 segments including terminal ileum, proximal ileum and jejunum.

Concomitant or previous medical therapies received

5. Prior or current medication for CD must include at least 1 of the following, and must fulfill additional criteria as described in Section 10.7 (Appendix 7) and Section 10.8 (Appendix 8), as applicable:

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

    OR

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

    OR

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

    OR

    d. Has previously demonstrated lack of initial response (ie, primary nonresponders), responded initially but then lost response with continued therapy (ie, secondary nonresponders), or were intolerant to 1 or more biologic agents at a dose approved for the treatment of CD (ie, infliximab, adalimumab, vedolizumab, or approved biosimilars for these agents).

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

6. Adhere to the following requirements for concomitant medication for the treatment of CD. The following medications are permitted provided that doses meeting the

requirements listed below are stable or have been discontinued prior to baseline within the timeframes specified below:

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

b. Oral corticosteroids at a prednisone-equivalent dose at or below 40 mg/day, or 9 mg/day of budesonide, and on stable dosing for at least 2 weeks; or if recently discontinued, must have been stopped for at least 2 weeks.

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

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

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

Screening laboratory tests

7. Criterion modified per Amendment 1.

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

a. Hemoglobin ≥8.0 g/dL.

b. White blood cells (WBCs) $\geq 3.5 \times 10^3/\mu L$.

c. Neutrophils $\geq 1.5 \times 10^3/\mu L$.

d. Platelets $\geq 100 \times 10^3/\mu L$.

e. Serum creatinine ≤1.5 mg/dL.

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

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

Tuberculosis

8. Is considered eligible according to the following tuberculosis (TB) screening criteria:

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

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

      OR

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

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

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

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

      Note: The QuantiFERON-TB or T-SPOT test are not required at screening for participants with a history of latent TB, if active TB has been ruled out, and if appropriate treatment has been initiated/completed as described above in Inclusion Criterion 8a.

   e. Have a chest radiograph (both posterior-anterior and lateral views) taken ≤12 weeks before the first administration of study intervention and read by a qualified physician to read radiogram (eg, a radiologist or pulmonologist), with no evidence of current, active TB or old, inactive TB. Chest computerized

tomography (CT) may also be performed if deemed appropriate by the investigator.

Contraception

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

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

9. A female participant of childbearing potential must have a negative urine pregnancy test result at screening and baseline.

10. Before first dose administration, a female participant must be:

    a. Not of childbearing potential

    b. Of childbearing potential and:

        - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 12 weeks after last dose (ie, the end of relevant systemic exposure). The method selected must meet local/regional regulations/guidelines for highly effective contraception.

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

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

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

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

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

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

General

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

14. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

5.2. Exclusion Criteria

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

1. Has complications of CD, such as symptomatic strictures or stenoses, short gut syndrome, or any other manifestation, that might be anticipated to require surgery, could preclude the use of the CDAI or other instruments 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. Participants with active fistulas may be included if there is no anticipation of a need for surgery and no abscesses are currently identified.

3. Criterion modified per Amendment 1.

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

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

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

Concomitant or previous medical therapies received

6. Criterion modified per Amendment 1.

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

a. IV corticosteroids received within 3 weeks of baseline

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

c. 6-thioguanine received within 4 weeks of baseline

d. Biologic agents:

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

2. Vedolizumab received within 16 weeks of baseline

3. Ustekinumab received within 16 weeks of baseline

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

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

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

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

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

Exception: Participants who have had limited exposure to ustekinumab at its approved labeled dosage AND have met the required washout criterion AND have not demonstrated failure or intolerance to ustekinumab.

Infections or predisposition to infections:

8. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent

urinary tract infection (eg, recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers.

9. Has current signs or symptoms of a clinically significant infection. Established nonserious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

10. Has a history of serious infection (eg, hepatitis, sepsis, pneumonia, or pyelonephritis), including any infection requiring hospitalization or IV antibiotics, during the 8 weeks before baseline.

11. Has evidence of a herpes zoster infection within 8 weeks before baseline.

12. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Participants with radiographic evidence of possible prior histoplasmosis or coccidioidomycosis will be excluded.

13. Has a chest radiograph within 12 weeks prior to the first administration of study intervention that shows an abnormality suggestive of a malignancy or current active infection, including TB.

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

15. Participants must undergo screening for human immunodeficiency virus (HIV). Any participant who has a history of HIV antibody positivity, or tests positive for HIV at screening, is not eligible for this study.

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

    a. Have a history of successful treatment (defined as being negative for HCV RNA at least 6 months after completing antiviral treatment) and have a negative HCV RNA test result at screening, OR

    b. While seropositive have a negative HCV RNA test result at least 6 months prior to screening and a negative HCV RNA test result at screening.

17. Participants who tests positive for hepatitis B virus (HBV) infection.

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

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

19. Has had a BCG vaccination within 12 months of screening.

Malignancy or increased potential for malignancy

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

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

Coexisting medical conditions or past medical history

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

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

24. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of adequate venous access.

25. Is known to have had a history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Disorders (5th edition) (DSM-V) criteria within 12 months before baseline.

26. Has unstable suicidal ideation or suicidal behavior in the last 6 months that may be defined as a Columbia-Suicide Severity Rating Scale (C-SSRS) rating at screening of: Suicidal Ideation with Intention to Act ("Ideation level 4"), Suicidal Ideation with Specific Plan and Intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt), and is considered to be at risk by the investigator based on an evaluation by a mental health professional. In addition, participants with C-SSRS ratings of Wish to be Dead ("Ideation level 1"), Non-Specific Active Suicidal Thoughts ("Ideation level 2"), Active Suicidal Ideation with Any Methods (Not Plan) without

Intent to Act ("Ideation level 3") or nonsuicidal self-injurious behavior who are determined to be at risk by the investigator may not be enrolled.

27. Known allergies, hypersensitivity, or intolerance to guselkumab or its excipients (refer to the IB[5]).

28. 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 administration of study intervention.

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

General

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

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

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

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

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3 Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

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

2. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (eg, contraceptive requirements).

3. Must 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 a study intervention discontinuation (SID) visit before he or she terminates study participation.

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

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

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

7. Must be willing and able to complete a daily diary to document clinical symptoms, AEs, etc.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is screen failure, the date seen and age at initial informed consent will be used.

Completion of screening within the specified screening window of approximately 8 weeks is required.

If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph, stool analysis, endoscopy), the participant will be considered a screen failure because he/she will not meet eligibility criteria, and the expired assessments (along with the non-time-specific laboratory tests) will have to be repeated on rescreening.

Additional criteria for retesting and rescreening are outlined below.

Retesting

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

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then start a new screening phase including the collection and testing of new laboratory specimens. Previous TB evaluation results (including the QuantiFERON-TB test, T-SPOT test, chest radiograph, and chest CT) and stool study results, and endoscopy results from the first screening event may be used if they meet the specified protocol criteria as described in Section 5.1. Sponsor's approval is required prior to the study site obtaining a new informed consent for rescreening.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

Participants will receive guselkumab 200 mg IV induction doses at Weeks 0, 4, and 8 (total of 3 IV doses), followed by guselkumab 200 mg SC maintenance doses as q4w starting at Week 12 through Week 44.

During LTE, participants will continue to receive the same study intervention regimen that they were receiving at the end of maintenance, with the first dose in the LTE being administered at Week 48.

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

Since 2 SC injections by using 100 mg/mL prefilled syringe (PFS) are administered at visits, each injection of study intervention should be given at a different location of the body. Recommended locations are abdomen and/or thigh.

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

Guselkumab will be manufactured and provided under the responsibility of the sponsor.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Guselkumab will be manufactured and provided under the responsibility of the Sponsor. Refer to the guselkumab IB[5] for a list of excipients. Guselkumab will be supplied as a 100 mg/mL sterile liquid in a single dose PFS assembled in an UltraSafe Plus™ Passive Needle Guard (PFS-U).

All study interventions must be stored according to the labeled storage condition, 2°C to 8°C and protected from exposure to light. Do not freeze the study interventions. The products are designed for single-use only.

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

Refer to the site Investigational Product Procedures Manual (IPPM) and Investigational Product Procedure Instructions (IPPI) for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention. 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 containing hazardous liquids, 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 immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees 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 IPPI.

6.3. Measures to Minimize Bias: Randomization and Blinding

As this is an open study, randomization and blinding procedures are not applicable. Central readers to assess the endoscopic data will be blinded to participant information including medical background, study site and visit.

6.4. Study Intervention Compliance

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

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

Compliance with the treatment schedule is strongly encouraged. Study-site personnel will keep a log of all study intervention dispensed and will compare the amount of study intervention dispensed with the amount returned. If participants administer study intervention at home in the LTE, participants will be instructed to record all at-home study intervention administrations on a diary card. Participants will also be instructed to contact the study site promptly of any issues of the product quality are found prior to the administration of the study intervention. Participants who are unable or unwilling or missed to have injections administered away from the site should contact the study site and follow the instruction of the study site. In this case, participants will be required to return to the site for administration of study intervention if deemed appropriate. Additional details may be provided in the site IPPM that is provided separately.

6.5. Concomitant Therapy

6.5.1. Concomitant Medications

Participants who are receiving oral 5-ASA compounds, oral corticosteroids, conventional immunomodulators (ie, AZA or 6-MP), antibiotics, and/or enteral nutrition for the treatment of CD at baseline should maintain a stable dose for the specified period before baseline, as defined in the Inclusion Criteria (Section 5.1).

In general, participants who are receiving these medications for CD at baseline (ie, Week 0) should maintain a stable dose through Week 48, with the exception of oral corticosteroids. Therapies can only be discontinued or reduced in dose after Week 0 if investigator judgment requires it because of toxicity or other medical necessity; even if the toxicity resolves, the therapy should not be restarted. Corticosteroids must be maintained at baseline doses through Week 12, and all participants must begin tapering corticosteroids at Week 12, unless medically not feasible (see further details in Section 6.5.1.1, Oral Corticosteroids Tapering).

Week 0 through Week 48

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

- Oral or rectal 5-ASA compounds.
- Immunomodulators (ie, AZA or 6-MP).
- Oral, parenteral, or rectal corticosteroids, including budesonide.
- Antibiotics as a primary treatment for CD.
- Parenteral or enteral nutrition as a treatment for CD.

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

Week 12 and through Week 48

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

During LTE (after Week 48 till the end of study):

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

6.5.1.1. Oral Corticosteroids Tapering

At Week 12, all participants who were taking corticosteroids at Week 0 must begin tapering corticosteroids. This tapering is mandatory, unless not medically feasible, and should follow the recommended schedule shown in Table 5. If participants experience worsening of their disease activity while tapering corticosteroids, further dose decreases may be suspended, and/or their oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator. The oral corticosteroid dose, however, may not be increased above the Week 0 dose unless due to medical necessity. For participants whose corticosteroid taper is interrupted, investigators are encouraged to resume tapering within 4 weeks. Tapering may exceed this schedule only if warranted by medical necessity (eg, participant experiencing corticosteroid-related side effects).

Table 5: 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	

6.5.2. Prohibited Concomitant Medications

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

- Immunomodulatory agents other than AZA or 6-MP (including, but not limited to, 6-thioguanine, cyclosporine, mycophenolate mofetil, tacrolimus, and sirolimus).
- Immunomodulatory biologic agents (including, but not limited to, TNF antagonists, natalizumab, ustekinumab, rituximab, vedolizumab).
- Experimental CD medications (including, but not limited to, upadacitinib, filgotinib, ozanimod, etrolizumab, brazikumab, mirikizumab, risankizumab, GS-5745).
- Thalidomide or related agents.

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

6.6. Dose Modification

No treatment/dose adjustment of study drug will be permitted throughout the study period.

6.7. Intervention After the End of the Study

This protocol is designed to provide participants with approximately 48 weeks of treatment plus up to approximately 3 additional years of treatment in the LTE depending on the timing of approval of guselkumab for CD.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

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

   Note: Other permitted CD-related surgeries (eg, to resolve long-standing complications such as strictures or for symptomatic nonhealing fistulas, in participants experiencing improvement on study intervention) other than minor procedures (eg, placement of a seton or cutaneous drainage of an abscess) should be postponed until after the FES visit, unless necessary to ensure participant well-being and/or safety.

3. The participant becomes pregnant or plans a pregnancy within the study period.
4. The participant (or the participant's representative) withdraws consent for administration of study intervention.
5. The participant develops a systemic opportunistic infection.
6. The participant is deemed ineligible according to the following TB screening criteria:
   - A diagnosis of active TB is made.
   - A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.
   - A participant undergoing evaluation has a chest radiograph or chest CT with evidence of current active TB and/or a positive QuantiFERON-TB test or T-SPOT test result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next study intervention administration and continued to completion (see also Section 8.2.6). Indeterminate QuantiFERON-TB test or borderline T-SPOT test results should be handled as described in Section 8.2.6. Participants with persistently indeterminate QuantiFERON-TB test results or borderline T-SPOT test may continue without treatment for latent TB if active TB is ruled out, their chest radiograph or chest CT shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor and recorded in the participant's source documents and initialed by the investigator.
   - A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
7. The participant has a serious adverse reaction that is related to an injection or an infusion, including an injection-site or infusion reaction, resulting in bronchospasm with wheezing and/or dyspnea that requires ventilatory support OR that results in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg.

8. The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
9. The participant has severe liver test abnormalities that are not transient and are not explained by other etiologies. Such abnormalities would include:
   - ALT or AST >8 x ULN
   - ALT or AST >5 x ULN for more than 2 weeks
   - ALT or AST >3 x ULN and TBL >2 x ULN or international normalized ratio [INR] >1.5
   - ALT or AST >3 x ULN and symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash) and/or eosinophilia (>5%)
10. The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allowing participants who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study intervention.
11. The investigator believes that for safety or tolerability reasons, it is in the best interest of the participant to discontinue study intervention.

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

1. Persistent inadequate response or worsening of CD or experience AEs consistent with clinically significant worsening of CD at any time during the study.

   These events must be evaluated by the investigator. A consultation with the Sponsor may also be considered, at the investigator's discretion. Discontinuation of study intervention must be considered in participants with clinically significant worsening of CD where continuation of the study intervention is not in the best interest of the participant.
2. The participant develops a serious infection, including but not limited to sepsis or pneumonia.
3. The participant reports suicidal ideation with intention to act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), or any suicidal behavior (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a postbaseline 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 Sponsor. Discussion of such participants with Sponsor is required.
4. The participant develops a severe injection-site or infusion reaction.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

Participants who terminate study participation will not be required to return for any follow-up assessments; however, these participants should complete the safety and efficacy evaluations specified for the SID visit in the appropriate SoA (Table 4) at the time they terminate study participation. No additional evaluations are performed after participant's withdrawal from the study.

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA summarizes the frequency and timing of efficacy, PK, immunogenicity, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: electrocardiogram (ECG) and vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) should be performed first, and then blood draws for PK or laboratory measurements. Blood collections for PK and PD assessments should be completed as outlined in the SoA (Section 1.3). Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

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).

The CDAI diary will be completed by participants during the screening period.

A minimum of 7 days of stool frequency and abdominal pain data during the screening period is required.

Women of childbearing potential must have a negative urine pregnancy test result at screening. Participants must be reminded that they are required to use a highly effective method of contraception during the study (as described in Inclusion Criteria [Section 5.1]) 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.

Participants must undergo testing for TB (Section 8.2.6) 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 or chest CT results.

Participants with a negative QuantiFERON-TB test or T-SPOT test result are eligible to continue with registration procedures.

Participants with a newly identified positive QuantiFERON-TB or T-SPOT test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB.

Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients.

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

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

Blood Sample Collection

Blood samples should be collected at the visits indicated in the SoA (Section 1.3). The date and time of collection will be recorded. When blood samples are to be collected for safety, PK, efficacy, and biomarker at the same time point, the order of blood draws will be samples for CRP, chemistry, hematology, and PK/Immunogenicity.

The total blood volume of approximately 210 mL will be collected through Week 48, and additional blood sampling of up to approximately 90 mL per year will be required if a participant is willing to enter LTE phase. Repeat or unscheduled samples taken for safety reasons or technical issues with the samples.

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 for the timing and frequency of all sample collections.

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

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IB[5])
- IPPM and IPPI
- Central Laboratory Manual
- eCRF completion instructions
- Patient recruitment materials
- ICF
- Participant Diary Card including CDAI (including PRO-2)

- Training guide for Investigators for Use of Prefilled syringe
- Endoscopy kit
- Imaging Manual (for ileocolonoscopy and device assisted enteroscopy)
- Laboratory kits

8.1. Efficacy Assessments

Efficacy evaluations will include the following:

- CDAI including PRO-2 score (the unweighted CDAI components of the total number of liquid or very soft stools and the AP score)
- Endoscopic assessments of the intestinal mucosa based on the presence and absence of mucosal ulcerations and the SES-CD and/or modified SES-CD

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

Endoscopic assessments of the intestinal mucosa will be evaluated during ileocolonoscopy or device assisted enteroscopy (see SB assessment) in all participants. A video endoscopic examination will be performed at Screening, Week 48, every 48 weeks after Week 48 (Optional), and at the end of the study. Video endoscopies will be assessed by a central facility that will be blinded to clinical characteristics of participants and study visit. A video endoscopic examination can be completed at the location where it can be visualized. The SES-CD score will be used to evaluate Endoscopic Improvement.[3,15] The SES-CD is based on the evaluation of 4 endoscopic components (presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions, and presence/type of narrowing/strictures) across 5 ileocolonic segments. Each endoscopic component is scored from 0 to 3 for each segment, resulting in a total score of up to 15 for each component, except for the narrowing component which can only attain a maximum total score of 11 because by definition, the presence of a narrowing that cannot be passed can be only observed once. In summary, an overall total SES-CD score is derived from the sum of all the component scores and can range from 0 to 56). Endoscopic healing, which is traditionally defined as the resolution (absence) of mucosal ulcers in response to a therapeutic intervention, will also be assessed.

Small bowel (SB) assessment will be performed optionally in participants who agree to participate in the SB assessment study and are deemed appropriate for their participation to SB assessment judged by the investigator. Participants who are eligible only with SB lesions should undergo SB assessment at Week 48 and at the end of study. Modalities to be used for the study are follows;

- Because of the difficulties attempting to push a slim, flexible instrument through the soft and lengthy SB, conventional colonoscopy cannot reach the proximal ileum and jejunum. Device-

assisted enteroscopy[12] including single-balloon endoscopy (SBE) and double-balloon endoscopy (DBE) are developed to overcome this issues and the usage of a balloon would grip the intestinal wall and prevent subsequent loop formation, allowing further advancement of scopes. Device-assisted enteroscopy is widely used to establish the diagnosis of CD, particularly if a patient complains of symptoms such as abdominal pain but ileocolonoscopy up to terminal ileum fails to establish a definite diagnosis of CD.[6] Modified SES-CD[15] will be used to evaluate endoscopic improvement in SB lesions. While 3 endoscopic components except for presence/type of narrowing/strictures for the evaluation of modified SES-CD is the same as that for original SES-CD, 3 SB segments of the SB will be applied to calculate modified SES-CD score instead of 5 ileocolonic segments for original SES-CD score; terminal ileum (≤10 cm from ileocecal valve), proximal ileum (10-300 cm from the ileocecal valve) and jejunum (SB proximally beyond the section defined as the proximal ileum), ranging from 0-27. Endoscopic lesions were defined as no mucosal activity (Modified SES-CD=0), mild disease (1≤Modified SES-CD<5) and ulcerative disease (Modified SES-CD≥5) and endoscopic healing is defined as modified SES-CD <5.[14]

8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.4 Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

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

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

8.2.1. Physical Examinations

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

8.2.2. Vital Signs

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

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

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

Study participants who are trained to self-inject study intervention at home will be trained to perform self-evaluation for injection-site reactions and reporting of AEs after administering study

interventions at home. Vital signs will only be assessed at the study site when study participants receive study intervention administration at the study site.

8.2.3. Electrocardiograms

A 12-lead ECG will be performed at screening.

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

8.2.4. Height and Weight

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

8.2.5. Infections

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

8.2.6. Tuberculosis Evaluation(s)

8.2.6.1. Initial Tuberculosis Evaluation

Participants must undergo testing for TB 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 and/or CT results. If either the QuantiFERON-TB test or T-SPOT test is positive, the participant is considered to have latent TB infection for the purposes of eligibility for this study.

Participants with a negative QuantiFERON-TB (or T-SPOT if performed) test result are eligible to continue with screening procedures. Participants with a newly identified positive QuantiFERON-TB (or T-SPOT if performed) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. Otherwise, the participant will be excluded from the study.

A participant whose first QuantiFERON-TB test result is indeterminate or T-SPOT test result is borderline should have the test repeated. In the event that the second QuantiFERON-TB test or T-SPOT test result is also indeterminate or borderline, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph or chest CT shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk

factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor and recorded in the participant's source documents and initialed by the investigator.

8.2.6.2. Ongoing Tuberculosis Evaluation

Early Detection of Active Tuberculosis

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

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

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

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

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph or chest CT, a repeat QuantiFERON TB or T-SPOT test, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment for latent TB is warranted.

Study intervention administration should be interrupted during the investigation. A positive QuantiFERON-TB test or T-SPOT test result should be considered detection of latent TB. If the QuantiFERON-TB test result is indeterminate or T-SPOT test result is borderline, the test should be repeated. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol. Participants who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study intervention and be encouraged to return for all subsequent scheduled study visits according to the SoA.

8.2.7. Hepatitis B monitoring

For participants who are eligible with surface antigen (HbsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV deoxy ribonucleic acid (DNA) test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.

8.2.8. Allergic Reaction

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

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

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

Participants who experience reactions following an injection or infusion that result in bronchospasm with wheezing and/or dyspnea that requires ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm Hg will not be permitted to receive additional study intervention.

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

8.2.9. Adverse Events Temporally Related to Infusion

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

8.2.10. Injection-Site Reaction

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

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

The C-SSRS defines 5 subtypes of suicidal ideation and 4 possible suicidal behaviors, as well as nonsuicidal 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.[8,10] Two versions of it will be used in this study: the 'Baseline/Screening' version of the C-SSRS will be conducted during the screening visit and the 'Since Last Visit' version of the C-SSRS will be completed at all other visits through the study period up to Week 48. During LTE, C-SSRS will be completed every 8 weeks.

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

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

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

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

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 nonsuicidal self-injurious behavior must be determined not to be at risk by the investigator in order to be enrolled. Any questions regarding eligibility of such participants should be discussed with Sponsor.

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 nonsuicidal self-injurious behavior: Participant risk is assessed by the investigator.

- Suicidal ideation levels 4 or 5 or any suicidal behavior: Participant risk assessed and referral to a mental health professional.

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

Any C-SSRS finding, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, should be reported on the AE eCRF.

8.2.12. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, and stool sample will be collected at scheduled study visits according to the SoA. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

The following tests will be performed by the central laboratory unless otherwise specified or approved by Sponsor.

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

  Sponsor and the clinical site will be notified if prespecified abnormal laboratory values defined in the Laboratory Manual are identified in any participant during the conduct of the study.
- **Inflammatory biomarkers** such as CRP and fecal calprotectin will also be included to assess the disease activities of CD for the participants.
- **Serology**: HIV antibody, HBV antibodies and surface antigen, and HCV antibody.
- **Abnormal liver function tests:** If laboratory testing for a participant who is enrolled in the study and receiving study intervention reveals an increase of serum aminotransferases (ALT or AST) to >3 x ULN and an increase of bilirubin to >2 x ULN, study intervention should be suspended immediately. In addition, laboratory tests for ALT, AST, alkaline phosphatase, and total bilirubin should be confirmed by a retest within 24 hours if possible, but no later than 72 hours following notification of test results. Additional clinical and laboratory studies may be performed to evaluate the underlying etiology of abnormal findings. See the separate instruction for additional information on monitoring and assessment of abnormal liver function tests.

- **Pregnancy testing:** Female participants of childbearing potential will undergo a urine pregnancy test at screening before study intervention administration, at a SID visit, and at the FES visit.

8.2.13. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

8.3. Adverse Events and Serious Adverse Events

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

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

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4 Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

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

All Adverse Events

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

Serious Adverse Events

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

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

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4 Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all 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.

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:

- AEs related to symptoms of CD
- AEs related to worsening or progression of CD

These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities, except where local regulations require expedited reporting of all SUSARs. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study intervention, the sponsor will report these events in an expedited manner.

8.3.4. Pregnancy

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

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

8.3.5. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first study intervention administration(s) in 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 for SAEs. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Treatment of Overdose

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

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

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

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

8.5. Pharmacokinetics

Serum samples will be used to evaluate the PK of guselkumab. Guselkumab concentration will be evaluated on blood drawn 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 sponsors designee. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers. Additional blood sampling may be considered when patient experienced serious adverse event. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.5.1. Evaluations

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

8.5.2. Analytical Procedures

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

8.6. Pharmacodynamics

C-reactive protein (CRP) and fecal calprotectin will be evaluated using blood and stool samples collected at visits as indicated in the SoA (Section 1.3).

8.7. Genetics

Pharmacogenomics are not evaluated in this study.

8.8. Biomarkers

No specific biomarkers other than serum or fecal inflammatory markers will be evaluated in this study.

8.9. Immunogenicity Assessments

Serum samples will be screened for antibodies binding to guselkumab and the titer of confirmed positive samples will be reported. Neutralizing antibodies will be assessed for positive samples. Other analyses may be performed to further characterize the immunogenicity of guselkumab. Antibodies to guselkumab will be evaluated on blood drawn 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 used to evaluate the immunogenicity of anti-guselkumab antibodies. Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

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

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 analyse the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

There will be 3 analysis plans supporting this protocol: one for the analysis based on Week 24 database lock (including efficacy and safety analysis through Week 24), second one for the analysis based on Week 48 database lock (including full data through Week 48 except LTE), and last one for the analysis based on the entire study result including LTE.

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

9.1. Statistical Hypotheses

No statistical hypothesis testing is planned in this study.

9.2. Sample Size Determination

As no statistical hypothesis testing based on any endpoint is planned in this study, the sample size was not calculated based on statistical considerations. The objective of the study is to assess the safety of guselkumab in the Japanese patients with moderately to severely active CD together with CNTO1959CRD3001 study, and the sample size was chosen to achieve this objective and provide additional safety information as much as possible.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Full Analysis Set	All enrolled participants who receive at least 1 dose of guselkumab.
Safety	All enrolled participants who receive at least 1 dose of guselkumab.
PK	All enrolled participants who receive at least 1 complete dose of guselkumab and have at least 1 valid blood sample drawn for PK analysis after their first dose of guselkumab.
Immunogenicity	All enrolled participants who receive at least 1 dose of guselkumab and have at least 1 observed postdose immune response data.

9.4. Statistical Analyses

9.4.1. General Considerations

Unless otherwise noted, efficacy analyses will be based on the Full Analysis Set, which is defined as all enrolled participants who had at least 1 dose of guselkumab in the study.

Efficacy analysis for SB assessment will only be performed among the participants who have assessment data at both baseline and Week 48 (or at the end of LTE period).

9.4.2. Safety Analyses

All safety analyses will be made on the Safety Population.

Adverse Events

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

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

- Frequency and type of AEs.
- Frequency and type of SAEs.
- Frequency and type of reasonably related AEs as assessed by the investigator.

- Frequency and type of AEs leading to discontinuation of study intervention.
- Frequency and type of infections.
- Frequency and type of AEs temporally associated with infusion.
- Frequency and type of injection-site reactions.

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

Clinical Laboratory Tests

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

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

Listings of participants with any abnormal postbaseline laboratory values of National Cancer Institute Common Terminology Criteria for Adverse Events grade ≥2 will also be provided.

9.4.3. Other Analyses

Pharmacokinetic Analyses

Pharmacokinetic analysis will be performed based on the PK analysis set.

Descriptive statistics, including arithmetic mean, SD, CV%, median, interquartile range, minimum, and maximum of the serum guselkumab concentrations will be calculated at each nominal sampling time point. These concentrations will be summarized over time.

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.

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

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

Immunogenicity Analyses

Immunogenicity analysis will be performed based on the immunogenicity analysis set.

The incidence and maximum titers of antibodies to guselkumab will be summarized for participants who are positive for antibodies to guselkumab.

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

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.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum guselkumab concentrations and biomarkers and/or efficacy measures might be analysed graphically.

9.5. Interim Analysis

There are 2 interim analysis planned at Week 24 database lock as well as Week 48 database lock before final database lock. Details will be described in analysis plan.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	adverse event
Alk P	alkaline phosphatase
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibody
ANA	antinuclear antibody
AP	abdominal pain
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
AZA	Azathioprine
BCG	Bacille Calmette-Guérin
BIO-Failure	biologic therapy failure or intolerance
BMI	body mass index
CBC	complete blood count
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CHF	congestive heart failure
CL	Clearance
CMV	Cytomegalovirus
CON-Failure	conventional therapy failure or intolerance
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerized tomography
CV	coefficient of variation
DCs	dendritic cells
DILI	drug induced liver injury
DM	diabetes mellitus
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EBV	Epstein-Barr virus
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
EU	European Union
FDA	Food and Drug Administration
FES	Final Efficacy and Safety
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV DNA	hepatitis B virus deoxyribonucleic acid
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee

IgG	immunoglobulin G
IgM	immunoglobulin M
IL	Interleukin
INR	international normalized ratio
IPPI	Investigational Product Procedure Instructions
IPPM	Investigational Product Procedures Manual
IRB	Institutional Review Board
IUS	intrauterine hormone-releasing system
IUD	intrauterine device
IV	Intravenous
LAM	lactational amenorrhea method
LKM(1)	liver kidney microsomal antibody (type 1)
LT	laboratory tests
LTE	long-term extension
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NSAID	nonsteroidal anti-inflammatory drug(s)
OTC	over the counter
pANCA	(perinuclear) anti-neutrophil cytoplasmic antibody
PD	Pharmacodynamic
PK	pharmacokinetic(s)
PPP	palmoplantar pustulosis
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PsA	psoriatic arthritis
PsO	plaque psoriasis
PT	prothrombin time
PTT	partial thromboplastin time
q4w	every 4 weeks
q8w	every 8 weeks
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SB	small bowel
SC	Subcutaneous
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SID	study intervention discontinuation (visit)
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
Th17	T helper 17
TIBC	Total iron binding capacity
TNF	tumor necrosis factor
TOC	Table of Contents
UC	Ulcerative colitis
ULN	upper limit of normal
V_z	volume of distribution during terminal phase
WBC	white blood cell (count)
WOCBP	woman of childbearing potential

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the SoA by the central laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count Hemoglobin Hematocrit	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory.	
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose Aspartate aminotransferase (AST)/Serum glutamic oxaloacetic transaminase Alanine aminotransferase (ALT)/Serum glutamic pyruvic transaminase	Total and Direct bilirubin Alkaline phosphatase Calcium Phosphate Albumin Total protein Follicle stimulating hormone (FSH)
	Note: Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 6: Liver Safety.	
Inflammatory Biomarkers	Serum C-reactive protein and fecal calprotectin	
Other Screening Tests	• Urine Pregnancy Testing for women of childbearing potential only • Serology (HIV antibody, hepatitis B virus antibodies and surface antigen [HBsAg], and hepatitis C virus antibody) • QuantiFERON-TB or T-SPOT • Stool sample for enteric pathogens (at either the central or a local laboratory)	

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

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

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

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

Protocol Amendments

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

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Protocol Supplementary Information, which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, 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 adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

Other Ethical Considerations

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

FINANCIAL DISCLOSURE

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

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

INFORMED CONSENT PROCESS

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

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

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

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

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

DATA PROTECTION

Privacy of Personal Data

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

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

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

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

Exploratory 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.

COMMITTEES STRUCTURE

No data monitoring committee is employed in this study.

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 exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator

agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study 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 exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

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

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

questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

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

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

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

CASE REPORT FORM COMPLETION

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 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 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 eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the electronic data capture (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.

SOURCE DOCUMENTS

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

The author of an entry in the source documents should be identifiable.

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

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

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

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

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

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 postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will 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.

ON-SITE AUDITS

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

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

RECORD RETENTION

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

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

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

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

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

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

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

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

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

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

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

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

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

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

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

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

If a serious and unexpected adverse event 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).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator. The following selection should be used to assess all adverse events (AE).

Related

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

Not Related

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

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

SEVERITY CRITERIA

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

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

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

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

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

SPECIAL REPORTING SITUATIONS

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

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention

- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- 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

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

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

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

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

Serious Adverse Events

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

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

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

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

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

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

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

Procedures

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

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

Contacting Sponsor Regarding Product Quality

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

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy and Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the nonestrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

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

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

Typical use failure rates may differ from those when used consistently and correctly.

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.*
• Intrauterine device (IUD)

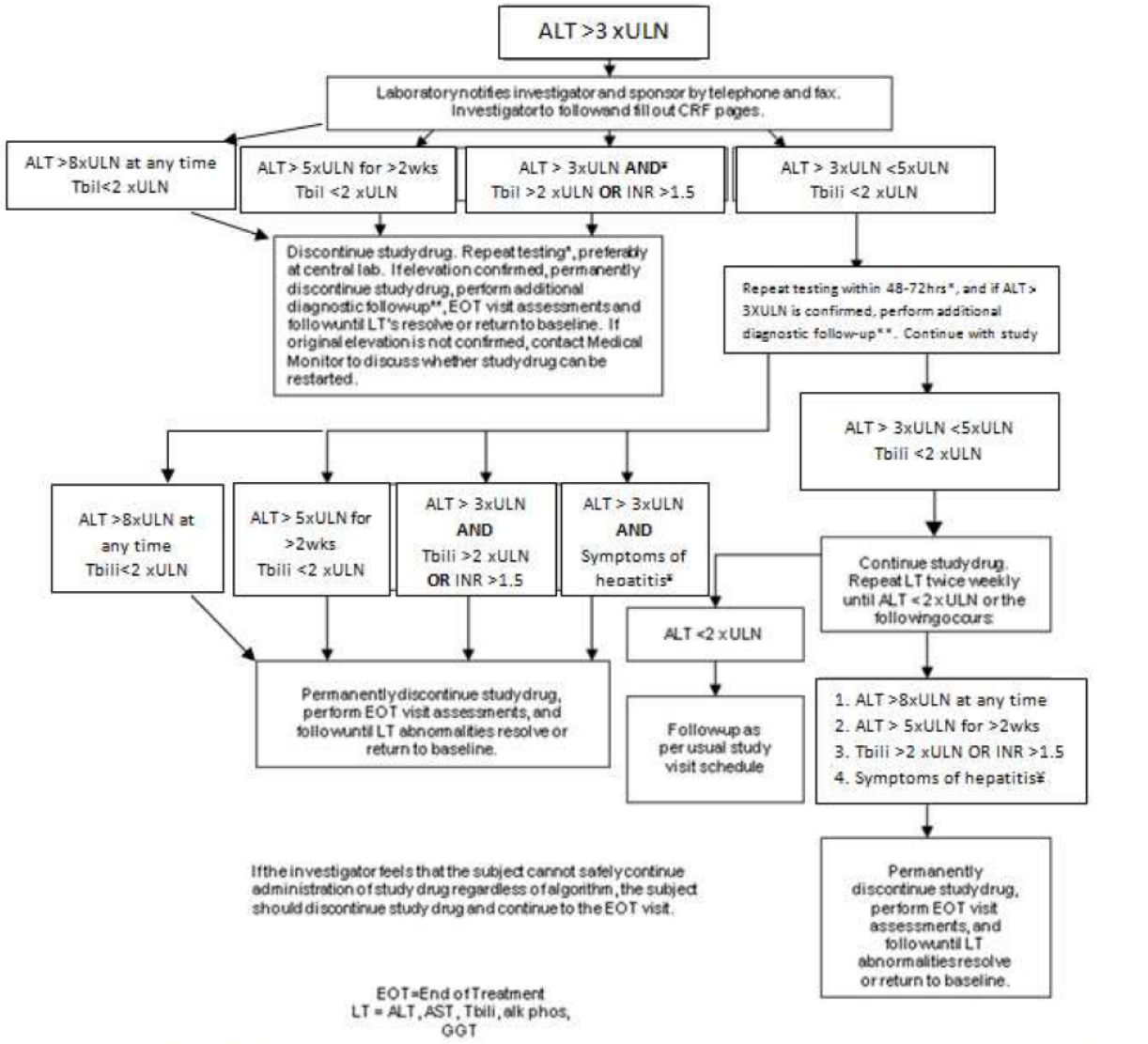
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] –Oral
• 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 condom with or without spermicide
• Diaphragm
• A combination of male condom with diaphragm
• Periodic abstinence (calendar, symptothermal, postovulation methods)
• Withdrawal (coitus-interruptus)
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. 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.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Guideline Algorithm for Monitoring, Assessment & Evaluation of Abnormal Liver Tests in Participants with no Underlying Liver Disease and normal baseline ALT, AST, Alkaline Phosphatase and Bilirubin

Although this algorithm is still applicable across all populations, it has been developed assuming normal liver function at baseline. For populations with pre-existing liver disease and/or AT increases at baseline, product teams are strongly encouraged to consult with Hepatic Safety Group for further guidance particularly for discontinuation criteria.

NOTE: "Liver tests" or "LT's" is the proper name for what are often called "liver function tests" or "LFT's"



*Repeat testing within 48-72 hours in patients with initial ALT elevations, particularly if these are not events reported previously with the drug. If ALT transient elevations have been already established as part of the safety profile, the required frequency of retesting can be decreased

¥ OR ALT >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

THE COMPLETE WORK-UP BELOW (ITEMS 1-5) SHOULD BE PERFORMED IN EVERY SITUATION WHERE "" APPEARS ABOVE. ITEMS 6-7 ARE OPTIONAL, TO BE CONSIDERED ON CASE-BY-CASE BASIS. ALL STUDIES SHOULD BE REPORTED WITH APPROPRIATE SOURCE DOCUMENTATION.**
THE STUDY MEDICAL MONITOR SHOULD BE NOTIFIED WHEN THE ABNORMALITIES ARE DETECTED AND PROVIDED WITH AN UPDATE OF THE RESULTS OF THE DIAGNOSTIC WORK-UP

The following definition of patterns of Drug Induced Liver Injury (DILI) is used when directing the work-up for potential DILI based on elevations of common laboratory tests (LT). A hepatologist consultation should be considered if clinically indicated for the diagnosis and management of potential DILI.

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

1. Obtain detailed history of present illness (abnormal LT's) including (if not already obtained at baseline) height, weight, body mass index (BMI). Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure (CHF), occupational exposure to hepatotoxins, diabetes mellitus (DM), gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other meds including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAID), over the counter (OTC) herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical examination, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy). Allow free text in case report form for other relevant history and physical information.
2. Mandatory liver ultrasound with consideration of further imaging (eg, computerized tomography [CT], magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), Doppler studies of hepatic vessels, if indicated based on ultrasound findings or clinical situation).

3. If total bilirubin (Tbili) is >2xULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with white blood count (WBC) and eosinophil count platelet count, international normalized ratio (INR), and total protein and albumin (compute globulin fraction) should also be documented. If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.
4. If initial LTs and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin M (anti-HAV IgM), anti-HAV total, hepatitis B surface antigen (HBsAg), anti-HBs, anti-HB core total, anti-HB core IgM, anti-hepatitis C virus (anti-HCV), anti-hepatitis E virus IgM (anti-HEV IgM) (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) screen.
   - If patient is immunosuppressed, test for HCV RNA and HEV RNA.
   - If HBsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in patients who are immunosuppressed.
   - If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.
5. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: Total protein and albumin (estimate globulin fraction and obtain quantitative immunoglobulins if elevated), antinuclear antibody (ANA), anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-liver-kidney microsomal antibodies (anti-LKM antibodies), anti-smooth muscle antibodies (ASMA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then gamma-glutamyl transferase (GGT), anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody (pANCA) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/Total iron binding capacity (TIBC) and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If patient is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.
6. A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

   A liver biopsy may be considered:

   - if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.

- if peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak alkaline phosphatase (Alk P) has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
- in cases of DILI where continued use or re-exposure to the implicated agent is expected.
- if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

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

10.7. Appendix 7: Definitions of Inadequate Response to or Intolerance of Corticosteroids or 6-MP/AZA and Corticosteroid Dependence

CORTICOSTEROIDS

Participants have failed to respond to corticosteroids if they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving at least 0.75 mg/kg/day or ≥40 mg/day of prednisone (or corticosteroid equivalent, given orally or intravenously) for 2 weeks; or ≥9 mg/day of budesonide given orally for at least 4 weeks. Evidence of CON-Failure must be documented in the participant's source documentation.

Participants are intolerant of corticosteroids if:

- They have developed clinically significant adverse events (eg, osteonecrosis or osteoporosis, psychosis, uncontrolled diabetes) unresponsive to dose reduction that, in the judgment of the investigator, precluded the use of corticosteroids to treat CD.

OR

- They have a medical condition that precludes the use of corticosteroids as a treatment for CD.

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

6-MERCAPTOPURINE (6-MP) or AZATHIOPRINE (AZA)

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

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

OR

- A lower dosage of 6-MP or AZA when country or local guidelines specify a different treatment regimen. (In such an event, the country or local guidelines needs to be included in the source document).

OR

- The dosage of 6-MP or AZA confirmed to be therapeutic for the participant with whole blood thioguanine nucleotide levels >200 pmol/8 x 10^8 red blood cells.

OR

- The highest tolerated dosage due to leukopenia, elevated liver enzymes, or nausea.

Participants are intolerant of 6-MP or AZA if:

- They have developed clinically significant adverse events (eg, pancreatitis, arthritis accompanied by high fever and/or rash, leukopenia, or persistently elevated liver enzymes) unresponsive to dose reduction that, in the judgment of the investigator, precluded the use of 6-MP or AZA to treat CD within the past 5 years.

OR

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

10.8. Appendix 8: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNF Antagonist Therapies (Infliximab or Adalimumab) Vedolizumab

The criteria for inadequate initial response, response followed by loss of response, or intolerance to infliximab, adalimumab, or vedolizumab are described in items I, II, and III, below.

1. Inadequate initial response to current or prior therapy with infliximab, adalimumab or vedolizumab (primary nonresponse)

Eligible participants must satisfy criteria a, b, and c.

a. Have received induction doses of:

1) Infliximab (2 or 3 doses of ≥ 5 mg/kg)

or

2) Adalimumab (at a dose of 160 mg followed by a dose ≥ 80 mg **or** at a dose of 80 mg followed by a dose ≥ 40 mg)

or

3) Vedolizumab (3 or 4 doses of 300 mg)

AND

b. Did not initially respond to these induction doses of infliximab, adalimumab or vedolizumab as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of CD, as assessed by a treating physician:

1) Lack of improvement or worsening in stool frequency

2) Lack of improvement or worsening in daily abdominal pain

3) Occurrence, lack of improvement, or worsening of fever thought to be related to CD

4) Lack of improvement or worsening in a draining fistula or development of a new draining fistula

5) Lack of improvement or worsening in rectal bleeding

6) Initiation or increase in antidiarrheal medication

These signs and symptoms of CD must have occurred ≥2 weeks after receiving the last induction dose of infliximab, adalimumab or vedolizumab and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having had an inadequate initial response to infliximab, adalimumab or vedolizumab therapy. This benchmark acknowledges that the CDAI is not routinely recorded in clinical practice.

It is acknowledged that previous treatment decisions could have been made based on evaluation of other measures that may be indicative of worsening disease (eg, elevations of inflammatory markers including but not limited to CRP or fecal calprotectin, and/or evidence of disease flare based on clinical imaging modalities including but not limited to ileocolonoscopy, CT and MRI). Under these circumstances, documentation of these specified measures of worsening disease activity can be accepted as evidence of inadequate response to prior biologic treatment. However, investigators should note that participants must meet protocol specified criteria for active disease (ie, clinical and endoscopic) during the current screening period.

AND

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

1) Provide the dates and doses of the failed infliximab, adalimumab or vedolizumab induction therapy.

2) Documents that the participant had persistence of disease activity following infliximab, adalimumab or vedolizumab induction therapy.

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

2. Initial response followed by loss of response to current or prior therapy with infliximab, adalimumab or vedolizumab (secondary nonresponse)

Eligible participants must satisfy criteria a, b, c, d.

a. Initially responded to induction therapy

AND

b. Have received at least 2 maintenance doses of:

1) Infliximab (at a dose of ≥5 mg/kg)

or

2) Adalimumab (at a dose of ≥40 mg)

or

3) Vedolizumab (at a dose of ≥300 mg)

AND

c. Have or had at least 1 of the following signs or symptoms related to recurrence of CD, as assessed by a treating physician:

1) Worsening in stool frequency

2) Worsening in daily abdominal pain

3) Occurrence or worsening in fever thought to be related to CD

4) Recurring drainage from a previously nondraining fistula or development of a new draining fistula

5) Worsening in rectal bleeding

6) Initiation or increase in antidiarrheal medication

These signs and symptoms of CD must have occurred ≥2 weeks after receiving the last maintenance dose of infliximab, adalimumab or vedolizumab, and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having lost response to infliximab, adalimumab or vedolizumab therapy. This benchmark acknowledges that the CDAI is not routinely recorded in clinical practice.

AND

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

1) Provide the dates and doses of the failed infliximab, adalimumab or vedolizumab maintenance therapy.

2) Documents that the participant had recurrence of disease activity despite infliximab, adalimumab or vedolizumab maintenance therapy.

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

3. Current or prior intolerance to therapy with infliximab, adalimumab or vedolizumab

Eligible participants must satisfy criteria a and b.

a. Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum sickness-like reaction); or 3) significant injection-site reaction. Definitions of these 3 criteria are provided below. Adverse reactions also must have followed ≥1 dose of infliximab, adalimumab or vedolizumab, and, in the treating physician's opinion, precluded continued use of the therapy.

1) A significant acute infusion/administration reaction is defined as an adverse reaction that was:

a) Manifested through ≥ 1 of the following symptoms.

- Fever greater than 100°F (37.8°C)
- Chills or rigors
- Itching
- Rash
- Flushing
- Urticaria or angioedema
- Breathing difficulties (dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor)
- Clinical hypotension (pallor, diaphoresis, faintness, syncope), blood pressure less than 90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure of greater than 20 mm Hg

AND

b) Occurred ≤24 hours after infusion/administration of infliximab, adalimumab or vedolizumab

AND

c) Was considered related to the infusion/administration of infliximab, adalimumab or vedolizumab.

2) A significant delayed infusion/administration reaction is defined as an adverse reaction that:

a) Was manifested through 1 or more of the following symptoms:

- Myalgias
- Arthralgias
- Fever greater than 100°F (37.8°C)
- Malaise
- Rash

AND

b) Occurred >24 hours and <15 days after infusion/administration of infliximab, adalimumab or vedolizumab

AND

c) Was considered related to the infusion/administration of infliximab, adalimumab or vedolizumab.

3) A significant injection-site reaction is defined as an adverse reaction that:

a) Was manifested through 1 or more of the following symptoms:

- Significant bruising
- Erythema
- Hemorrhage
- Irritation
- Pain
- Pruritus
- "Injection-site reaction"

AND

b) Occurred within 24 hours of an SC injection of adalimumab

AND

c) Was considered related to the injection.

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

1) Provides the date of discontinuation of infliximab, adalimumab or vedolizumab.

2) Documents that the participant had intolerance to infliximab, adalimumab or vedolizumab.

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

10.9. Appendix 9: Definition of Minimal Exposure to Ustekinumab

Participants who have had limited exposure to ustekinumab at its approved labeled dosage **AND** have met the required washout criterion **AND** have not demonstrated failure or intolerance to ustekinumab as defined further below are eligible for entry into this protocol.

Participants who have had exposure to ustekinumab as an investigational agent (ie, exposure to ustekinumab from participation in prior ustekinumab clinical studies) or exposure to ustekinumab as an off-label treatment at their physician's discretion **are ineligible** for entry into this protocol.

Participants with prior exposure to other anti-IL-12/23 (ie, briakinumab) or anti-IL-23 (ie, including but not limited to risankizumab, brazikumab, and mirikizumab) agents **are ineligible** for entry into this protocol.

Participants MUST meet all of criteria 1, 2, and 3 below to qualify for entry into this protocol as having had minimal exposure to ustekinumab, and provided that all other entry criteria as described in Sections 5.1 and 5.2 have been satisfied.

1. **The criteria for minimal exposure to ustekinumab at its approved label dosage is defined as follows:**
   a. No more than one induction dose of ustekinumab (~6 mg/kg IV)
   b. No more than one maintenance dose of ustekinumab (90 mg SC) 8 weeks after the single induction dose
2. **The required washout period from ustekinumab is defined as followed:**

   Participants must have been discontinued from ustekinumab for at least 16 weeks prior to the Week 0 dosing visit of this protocol
3. **The following documentation to confirm the discontinuation of ustekinumab treatment for CD for reasons other than inadequate response or intolerance MUST be provided:**

   Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization / denial notifications) that:
   a. Provide the dates and doses of ustekinumab for the treatment of CD; AND
   b. Provide the date of discontinuation of ustekinumab for the treatment of CD; AND
   c. Indicate the participant had discontinued ustekinumab treatment for reasons other than inadequate response and/or intolerance (eg, loss of insurance); AND
   d. Indicate the participant **did not** discontinue ustekinumab treatment for CD due to inadequate response and/or intolerance. See further details under the NOTE section below for evidence indicative of inadequate response and/or intolerance.

NOTE:

The following is considered evidence of inadequate response and/or intolerance to ustekinumab treatment for CD. Participants who meet these criteria **are ineligible** to enter this protocol.

Evidence of inadequate response to ustekinumab that had precluded continuation of previous treatment with ustekinumab for CD:

- Lack of improvement or worsening in stool frequency
- Lack of improvement or worsening in daily abdominal pain
- Occurrence, lack of improvement, or worsening of fever thought to be related to CD
- Lack of improvement or worsening in a draining fistula or development of a new draining fistula

- Lack of improvement or worsening in rectal bleeding
- Initiation or increase in antidiarrheal medication

These signs and symptoms of CD are offered only as a benchmark and acknowledges that the CDAI is not routinely recorded in clinical practice.

Evidence of intolerance to ustekinumab that had precluded continuation of previous treatment with ustekinumab for CD:

Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum sickness-like reaction); or 3) significant injection-site reaction.Definitions of these 3 criteria are provided below.

- **A significant acute infusion/administration reaction is defined as an adverse reaction that was:**
  a. Manifested through ≥ 1 of the following symptoms.
     - Fever greater than 100°F (37.8°C)
     - Chills or rigors
     - Itching
     - Rash
     - Flushing
     - Urticaria or angioedema
     - Breathing difficulties (dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor)
     - Clinical hypotension (pallor, diaphoresis, faintness, syncope), blood pressure less than 90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure of greater than 20 mm Hg

     AND

  b. Occurred ≤24 hours after infusion/administration of ustekinumab

     AND

  c. Was considered related to the infusion/administration of ustekinumab
- **A significant delayed infusion/administration reaction is defined as an adverse reaction that:**
  a. Was manifested through 1 or more of the following symptoms:
     - Myalgias
     - Arthralgias
     - Fever greater than 100°F (37.8°C)
     - Malaise
     - Rash

     AND

  b. Occurred >24 hours and <15 days after infusion/administration of ustekinumab

     AND

  c. Was considered related to the infusion/administration of ustekinumab

- **A significant injection-site reaction is defined as an adverse reaction that:**
  a. Was manifested through 1 or more of the following symptoms:
     - Significant bruising
     - Erythema
     - Hemorrhage
     - Irritation
     - Pain
     - Pruritus
     - "Injection-site reaction"

     AND

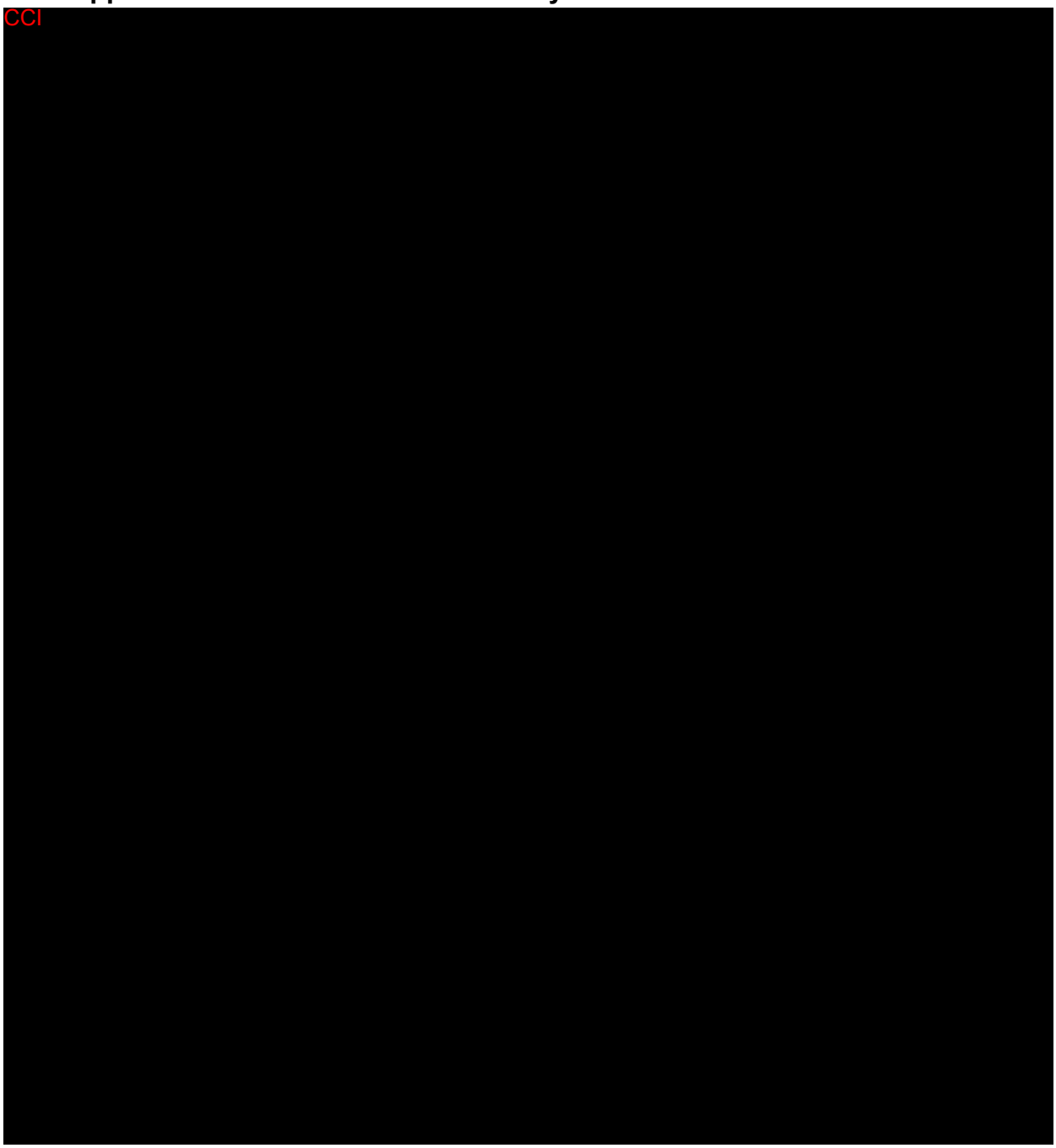
  b. Occurred within 24 hours of an SC injection of ustekinumab.

     AND

  c. Was considered related to the SC injection of ustekinumab.

10.10. Appendix 10: Crohn's Disease Activity Index

CCI



10.11. Appendix 11: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA test is **negative**, the participant ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this protocol. For participants who are eligible with negative HBsAg, and positive core antibody (anti-HBc) and/or surface antibody (anti-HBs), and negative HBV DNA test, HBV DNA quantitation should be monitored at least every 3 months or shorter.

These eligibility criteria based on HBV test results are also represented in Table 6 below.

Table 6: Eligibility based on hepatitis B virus test results

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

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

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

10.12. Appendix 12: Protocol Amendment History

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

11. REFERENCES

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Pharmaceutical K.K.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

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

Signature

User	Date	Reason
PPD	10-Dec-2020 23:49:25 (GMT)	Document Approval