Janssen Research & Development *

Clinical Protocol

Protocol Title

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants With Moderately to Severely Active Crohn's Disease

GRAVITI

Short Title

A Phase 3 Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Crohn's Disease

Protocol CNTO1959CRD3004 Amendment 2; Phase 3

AMENDMENT 2

CNTO 1959 (guselkumab)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

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

Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No. 536/2014.

IND: 133845
EU TRIAL NUMBER: 2023-504737-41

Status:	Approved
Date:	04 October 2024
Prepared by:	Janssen Research & Development, LLC
EDMS number:	EDMS-RIM-163296, 3.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document	Date
Amendment 2	04 October 2024
Amendment 1	13 September 2023
Original Protocol	03 September 2021

Amendment 2 (04 October 2024)

Overall Rationale for the Amendment: Extended the overall duration of the GRAVITI study from approximately 109 weeks to 265 weeks, to align with a health authority commitment. Timepoints for assessments were added/updated accordingly. In addition, edits were made to bring this protocol into compliance with European Union Clinical Trial Regulation (EU-CTR) requirements (Regulation [EU] 536/2014).

The changes made to the clinical protocol CNTO1959CRD3004 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.11, Appendix 11: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Synopsis, Overall Design, Intervention Groups and Duration; Section 1.3 Schedule of Activities, Table 3; Section 4.1 Overall Design; Section 6.3 Measures to Minimized Bias	Updated text to reflect that guselkumab treatment will continue for participants through Week 248. In the Synopsis only, also added clarification that participants will continue on guselkumab treatment if they are, in the opinion of the investigator, benefiting from study intervention.	The study duration was extended to align with a health authority commitment.
Synopsis, Overall Design; Section 4.1 Overall Design	Clarified that an additional DBL is planned for Week 96.	
Synopsis, Intervention Groups and Duration; Section 4.1 Overall Design; Section 4.2 Scientific Rationale for Study Design	Updated the study duration to reflect the extension of the extension treatment phase (from 72 weeks to 224 weeks) and changed the overall study duration from up to 109 weeks to 265 weeks (approximately 5 years).	
Section 1.2 Schema, Figure 1	Updated study schema to include the extension of the study (also extended the extension period and guselkumab treatment lines to Week 248).	
Section 1.3 Schedule of Activities, Table 3	Added "Dispense study intervention," "Self-administration training," and "Administer study intervention" to the Week 96 visit. Updated the notes for these rows as needed.	
Section 1.3 Schedule of Activities, Table 4	Added a new SoA for Weeks 100 to 248.	
Section 1.3 Schedule of Activities, Table 5	Removed the "Visits Required" column from Part a of the table and deleted footnote c. Updated the last 2 rows from Part a of the table to account for the extension of the study (ie, changed Week 96 to Week 248). In the note for the second to last row of Part a of the table, clarified that the video ileocolonoscopy at the SID visit is optional for participants who discontinue after	

Section Number and Name	Description of Change	Brief Rationale
	Week 48 and before Week 96. Also added that video ileocolonoscopy should be performed if the SID visit occurs at Week 96. Added footnote "a" to Part b of the table to indicate which assessments are not required for SID visits occurring at Week 96 or afterwards. Added footnote "b" to Part b of the table to indicate which assessments are not required for FES visits occurring after Week 108. Also in Part b of the table, expanded the note for the daily diary to clarify when the collection of daily diary information will conclude. Added a note to "Hematology and chemistry" row describing when only chemistry laboratory assessments should be performed.	
Section 3 Objectives and Endpoints; Section 9 Statistical Considerations	Edited the final sentence in the paragraph that refers to the SAP.	
Section 4.1 Overall Design; Section 6.1 Study Intervention(s) Administered	Added references to the new Figure 3.	
Section 4.2 Scientific Rationale for Study Design	Clarified that the extension will give participants who in the opinion of the investigator are benefiting from study intervention continued access to treatment. Also included a reference to the SoA in the final sentence.	
Section 4.2.1 Study-specific Ethical Design Considerations; Section 8 Study Assessments and Procedures	Updated the total blood volume to be collected (and the timing for collection) from each participant.	
Section 4.4 End of Study Definition	Updated the statement on when a participant will be considered to have completed the extension treatment phase and the statement on participants who prematurely discontinue study intervention after Week 24 (in both statements updated Week 96 to Week 248, to account for the extension of the study).	
Section 6.1 Study Intervention(s) Administered	Updated Figure 2 (Dose Regimens for the Treatment Phases from Week 0 Through Week 96) to include guselkumab dosing at Week 96. Added Figure 3 to specify dose regimens for the extension treatment phase from Week 100 through Week 248. In the "Self-administration of Study Intervention at Home" subheading, added language on training at Week 96 using the correct device based on assigned treatment regimen. Also edited language on self-administration of study intervention at home to reflect the extension of the study.	

Section Number and Name	Description of Change	Brief Rationale
Section 6.8.1 Concomitant Medications	Edited the title of the "After Week 48 and Through Week 96" subheading (deleted "and Through Week 96") to reflect the extension of the study.	
Section 8 Study Assessments and Procedures, Table 7	Updated "Screening through Week 96" to "through Week 248," to reflect the extension of the study.	
Section 8.2.4 Clinical Safety Laboratory Assessments	Under "Pregnancy testing", added that urine pregnancy tests are to be performed before each study intervention administration on-site, and added a reference to the SoA.	
Section 9.4.4 Tertiary Endpoints	Edited text to clarify that the tertiary endpoints are evaluated at applicable timepoints through Week 96.	
Title Page	Added sentence on new EU regulation.	To comply with EU-CTR requirements.
Title Page; Synopsis	Replaced EudraCT number with EU Clinical Trial Number.	
Synopsis	Added a summary of Benefit/Risk Assessment.	
Section 8.3.4 Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events	Updated safety reporting text.	
Section 10.5.4 Data Protection	Updated language under Privacy of Personal Data to align with Sponsor's protocol template and added a new paragraph on measures to be taken in the event of a data security breach.	
Section 10.5.13 Record Retention	Added text regarding record retention under EU regulation, per EU-CTR requirement.	
Synopsis	Added IND number.	To comply with the Sponsor's protocol template.
Section 6.8.2 Prohibited Concomitant Medications	Added "etrasimod" to the list of experimental Crohn's disease medications.	To update list of treatment options available.
Section 10.5.1 Regulatory and Ethical Considerations	Added Post-marketing Study paragraph.	To comply with local regulations.
Section 10.6.1 Adverse Events Definitions and Classifications	Added final sentence to "Unlisted (Unexpected) AE/RSI" specifying that an AE will be determined by whether it is listed in an appropriate document.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

TABLE OF CONTENTS

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 2

TABLE OF CONTENTS 5

LIST OF IN-TEXT TABLES AND FIGURES 8

1. PROTOCOL SUMMARY 9
1.1. Synopsis 9
1.2. Schema 15
1.3. Schedule of Activities (SoA) 16

2. INTRODUCTION 30
2.1. Study Rationale 30
2.2. Background 31
2.3. Benefit-risk Assessment 32
2.3.1. Risks for Study Participation 32
2.3.2. Benefits for Study Participation 36
2.3.3. Benefit-risk Assessment for Study Participation 37

3. OBJECTIVES AND ENDPOINTS 37

4. STUDY DESIGN 39
4.1. Overall Design 39
4.2. Scientific Rationale for Study Design 42
4.2.1. Study-specific Ethical Design Considerations 44
4.3. Justification for Dose 45
4.4. End of Study Definition 46

5. STUDY POPULATION 46
5.1. Inclusion Criteria 46
5.2. Exclusion Criteria 52
5.3. Lifestyle Considerations 57
5.4. Screen Failures 57
5.5. Criteria for Temporarily Delaying Enrollment, Randomization or Administration of Study Intervention 58

6. STUDY INTERVENTION AND CONCOMITANT THERAPY 59
6.1. Study Intervention(s) Administered 59
6.1.1. Combination Products 62
6.2. Preparation/Handling/Storage/Accountability 62
6.3. Measures to Minimize Bias: Randomization and Blinding 64
6.4. Study Intervention Compliance 65
6.5. Dose Modification 65
6.5.1. Rescue Medication 65
6.6. Continued Access to Study Intervention After the End of the Study 66
6.7. Treatment of Overdose 66
6.8. Concomitant Therapy 66
6.8.1. Concomitant Medications 66
6.8.1.1. Oral Corticosteroids Tapering 67
6.8.2. Prohibited Concomitant Medications 68
6.8.3. Vaccinations (Including COVID-19) 69

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 69
7.1. Discontinuation of Study Intervention 69
7.2. Participant Discontinuation/Withdrawal From the Study 71
7.2.1. Withdrawal From the Use of Research Samples 71

7.3. Lost to Follow-up 72

8. STUDY ASSESSMENTS AND PROCEDURES 73
8.1. Efficacy Assessments 75
8.2. Safety Assessments 78
8.2.1. Physical Examinations 78
8.2.2. Vital Signs 78
8.2.3. Electrocardiogram 78
8.2.4. Clinical Safety Laboratory Assessments 79
8.2.5. Columbia-Suicide Severity Rating Scale 79
8.2.6. Concomitant Medication Review 81
8.2.7. Injection-site Reactions 81
8.2.8. Hypersensitivity Reactions 81
8.2.9. Infections 82
8.2.10. Tuberculosis Evaluation 82
8.2.10.1. Initial Tuberculosis Evaluation 82
8.2.10.2. Ongoing Tuberculosis Evaluation 83
8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting 83
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information 84
8.3.2. Method of Detecting Adverse Events and Serious Adverse Events 84
8.3.3. Follow-up of Adverse Events and Serious Adverse Events 84
8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events 85
8.3.5. Pregnancy 85
8.3.6. Adverse Events of Special Interest 85
8.4. Pharmacokinetics 86
8.4.1. Evaluations 86
8.4.2. Analytical Procedures 86
8.4.3. Pharmacokinetic Parameters and Evaluations 86
8.5. Pharmacogenomics 87
8.6. Biomarkers 87
8.6.1. Serum-based Biomarkers 88
8.6.2. Whole Blood-based Biomarkers 88
8.6.3. Biopsy-based Biomarkers 88
8.6.4. Pharmacodynamics 88
8.7. Immunogenicity Assessments 88
8.8. Medical Resource Utilization and Health Economics 89

9. STATISTICAL CONSIDERATIONS 89
9.1. Statistical Hypotheses 89
9.2. Sample Size Determination 89
9.3. Populations for Analysis Sets 90
9.4. Statistical Analyses 91
9.4.1. General Considerations 91
9.4.2. Primary Endpoints 91
9.4.3. Secondary Endpoints 94
9.4.4. Tertiary Endpoints 96
9.4.5. Safety Analyses 96
9.4.6. Other Analyses 97
9.5. Interim Analysis 98

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 99
10.1. Appendix 1: Abbreviations and Definitions 100
10.2. Appendix 2: Definitions of Inadequate Response to or Intolerance of Corticosteroids or 6-Mercaptopurine/Azathioprine/Methotrexate and Corticosteroid Dependence 102

10.3. Appendix 3: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to Tumor Necrosis Factor Antagonist Therapies (Infliximab, Adalimumab, or Certolizumab Pegol), Vedolizumab, or Approved Biosimilars 104
10.4. Appendix 4: Hepatitis B Virus (HBV) Screening With HBV DNA Testing 109
10.5. Appendix 5: Regulatory, Ethical, and Study Oversight Considerations 110
10.5.1. Regulatory and Ethical Considerations 110
10.5.2. Financial Disclosure 113
10.5.3. Informed Consent Process 113
10.5.4. Data Protection 114
10.5.5. Long-term Retention of Samples for Additional Future Research 115
10.5.6. Committees Structure 115
10.5.7. Publication Policy/Dissemination of Clinical Study Data 115
10.5.8. Data Quality Assurance 117
10.5.9. Case Report Form Completion 117
10.5.10. Source Documents 118
10.5.11. Monitoring 119
10.5.12. On-Site Audits 119
10.5.13. Record Retention 119
10.5.14. Study and Site Start and Closure 120
10.6. Appendix 6: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 121
10.6.1. Adverse Event Definitions and Classifications 121
10.6.2. Attribution Definitions 122
10.6.3. Severity Criteria 122
10.6.4. Special Reporting Situations 123
10.6.5. Procedures 123
10.6.6. Product Quality Complaint Handling 125
10.6.7. Contacting Sponsor Regarding Safety, Including Product Quality 125
10.7. Appendix 7: Contraceptive and Barrier Guidance 126
10.8. Appendix 8: Crohn's Disease Activity Index 129
10.9. Appendix 9: Guideline Algorithm for Monitoring, Assessment and Evaluation of Abnormal Liver Tests 130
10.10. Appendix 10: Study Conduct During a Natural Disaster 134
10.11. Appendix 11: Protocol Amendment History 136

11. REFERENCES 138

INVESTIGATOR AGREEMENT 140

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

Table 1: Schedule of Activities: Screening Phase 16
Table 2: Schedule of Activities: Main Treatment Phase Weeks 0 to 24 18
Table 3: Schedule of Activities: Extension Treatment Phase Weeks 28 to 96 21
Table 4: Schedule of Activities: Extension Treatment Phase Weeks 100 to 248 26
Table 5: Schedule of Activities: Study Intervention Discontinuation (SID) Visit and the Final Efficacy and Safety (FES) Follow-up Visit 27
Table 6: Recommended Tapering Schedule for Oral Corticosteroids 68
Table 7: Volume of Blood to be Collected From Each Participant 74
Table 8: Power to Detect a Treatment Effect of Guselkumab Based on Proportion of Participants Achieving Clinical Remission at Week 12 or Endoscopic Response at Week 12 90
Table 9: Eligibility Based on Hepatitis B Virus Test Results 109
Table 10: Patterns of DILI Based on Elevations of Liver Tests 133

FIGURES

Figure 1: Schematic Overview of the Study 15
Figure 2: Dose Regimens for the Treatment Phases From Week 0 Through Week 96 60
Figure 3: Dose Regimens for the Extension Treatment Phase From Week 100 Through Week 248 60

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants With Moderately to Severely Active Crohn's Disease

IND: 133845
EU Trial Number: 2023-504737-41

Short Title: A Phase 3 Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Crohn's Disease

Guselkumab is a fully human immunoglobulin G1 lambda monoclonal antibody that binds to human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 mediated intracellular signaling, activation and cytokine production.

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

BENEFIT/RISK ASSESSMENT

Guselkumab, an IL-23 antagonist, has a well-defined long-term safety profile and has been extensively studied in the approved indications of adults with moderate to severe psoriasis and adults with active psoriatic arthritis. The Phase 2 results for guselkumab in participants with Crohn's disease (CNTO1959CRD3001; GALAXI 1) also provided a scientific and clinical rationale for pursuing the development of guselkumab in patients with moderately to severely active Crohn's disease and for the investigation of guselkumab in this study. Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with guselkumab are justified by the anticipated benefits that may be afforded to participants with moderately to severely active Crohn's disease. More detailed information about the known and expected benefits and risks of guselkumab may be found in the Investigator's Brochure (IB).

OBJECTIVES AND ENDPOINTS

The primary and secondary objectives and endpoints of the study are listed below.

Objectives	Endpoints
Primary	
• To evaluate the efficacy, including clinical remission and endoscopic response, of guselkumab SC induction	• Clinical remission (CDAI score <150) at Week 12 • Endoscopic response (≥50% improvement from baseline in the SES-CD score) at Week 12
Secondary	
• To evaluate the efficacy of guselkumab SC across a range of outcome measures	• Clinical remission at Week 24 • PRO-2 remission (an AP mean daily score ≤1 and SF mean daily score ≤3 and no worsening of AP or SF from baseline) at Week 12

Objectives	Endpoints
	• Clinical response (decrease from baseline in CDAI ≥100 points or clinical remission) at Week 12
• To evaluate the safety of guselkumab SC	• Summary of AEs, such as SAEs and AEs leading to discontinuation of study intervention

Abbreviations: AE=adverse event; AP=abdominal pain; CDAI=Crohn's Disease Activity Index; PRO=Patient-reported Outcome; SAE=serious adverse event; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; SF=stool frequency

Hypotheses

The co-primary hypotheses of this study are that guselkumab is superior to placebo in inducing clinical remission at Week 12 and guselkumab is superior to placebo in inducing endoscopic response at Week 12 among participants with moderately to severely active Crohn's disease.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab subcutaneous (SC) induction dosing. The target population is adult participants with moderately to severely active Crohn's disease (of at least 3 months duration) with colitis, ileitis, or ileocolitis previously confirmed by radiography, histology, and/or endoscopy. To be eligible for the study, participants must also have endoscopic evidence of active Crohn's disease, and have demonstrated an inadequate response or failure to tolerate previous conventional therapy (oral corticosteroids or the immunomodulators azathioprine [AZA], 6-mercaptopurine [6-MP] or methotrexate [MTX]; CON-Failure) or biologic therapy (infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars for these agents; BIO-Failure).

Overall, the study will evaluate guselkumab SC treatment through 12 weeks of induction therapy and at least 12 weeks of maintenance therapy. At Week 24, all participants will enter the extension phase and receive the same treatment regimen that they were receiving at Week 24. The study will be unblinded after the last participant completes the Week 48 evaluations and the Week 48 database lock (DBL) is completed. Upon study unblinding, placebo participants who have not been rescued with guselkumab (see Intervention Groups and Duration section) will be discontinued from study intervention and have a final efficacy and safety (FES) follow-up visit. All other participants who in the opinion of the investigator are benefiting from study intervention will continue on guselkumab treatment through Week 248.

In general, participants who are receiving oral 5-aminosalicylic acid compounds, oral corticosteroids, conventional immunomodulators (AZA, 6-MP, or MTX), antibiotics, and/or enteral nutrition for the treatment of Crohn's disease at baseline should maintain a stable dose for a specified period before baseline and through Week 48, with the exception of oral corticosteroids. Starting at Week 12, all participants who were taking corticosteroids at Week 0 must begin tapering their corticosteroid dose. This tapering is mandatory, unless not medically feasible.

Participants who discontinue study intervention early should return for a study intervention discontinuation (SID) visit. All randomized participants should complete the FES follow-up visit approximately 12 weeks after the last dose of study intervention.

Efficacy, safety, pharmacokinetics (PK), immunogenicity, and biomarkers will be assessed according to the Schedule of Activities (SoA). A blood sample for pharmacogenomic research will be collected only from participants who consent to this component of the protocol (where local regulations permit).

Database locks are planned for Week 24, Week 48, Week 96, and when the last participant completes the last scheduled assessment as shown in the SoA. Additional DBLs may be added as necessary.

End of Study

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

NUMBER OF PARTICIPANTS

The target sample size is 318 participants. Participants who had an inadequate response or failure to tolerate biologic therapy will comprise approximately 35% to 65% of the population.

INTERVENTION GROUPS AND DURATION

The overall study duration is up to 265 weeks. The study comprises of the following phases:

1. Screening phase: up to 5 weeks
2. Main treatment phase: 24 weeks
3. Extension treatment phase: 224 weeks
4. Post-treatment phase (FES follow-up visit): until approximately 12 weeks after the last dose of study intervention

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

- 106 participants to guselkumab CCI at Weeks 0, 4, and 8 followed by guselkumab CCI every 4 weeks (q4w) through Week 24
- 106 participants to guselkumab CCI at Weeks 0, 4, and 8 followed by guselkumab CCI every 8 weeks (q8w) through Week 24
- 106 participants to placebo SC q4w from Week 0 through Week 24

The randomization will be stratified by baseline Crohn's Disease Activity Index (CDAI) score (≤300 or >300), baseline Simple Endoscopic Score for Crohn's Disease (SES-CD) score (≤12 or >12), and BIO-Failure status (Yes or No) at baseline (Week 0).

During the extension phase, all participants will continue to receive the same treatment regimen that they were receiving at Week 24.

Upon study unblinding after Week 48 DBL, placebo participants who have not been rescued with guselkumab will be discontinued from study intervention and have an FES follow-up visit. All other participants who in the opinion of the investigator are benefiting from study intervention will continue on guselkumab treatment through Week 248.

All participants in the placebo group who meet at least 1 of the rescue criteria at Weeks 12 and 16 will receive rescue treatment, ie, guselkumab CCI at Weeks 16, 20, and 24 followed by guselkumab CCI every 8 weeks (q8w). To maintain the blind, participants randomized to guselkumab who meet at least 1 of the rescue criteria will continue their assigned treatment regimen and receive blinded sham rescue matching placebo SC injection.

Description of Interventions

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

Guselkumab will be provided in 2 dose strengths: guselkumab CCI in a single-dose prefilled syringe with YpsoMate autoinjector (PFS-Y) and CCI in a single-dose prefilled syringe with an UltraSafe Plus™ Passive Needle Guard (PFS-U). Matching placebo will be provided as CCI in a single-dose PFS-Y and as CCI in a single dose PFS-U.

EFFICACY EVALUATIONS

Efficacy evaluations will include the following:

- CDAI
- PRO-2 (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 SES-CD
- Histologic assessments
- Inflammatory pharmacodynamic (PD) markers including C-reactive protein (CRP) and fecal calprotectin
- Fistula assessment
- PRO measures to assess health-related quality of life outcomes including Inflammatory Bowel Disease Questionnaire (IBDQ) and Patient-reported Outcomes Measurement Information System (PROMIS)-29
- Patient-reported symptom measures including Bristol Stool Form Scale (BSFS) and AP-Numerical Rating Scale (AP-NRS)

PHARMACOKINETIC EVALUATIONS

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

PHARMACOGENOMIC (DNA) EVALUATIONS

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

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Inflammatory PD markers (CRP and fecal calprotectin) will be evaluated using blood and fecal samples.

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab treatment and/or Crohn's disease. Assessments will include the evaluation of relevant biomarkers in serum, whole blood, and ileocolonic biopsy samples, where local regulations permit.

IMMUNOGENICITY EVALUATIONS

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

SAFETY EVALUATIONS

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

STATISTICAL METHODS

Sample Size Determination

Sample sizes were determined by the power to detect a significant difference in clinical remission at Week 12 and in endoscopic response at Week 12 (co-primary endpoints) between the combined guselkumab group and the placebo group, using a 2-sided chi-square test with 0.05 significance level. The assumed rates are 50% versus 15% (guselkumab versus placebo) for clinical remission and 30% versus 13% for endoscopic response. The study is sized such that the guselkumab therapy achieves >90% power for the co-primary endpoints compared with placebo. This sample size also provides >90% power for all secondary endpoints.

Efficacy Analyses

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

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

The co-primary endpoints (clinical remission at Week 12 and endoscopic response at Week 12) will be analyzed based on the primary estimand, considering treatment groups, population, variable, intercurrent event (ICE) strategies, and population-level summary. After accounting for the ICE strategies, participants whose responder status is missing for a co-primary endpoint will be considered to be a non-responder for that co-primary endpoint.

Statistical testing will be performed at a significance level of 0.05 (2-sided). The Type I error will be controlled over the co-primary, secondary, and selected Week 48 tertiary endpoints in the multiplicity-controlled testing procedure. The testing procedure begins with sequential tests as follows:

- For the co-primary endpoints, clinical remission at Week 12 will be tested first, followed by endoscopic response at Week 12.
- The analyses for the 3 secondary endpoints listed below will be performed sequentially contingent upon the success of both co-primary endpoint analyses.

- Clinical remission (CDAI score <150) at Week 24, the test between the high dose group (CCI [redacted] q4w) and the placebo group will be performed first, followed by the test between the low dose group (CCI [redacted] q8w) and the placebo group
- PRO-2 remission at Week 12 (defined as an AP mean daily score at or below 1 and stool frequency (SF) mean daily score at or below 3, ie, AP ≤1 and SF ≤3, and no worsening of AP or SF from baseline)
- Clinical response (decrease from baseline in CDAI ≥100 points or clinical remission) at Week 12

Two tertiary endpoints (clinical remission at Week 48, endoscopic response at Week 48) will be added at the end of the multiplicity-controlled testing procedure above; the full testing procedure will be specified in the Statistical Analysis Plan. Other tertiary endpoints will not be multiplicity-controlled, and nominal p-values will be presented.

Safety Analyses

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

Other Analyses

Pharmacokinetic Analyses

Serum guselkumab concentration over time will be summarized for each treatment group using descriptive statistics. Population PK modeling may be conducted when appropriate. If these population PK analyses are conducted, the results of these analyses will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

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

Pharmacogenomic Analyses

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

Biomarker Analyses

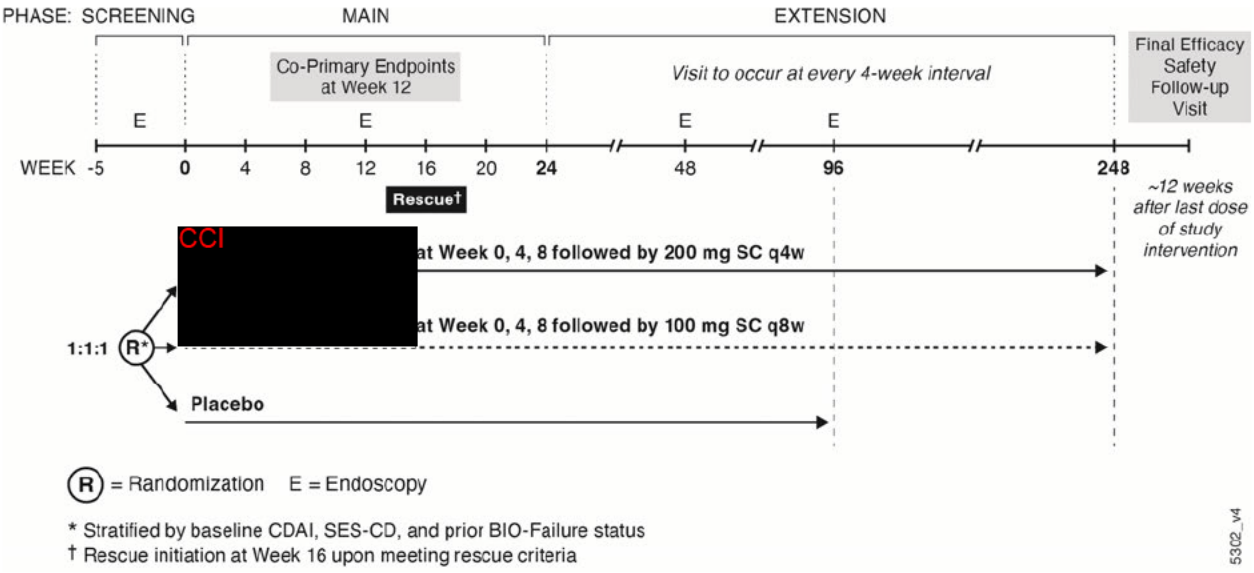
Changes in serum protein analytes and whole blood ribonucleic acid (RNA) obtained over time will be summarized by intervention group where local regulations permit. Associations between baseline levels and changes from baseline in select biomarkers and response to treatment will be explored. RNA analyses will be summarized in a separate technical report.

Immunogenicity Analyses

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

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities: Screening Phase

Study Procedures	Screening (Within 5 weeks)	Notes
Administrative		
Informed consent	X	
Inclusion/exclusion criteria	X	
Medical history and demographics	X	
ECG	X	
Chest radiograph	X	Chest radiograph must be obtained within 12 weeks before the Week 0 visit. Note: A chest CT scan is also acceptable if obtained instead of a chest radiograph outside of the protocol.
TB evaluation/other infection assessment	X	All participants will undergo TB testing within 2 months before the Week 0 visit. More information on TB evaluation is provided in Section 8.2.10 and inclusion criterion 9.
Stool studies to evaluate for enteric pathogens	X	Stool studies for enteric pathogens may be performed at screening at either the central or a local laboratory and must include a stool culture and *Clostridioides difficile* (formerly known as *Clostridium difficile*) toxin assay. Although stool studies may be processed at either the central or local laboratory, the central laboratory is preferred when available. Stool studies must have been performed within 4 months before Week 0. Additional testing, such as ova and parasites or *Escherichia coli* O157:H7 assessment, may be performed at the investigator's clinical discretion.
HBV and HCV testing	X	
HIV testing	X	
Provide Symptom and Health Diary (CDAI, BSFS, AP-NRS) and training	X	Provide participants with the take-home paper diary and provide training on diary completion. The diary information collected prior to the randomization visit will be used to calculate the CDAI, BSFS, and AP-NRS score at baseline (Week 0). A minimum of 7 days of CDAI data during the screening period is required to calculate the CDAI score at baseline (Week 0).
Schedule video ileocolonoscopy	X	During the initial screening visit the video ileocolonoscopy should be scheduled, if feasible. The screening ileocolonoscopy will be performed at least 10 days before but no more than approximately 3 weeks before the Week 0 visit to prevent interfering with the collection of CDAI data for the Week 0 visit.
Safety Assessments		
Physical examination	X	A complete, detailed physical examination should be performed at the screening visit for study eligibility assessment.
Weight	X	
Height	X	
Vital signs	X	Temperature, pulse/heart rate, respiratory rate, and blood pressure
Serum pregnancy test	X	Must be performed in female participants of childbearing potential.
Follicle stimulating hormone	X	Consider testing in women with no menses for ≥12 months without an alternative medical cause (see Section 10.8 for further guidance).

Study Procedures	Screening (Within 5 weeks)	Notes
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. The investigator or trained study site personnel will interview the participant and complete the C-SSRS.
Efficacy Assessments		
Fistula assessment	X	
Video ileocolonoscopy	X	To prevent interfering with the collection of CDAI data for the Week 0 visit, the screening ileocolonoscopy will be performed at least 10 days before but no more than approximately 3 weeks before the Week 0 visit.
Stool sample (fecal calprotectin)	X	If stool samples are collected around the time of the screening ileocolonoscopy, they must be collected before the start of the bowel preparation for ileocolonoscopy (through on-site or at-home collection).
CRP	X	
Clinical Laboratory Assessments		
Hematology and chemistry	X	
Pharmacodynamics and Biomarkers		
Ileocolonoscopy biopsy sample collections for histology	X	Refer to the biopsy manual for details on the biopsy sample collection.
Ileocolonoscopy biopsy sample collections for exploratory RNA and protein assessments (where local regulations permit).	X	Refer to the biopsy manual for details on the biopsy sample collection.
Ongoing Participant Review		
Concomitant therapy	X	Concomitant therapies should be documented after signing informed consent and should remain stable for the duration of the screening period (see Concomitant Therapy section).
Adverse events	X	The reporting of adverse events should begin after the informed consent is signed and should continue for the duration of the screening period.

Abbreviations: AP-NRS=Abdominal Pain-Numerical Rating Scale; BSFS=Bristol Stool Form Scale; CDAI= Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; ECG=electrocardiogram; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; RNA=ribonucleic acid; TB= tuberculosis

Table 2: Schedule of Activities: Main Treatment Phase Weeks 0 to 24

Week[a,b]:	0	4	8	12	16	20	24	Notes
Study Procedures[c]								
Administrative								
Inclusion/exclusion criteria	X							
Review medical history	X							Verify any additional changes since medical history review at screening visit.
Study Intervention Administration								
Randomization	X							Randomization should be performed within approximately 5 weeks after screening/informed consent signing.
Dispense study intervention	X	X	X	X	X	X	X	
Administer study intervention	X	X	X	X	X	X	X	All procedures/assessments described in this SoA table are to be completed prior to study intervention administration on site, unless otherwise specified. PRO assessments should be completed first, followed by the C-SSRS assessment, and then any other clinical procedures, tests, or consultations.
Study intervention accountability	X	X	X	X	X	X	X	
Safety Assessments								
Physical examination	X	X	X	X	X	X	X	A targeted physical examination will be performed (see Section 8.2.1).
Vital signs	X	X	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 SC injection.
Urine pregnancy test	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	If TB is suspected at any time, study intervention should be withheld and an immediate and thorough investigation should be undertaken. More information on TB evaluation is provided in Section 8.2.10.
Injection-site evaluation	X	X	X	X	X	X	X	An injection-site reaction is any adverse reaction at an SC study intervention injection site. Injection sites will be evaluated for reactions, and any injection-site reaction will be recorded as an AE.
C-SSRS	X	X	X	X	X	X	X	The C-SSRS should be completed after all PRO assessments and before any other tests, procedures, or other consultations to prevent influencing participant perceptions. The investigator or trained study site personnel will interview the participant and complete the C-SSRS.
Efficacy Assessments								
Collect and review Symptom and Health Diary (CDAI, BSFS, AP-NRS)	X	X	X	X	X	X	X	Diary information should be completed daily, and participants should bring their diaries to each on-site visit. The daily diary includes patient-reported data for the CDAI, BSFS, and AP-NRS. CDAI: The most recent hematocrit value obtained during the screening window will be used to calculate CDAI at Week 0. For all other visits, the most recent hematocrit value obtained will be used to calculate the CDAI.
Weight	X	X	X	X	X	X	X	Weight measurement is used to support CDAI assessments, PK modeling, and safety.
Fistula assessment	X	X	X	X	X	X	X	

Week[a,b]:	0	4	8	12	16	20	24	Notes
Study Procedures[c]								
Video ileocolonoscopy				X				To prevent interfering with the collection of CDAI data, the video ileocolonoscopy must be performed at least 10 days before or at the designated visit (ie, Week 12). If performed on the day of the designated visit, the 7 days before the initiation of the ileocolonoscopy preparation should be utilized to calculate CDAI scores for these visits.
Stool sample (fecal calprotectin)	X	X	X	X			X	Week 0: Not required if sample already collected within 2 weeks of the Week 0 visit. Week 12: Stool sample collection (through on-site or at-home collection) must be obtained before the start of a bowel preparation if there is a coinciding ileocolonoscopy scheduled for that visit.
CRP	X	X	X	X	X	X	X	Week 0: Not required if sample already collected within 2 weeks of the Week 0 visit.
Patient-reported Outcomes								
IBDQ	X		X	X			X	IBDQ and PROMIS-29 should be administered before the C-SSRS and before any clinical procedures or tests are performed. These assessments are completed by participants on-site using the provided tablet.
PROMIS-29	X		X	X			X	
Clinical Laboratory Assessments								
Hematology and chemistry	X	X	X	X	X	X	X	Week 0: Laboratory tests are not required if screening laboratory tests were performed within 2 weeks of the Week 0 visit.
Pharmacokinetics and Immunogenicity								
Study intervention serum concentration	X	X	X	X	X	X	X	Blood samples should be collected before the administration of study intervention. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of PK sample collections.
Assessment for antibody to study intervention	X	X	X	X			X	Blood samples should be collected before the administration of study intervention. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of sample collections.
Pharmacodynamics and Biomarkers								
Whole blood sample collection for RNA analysis (where local regulations permit)	X	X		X			X	Whole blood for RNA analysis will be collected from all participants in the study to assess the RNA transcriptome related to both Crohn's disease and response to guselkumab.
Serum biomarkers (where local regulations permit)	X	X		X			X	Serum biomarkers will be collected from all participants in the study to assess peripheral proteins related to both Crohn's disease and response to guselkumab.
Ileocolonoscopy biopsy sample collections for histology				X				Refer to the biopsy manual for details on the biopsy sample collection.
Ileocolonoscopy biopsy sample collections for exploratory RNA and protein assessments (where local regulations permit).				X				Refer to the biopsy manual for details on the biopsy sample collection.

Week[a,b]:	0	4	8	12	16	20	24	Notes
Study Procedures[c]								
Pharmacogenomics (DNA)								
Genetic (DNA) evaluation (where local regulations permit)	X							Whole blood will be collected only from participants who consent to participate in the optional DNA analysis. The pharmacogenomic (DNA) sample should be collected at the specified time point; however, if necessary it may be collected later without constituting a protocol deviation.
Ongoing Participant Review								
Concomitant therapy	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	
Crohn's disease-related surgeries and procedures	X	X	X	X	X	X	X	The Week 12 ileocolonoscopy should not be included in this category.

Footnotes:

a. If a participant discontinues study intervention prior to the Week 24 visit, the participant should complete the evaluations as detailed under the SID visit at the time of SID. In addition, the participant should return for an FES follow-up visit approximately 12 weeks after their last study intervention administration. For additional details, see Table 5.

b. The visit window should be ±4 days for each visit up to and including Week 12; after Week 12 to end of study, the visit window should be ±7 days. Post-randomization scheduled study visit dates should be based on the participant's randomization date.

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

Abbreviations: AE=adverse event; AP-NRS=Abdominal Pain-Numerical Rating Scale; BSFS=Bristol Stool Form Scale; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; DNA=deoxyribonucleic acid; IBDQ=Inflammatory Bowel Disease Questionnaire; FES=final efficacy and safety; PK=pharmacokinetic(s); PRO=patient-reported outcome; PROMIS=Patient-reported Outcomes Measurement Information System; RNA=ribonucleic acid; SC=subcutaneous; SID=study intervention discontinuation; SoA=Schedule of Activities; TB=tuberculosis

Table 3: Schedule of Activities: Extension Treatment Phase Weeks 28 to 96

Week[a,b]:	28	32	36	40	44	48[c]	52[d]	56	60[d]	64	68[d]	72	76[d]	80	84[d]	88	92[d]	96	Notes
Study Procedures[e]																			
Study Intervention Administration																			
Dispense study intervention	X	X	X	X	X	X		X		X		X		X		X		X	Study intervention for at-home administration at Weeks 52, 60, 68, 76, 84, and 92 will be supplied to participants during the on-site visits at Weeks 48, 56, 64, 72, 80, and 88, respectively. Study intervention for at-home administration will be supplied at Week 96 for participants continuing in the study.
Self-administration training	X	X																X	At the Week 28 and 32 visits, participants who opt to self-administer will receive training (per investigator discretion and/or allowed per local regulation) on how to self-administer study intervention. A caregiver may also be trained to administer study intervention. At Week 96, all participants continuing in the study who were not previously trained should receive training on how to self-administer study intervention if allowed by local regulation and per investigator's discretion. The training with the correct device based on assigned treatment regimen must be documented prior to starting at-home administration after Week 96. If needed, participants (or their caregivers) can be trained at later time points.
Administer study intervention	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X	All procedures/assessments described in this SoA table are to be completed prior to study intervention administration on site, unless otherwise specified. PRO assessments should be completed first, followed by the C-SSRS assessment, and then any other clinical procedures, tests, or consultations. Upon completion of training and at the discretion of the investigator and participant, self-administration of study intervention (or administration by a caregiver) at the investigative site may begin from the Week 36 visit onwards. The self-administrations of study intervention

Week[a,b]:	28	32	36	40	44	48[c]	52[d]	56	60[d]	64	68[d]	72	76[d]	80	84[d]	88	92[d]	96	Notes
Study Procedures[e]																			
																			on-site should be done in the presence of study site staff. Starting from Week 52 up to Week 92, participants may self-administer (or their caregivers may administer) study intervention at home every 8 weeks, at the visits where only a single injection is required, if allowed per local regulation. Participants are provided a study medication diary to record at-home study intervention administration and will receive instructions on how to self-evaluate any injection-site reaction. Participants will also be instructed to report AEs related to injection-site reactions to the site promptly. Participants who are unable or unwilling to have study injections administered at home will be required to return to the site for administration of study intervention injection.
Study intervention accountability	X	X	X	X	X	X		X		X		X		X		X		X	
Safety Assessments																			
Physical examination	X	X	X	X	X	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	A targeted physical examination will be performed (see Section 8.2.1). Assessment is not required at visits performed via telemedicine contact.
Vital signs	X	X	X	X	X	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	Includes temperature, pulse/heart rate, respiratory rate, and blood pressure. Must be obtained prior to and approximately 30 minutes after the SC injection. Assessment is not required at visits performed via telemedicine contact.
Urine pregnancy test	X	X	X	X	X	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	Must be performed before every study intervention administration in female participants of childbearing potential. Assessment is not required at visits performed via telemedicine contact.
TB evaluation/other	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X	If TB is suspected at any time, study intervention should be withheld and an

Week[a,b]:	28	32	36	40	44	48[c]	52[d]	56	60[d]	64	68[d]	72	76[d]	80	84[d]	88	92[d]	96	Notes
Study Procedures[e]																			
infection assessment																			immediate and thorough investigation should be undertaken. More information on TB evaluation is provided in Section 8.2.10.
Injection-site evaluation	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	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. Participants are trained to perform self-evaluation for injection-site reactions and reporting of AEs.
C-SSRS	X	X	X	X	X	X		X		X		X		X		X		X	The C-SSRS should be completed after all PRO assessments and before any other tests, procedures, or other consultations to prevent influencing participant perceptions. The investigator or trained study site personnel will interview the participant and complete the C-SSRS.
Efficacy Assessments																			
Collect and review Symptom and Health Diary • CDAI • BSFS • AP-NRS	 X X X	 X X X	 X X X	 X X X	 X X X	 X X X	T	X	T	X	T	X	T	X	T	X	T	X	Diary information should be completed daily, and participants should bring their diaries to each on-site visit. The daily diary includes patient-reported data for the CDAI, BSFS, and AP-NRS. Collection for BSFS and AP-NRS will conclude at Week 48. The most recent hematocrit value obtained will be used to calculate the CDAI.
Weight	X	X	X	X	X	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	Weight measurement is used to support CDAI assessments, PK modeling, and safety. Weight measurement is <u>not</u> required at visits performed via telemedicine contact.
Fistula assessment	X	X	X	X	X	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	T[f]	X	Assessment is <u>not</u> required at visits performed via telemedicine contact.
Video ileocolonoscopy						X												X	To prevent interfering with the collection of CDAI data, the video ileocolonoscopy must be performed at least 10 days before or at the designated visit (ie, Week 48 and Week 96). If performed on the day of the designated

Week[a,b]:	28	32	36	40	44	48[c]	52[d]	56	60[d]	64	68[d]	72	76[d]	80	84[d]	88	92[d]	96	Notes
Study Procedures[e]																			
																			visit, the 7 days before the initiation of the ileocolonoscopy preparation should be utilized to calculate CDAI scores for these visits.
Stool sample (fecal calprotectin)						X				X								X	Week 48 and Week 96: Stool sample collection (through on-site or at-home collection) must be obtained before the start of a bowel preparation if there is a coinciding ileocolonoscopy scheduled for that visit.
CRP		X		X		X				X				X				X	
Patient-reported Outcomes																			
IBDQ						X				X				X				X	IBDQ and PROMIS-29 should be administered before the C-SSRS and before any clinical procedures or tests are performed. These assessments are completed by participants on-site using the provided tablet.
PROMIS-29						X				X				X				X	
Clinical Laboratory Assessments																			
Hematology and chemistry		X		X		X				X				X				X	The most recent hematocrit value obtained will be used to calculate the CDAI.
Pharmacokinetics and Immunogenicity																			
Study intervention serum concentration		X		X		X				X				X				X	Blood samples should be collected before the administration of study intervention. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of PK sample collections.
Assessment for antibody to study intervention		X		X		X				X				X				X	Blood samples should be collected before the administration of study intervention. All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of sample collections.
Pharmacodynamics and Biomarkers																			
Whole blood sample collection for RNA analysis (where local regulations permit)						X												X	Whole blood for RNA analysis will be collected from all participants in the study to assess the RNA transcriptome related to both Crohn's disease and response to guselkumab.

Week[a,b]:	28	32	36	40	44	48[c]	52[d]	56	60[d]	64	68[d]	72	76[d]	80	84[d]	88	92[d]	96	Notes
Study Procedures[e]																			
Serum biomarkers (where local regulations permit)						X												X	Serum biomarkers will be collected from all participants in the study to assess peripheral proteins related to both Crohn's disease and response to guselkumab.
Ileocolonoscopy biopsy sample collections for histology						X												X	Refer to the biopsy manual for details on the biopsy sample collection.
Ileocolonoscopy biopsy sample collections for exploratory RNA and protein assessments (where local regulations permit).						X												X	Refer to the biopsy manual for details on the biopsy sample collection.
Ongoing Participant Review																			
Concomitant therapy	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X	
Adverse events	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X	
Crohn's disease-related surgeries and procedures	X	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X	T	X	The Week 48 and Week 96 ileocolonoscopies should not be included in this category.

Footnotes:

a. If a participant discontinues study intervention prior to the Week 96 visit, the participant should complete the evaluations as detailed under the SID visit at the time of SID. In addition, the participant should return for an FES follow-up visit approximately 12 weeks after their last study intervention administration. For additional details, see Table 5.

b. The visit window should be ±7 days. Post-randomization scheduled study visit dates should be based on the participant's randomization date.

c. Study will be unblinded after the last participant completes the Week 48 evaluations and the Week 48 DBL is completed. Upon study unblinding, placebo participants who have not been rescued with guselkumab will be discontinued from study intervention and have an FES follow-up visit. All other participants will continue on guselkumab treatment through Week 248.

d. Participants can opt to conduct this visit via telemedicine contact (if allowed per local regulation and per investigator discretion). Otherwise, this visit will be conducted on-site.

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

f. Assessment is not required if a participant has a telemedicine visit.

Abbreviations: AE=adverse event; AP-NRS=Abdominal Pain-Numerical Rating Scale; BSFS=Bristol Stool Form Scale; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; DBL=database lock; IBDQ=Inflammatory Bowel Disease Questionnaire; FES=final efficacy and safety; PK=pharmacokinetic(s); PRO=patient-reported outcome; PROMIS=Patient-reported Outcomes Measurement Information System; RNA=ribonucleic acid; SC=subcutaneous; SID=study intervention discontinuation; SoA=Schedule of Activities; T=telemedicine visit (if allowed per local regulation and per investigator discretion); TB=tuberculosis

Table 4: Schedule of Activities: Extension Treatment Phase Weeks 100 to 248

Interval/Visit	q4w[a]	q8w[a]	q16w[a,b]	Notes
Study Procedure				
On-site visit			X	All participants in the study must have an on-site visit for their last dosing visit at Week 248. For participants who opt for at-home administration, on-site visits will be held at Weeks 112, 128, 144, 160, 176, 192, 208, 224, and 240. Participants that cannot opt for at-home administration will have on-site visits either q4w or q8w according to their assigned treatment regimen.
Telemedicine/phone call[c]	X			Site should contact participants to remind them about at-home study intervention administration (as applicable), and to assess the well-being and safety of participants.
Study Intervention Administration				
Self-administration training			X	Re-training on self-administration (or administration by a caregiver) as needed.
Dispense study intervention			X	Study intervention will be supplied to participants who opt for at-home administration during on-site visits.
Administer study intervention	X (q4w regimen)	X (q8w regimen)		Study intervention will be self-administered (or administered on-site per local regulation) according to the assigned dose regimen. Last dose of study intervention will be Week 248. Participants who are unable/unwilling to have study injections administered at home are required to return to the site for administration of study intervention.
Safety Assessments				
Physical examination			X	A targeted physical examination will be performed (see Section 8.2.1).
Vital signs			X	Includes temperature, pulse/heart rate, respiratory rate, and blood pressure. Must be obtained prior to and approximately 30 minutes after the SC injection.
Urine pregnancy test		X		Must be performed at least q8w starting from Week 96 (on-site or at home) in female participants of childbearing potential. When performed, a negative urine pregnancy test result must be available before study intervention administration.
TB evaluation/other infection assessment	X			If TB is suspected at any time, study intervention should be withheld and an immediate and thorough investigation should be undertaken. More information on TB evaluation is provided in Section 8.2.10.
Injection-site evaluation	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. Participants are trained to perform self-evaluation for injection-site reactions and reporting of AEs.
C-SSRS			X	C-SSRS should be completed before any other tests, procedures, or consultations to prevent influencing participant perceptions. The investigator/trained study site personnel will interview the participant and complete the C-SSRS.
Clinical Laboratory Assessments				
Chemistry			X	
Ongoing Participant Review				
Concomitant therapy	X			
AEs	X			
Crohn's disease-related surgeries and procedures	X			

Footnotes:

a. The visit window should be ±7 days.

b. Study procedures should be performed on-site when they coincide with a q16w visit and at Week 248 (eg, urine pregnancy test, TB evaluation/other infection assessment, injection-site evaluation, concomitant therapy, AEs, and Crohn's disease-related surgeries and procedures).

c. All participants should have visits q4w via telemedicine (if allowed per local regulation) between on-site visits.

Abbreviations: AE=adverse event; C-SSRS=Columbia-Suicide Severity Rating Scale; q4w=every 4 weeks; q8w=every 8 weeks; q16w=every 16 weeks; SC=subcutaneous; TB=tuberculosis

Table 5: Schedule of Activities: 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, as outlined below

	SID[a]	FES[b]	Notes
Participant terminates study participation at any time during the study	X		Evaluations for SID should be completed prior to participant terminating study participation
Participant discontinues study intervention at or prior to the Week 12 visit	X*	X#	* If the SID visit occurs at or after the Week 8 time point, video ileocolonoscopy and biopsy samples should be done at the SID visit. # If the SID visit occurs prior to the Week 8 time point, video ileocolonoscopy and biopsy samples should be done at the FES follow-up visit instead of the SID visit.
Participant discontinues study intervention after Week 12 and up to the Week 48 visit	X	X	Discontinuation after Week 12 (visit and ileocolonoscopy) and before Week 44: A video ileocolonoscopy (with biopsy samples) is optional to be performed as part of the SID visit. Discontinuation at Week 44 or Week 48: A video ileocolonoscopy (with biopsy samples) is required at the Week 48 visit (or can be performed as part of SID visit).
Participant discontinues study intervention after Week 48 and up to Week 248	X	X	The video ileocolonoscopy at the SID visit is optional for participants who discontinue after Week 48 and before Week 96, since these participants would have completed the procedure as part of the Week 48 visit. Discontinuation at Week 96: A video ileocolonoscopy (with biopsy samples) is required at the Week 96 visit (or can be performed as part of SID visit if the SID visit occurs at Week 96). Note: Upon study unblinding (after Week 48 DBL), placebo participants who have not been rescued with guselkumab will be discontinued from study intervention and will have only an FES follow-up visit.
Participant completes the 248-week study		X	The FES follow-up visit should occur approximately 12 weeks after the last study intervention administration.

Footnotes:

a. The SID visit should be completed at the time of SID.

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

Abbreviations: DBL=database lock; FES=final efficacy and safety; SID=study intervention discontinuation (visit)

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

Period:	SID	FES	
Study Procedures			**Notes:**
Safety Assessments			
Physical examination	X	X	A targeted physical examination will be performed (see Section 8.2.1).
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, study intervention should be withheld and an immediate and thorough investigation should be undertaken. More information on TB evaluation is provided in Section 8.2.10.
C-SSRS	X	X	The C-SSRS should be completed after all PRO assessments and before any other tests, procedures, or other consultations to prevent influencing participant perceptions. The investigator or trained study site personnel will interview the participant and complete the C-SSRS.
Efficacy Assessments			
Collect and review Symptom and Health Diary • CDAI • BSFS • AP-NRS	 X[a] X[a] X[a]	X[b]	For the FES follow-up visit, daily diary information should be collected for at least 14 days before the visit. The daily diary includes patient-reported data for the CDAI. The most recent hematocrit value obtained will be used to calculate the CDAI. Collection of daily diary information will conclude at Week 108/FES visit (if the FES visit occurs prior to Week 108). Collection of BSFS and AP-NRS will conclude at Week 48/the SID visit (if the SID visit occurs prior to Week 48).
Weight	X[a]	X[b]	Weight measurement is used to support CDAI assessments, PK modeling, and safety.
Fistula assessment	X[a]		
Video ileocolonoscopy	X[a]	X[#,b]	See notes in Table 5 (a). Ileocolonoscopy is not required at the FES follow-up visit. [#] However, if the SID visit occurs prior to the Week 8 time point, video ileocolonoscopy should be done at the FES follow-up visit instead of the SID visit.
Stool sample (fecal calprotectin)	X[a]	X[#,b]	Stool samples required for this visit must be obtained (through on-site or at-home collection) before the start of the bowel preparation for the video ileocolonoscopy that is also scheduled for the visit. See notes in Table 5 (a). Stool sample is not required at the FES follow-up visit. [#] However, if the SID visit occurs prior to the Week 8 time point, stool sample should be done at the FES follow-up visit instead of the SID visit.
CRP	X[a]	X[b]	
Patient-reported Outcomes			
IBDQ	X[a]		PRO assessments for efficacy. IBDQ and PROMIS-29 should be administered before the C-SSRS and before any clinical procedures or tests are performed.
PROMIS-29	X[a]		
Clinical Laboratory Assessments			
Hematology and chemistry	X	X	For SID visit that occurs after Week 96, only the chemistry laboratory assessments should be performed. For FES visit that occurs after Week 108, only the chemistry laboratory assessments should be performed.

Period:	SID	FES	
Study Procedures			**Notes:**
Pharmacokinetics/Immunogenicity			
Study intervention serum concentration	X[a]	X[b]	All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of PK sample collections.
Assessment for antibody to study intervention	X[a]	X[b]	All reasonable attempts should be made to collect samples at the scheduled time points and record the actual times of sample collections.
Pharmacodynamics and Biomarkers			
Whole blood sample collection for RNA analysis (where local regulations permit)	X[a]		Whole blood for RNA analysis will be collected from all participants in the study to assess the RNA transcriptome related to both Crohn's disease and response to guselkumab.
Serum biomarkers (where local regulations permit)	X[a]		Serum biomarkers will be collected from all participants in the study to assess peripheral proteins related to both Crohn's disease and response to guselkumab
Ileocolonoscopy biopsy sample collections for histology	X[a]	X[#,b]	See notes in Table 5 (a). Ileocolonoscopy biopsy is not required at the FES follow-up visit. # If the SID visit occurs prior to the Week 8 time point, biopsy samples should be done at the FES follow-up visit instead of the SID visit.
Ileocolonoscopy biopsy sample collections for exploratory RNA and protein assessments (where local regulations permit).	X[a]	X[#,b]	See notes in Table 5 (a). Ileocolonoscopy biopsy is not required at the FES follow-up visit. # If the SID visit occurs prior to the Week 8 time point, biopsy samples should be done at the FES follow-up visit instead of the SID visit.
Ongoing Participant Review			
Concomitant therapy	X	X	
Adverse events	X	X	
Crohn's disease-related surgeries and procedures	X	X	The ileocolonoscopy at the SID and FES visits should not be included in this category.

Footnotes:

a. Not required for an SID visit that occurs at Week 96 and afterwards.

b. Not required for any FES visit that occurs after Week 108.

Abbreviations: AP-NRS=Abdominal Pain-Numerical Rating Scale; BSFS=Bristol Stool Form Scale; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; FES=final efficacy and safety; IBDQ=Inflammatory Bowel Disease Questionnaire; PK=pharmacokinetic(s); PRO=patient-reported outcome; PROMIS=Patient-reported Outcomes Measurement Information System; q4w=every 4 weeks; q8w=every 8 weeks; RNA=ribonucleic acid; SC=subcutaneous; SID=study intervention discontinuation; TB=tuberculosis

2. INTRODUCTION

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

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

Guselkumab is currently being studied in participants with Crohn's disease (see details in Section 2.2).

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

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

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

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Crohn's disease is a chronic, progressive and potentially life-threatening disorder which may affect any part of the gastrointestinal (GI) tract. Inflammation penetrates the lining of the GI tract and often causes ulcers to form. Symptoms may include abdominal pain (AP), diarrhea, fatigue, and weight loss/anorexia. Painful perianal disease, strictures, and fistulas are common. Patients with high disease burden often require at least one surgical intervention.

The pathophysiology of IBD is complex and thought to be multifactorial. The primary aim of pharmacotherapy is to control the inflammatory response, thereby relieving symptoms and promoting mucosal healing. The specific goals of IBD management include the treatment of acute exacerbations, prevention of relapses, treatment of specific complications, and surveillance of malignant transformation (D'Haens 2014; Lichtenstein 2018).

Historically, the treatment of Crohn's disease has relied mainly on corticosteroids and immunosuppressive medications such as thiopurines or methotrexate. Although corticosteroids reduce mortality in Crohn's disease patients, corticosteroids are associated with multiple significant adverse effects and therefore are not suitable for long-term treatment. Approximately 2 decades ago, tumor necrosis factor alpha (TNFα) inhibitors such as infliximab, adalimumab, and

certolizumab became available for treatment of patients with moderately to severely active Crohn's disease, especially those who did not respond to corticosteroids, or were refractory or intolerant to conventional immunosuppressive medications (Nielsen 2013). In recent years, other biologics have become available, such as the anti-α4β7-integrin monoclonal antibody (ie, vedolizumab) and the IL-12/23p40 antibody (ie, ustekinumab). Current treatment guidelines recommend the use of TNFα inhibitors, vedolizumab, or ustekinumab based on their efficacy and safety profiles (Lichtenstein 2018; Torres 2020). However, despite the availability of these therapies, many patients experience primary or secondary nonresponse, hence the unmet medical need remains high and underscores the need for novel treatment options that provide greater therapeutic value to patients (Gordon 2015; Sandborn 2016).

Currently, the GALAXI clinical program is evaluating guselkumab intravenous (IV) induction dosing followed by subcutaneous (SC) maintenance dosing in participants with moderately to severely active Crohn's disease who have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy. Under the GALAXI protocol, there are 3 separate studies (Phase 2 study GALAXI 1 and Phase 3 studies GALAXI 2 and GALAXI 3). Results from the GALAXI 1 study show that guselkumab IV induction demonstrated greater improvements compared to placebo across the key clinical efficacy and endoscopic outcome measures at Week 12 (Danese 2021; Sandborn 2020b).

In the current study, the sponsor is interested in assessing SC administration of guselkumab for the induction phase of Crohn's disease treatment. Subcutaneous delivery of biologic agents has become a valuable alternative to IV administration across many disease areas (De Cock 2016; Gardulf 2007; Tetteh 2014; Usmani 2021). Although the pharmacokinetic (PK) profiles of SC and IV routes of administrations differ, SC administration has proven effective, safe, well-tolerated, and is generally preferred by patients and healthcare providers due to the greater flexibility and ease of administration for patients or their caregivers in their preferred setting (Gardulf 2007; Usmani 2021). In addition, SC administration has resulted in reduced drug delivery-related healthcare costs and resource utilization (Bittner 2018). In short, SC administration has become an attractive alternative to more invasive and time-consuming IV infusions.

Considering the GALAXI 1 results and the potential benefits of SC induction dosing to patients and healthcare systems, the aim of this study is to evaluate the efficacy, safety, and PK/pharmacodynamics (PD) profile of guselkumab SC induction compared with placebo in participants with moderately to severely active Crohn's disease.

2.2. Background

Nonclinical Studies

For the most current information on nonclinical development, refer to the guselkumab IB.

Clinical Studies

The clinical development program for guselkumab includes studies in adult participants with psoriasis, psoriatic arthritis, palmoplantar pustulosis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, familial adenomatous polyposis, hidradenitis suppurativa, lupus nephritis, and giant cell arteritis, as well as healthy participants. For a full list of completed and ongoing clinical studies, refer to the guselkumab IB.

Overall, through July 2021 (the data cutoff date for the guselkumab IB edition 12), an estimated 7,827 participants have been exposed to guselkumab across all indications in the clinical development program. As of July 2021, an estimated 703 healthy participants, 4,068 participants with psoriasis, 109 participants with rheumatoid arthritis, 1,509 participants with psoriatic arthritis, 182 participants with palmoplantar pustulosis, 472 participants with Crohn's disease, 175 participants with hidradenitis suppurativa, 540 participants with ulcerative colitis, 51 participants with familial adenomatous polyposis, 2 participants with giant cell arteritis, 7 participants with lupus nephritis, and 9 participants with systemic sclerosis have been exposed to guselkumab.

The overall clinical development program of guselkumab in participants with moderately to severely active Crohn's disease consists of the GALAXI program (CNTO1959CRD3001) and the CNTO1959CRD3004 SC induction study. The ongoing clinical program for guselkumab in Crohn's disease (CNTO1959CRD3001; GALAXI) is designed to evaluate the safety and efficacy of guselkumab compared with placebo and an active control (ustekinumab) in participants with moderately to severely active Crohn's disease, who have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy. The GALAXI program consists of 3 separate studies being conducted under a single protocol. GALAXI 1 was a 48-week Phase 2 dose-ranging study of the efficacy of guselkumab IV induction with doses of CCI [redacted] IV administered at Weeks 0, 4, and 8. GALAXI 2 and GALAXI 3 studies are 2 identical 48-week Phase 3 confirmatory studies. Participants who complete the 48-week Phase 2 or Phase 3 studies may be eligible to enter the long-term extension.

2.3. Benefit-risk Assessment

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

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Clinical worsening of Crohn's disease	The benefit-risk of guselkumab for the treatment of moderately to severely active Crohn's disease has not been established.	• During the study, participants will be permitted to continue treatment of Crohn's disease with certain concomitant medications (Section 6.8). • Participants will discontinue study intervention if it is not in their best interest or if they

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		need to initiate protocol-prohibited medications including certain biologics (Sections 6.8 and 7.1). • Participants in the placebo group who meet at least 1 of the rescue criteria will receive guselkumab (Section 6.5.1).
Risks Due to Study Intervention Guselkumab		
Serious infections and reactivation of latent infections	Available animal and human data suggest that blockade of IL-23 may be associated with an increased infection risk. Infections have been identified as adverse reactions of guselkumab, including respiratory infections, herpes simplex and tinea infections and gastroenteritis.	• Participants with a history of, or ongoing, chronic or recurrent infectious disease, including HIV, HBV or HCV, will be excluded from the study. Similarly, participants with evidence of active or untreated latent TB will be excluded from the study (Sections 5.1 and 5.2). • Participants who have received a live viral or bacterial vaccination within 4 weeks prior to screening will be excluded from the study. In addition, participants must agree not to receive a live viral or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention (Sections 5.2 and 5.3). • Participants will be instructed to seek medical attention if they develop signs or symptoms suggestive of an infection, and investigators are instructed in the protocol to monitor for signs or symptoms of infections, including tuberculosis (Sections 8.2.9 and 8.2.10). • 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

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		intervention should be withheld until the clinical assessment is complete (Sections 7.1 and 8.2.9).
Hypersensitivity reactions, including serious hypersensitivity reactions	Serious hypersensitivity reactions including anaphylaxis have been reported in postmarketing experience with guselkumab in psoriasis patients.	• Participants with known allergy, hypersensitivity, or intolerance to guselkumab or its excipients will be excluded from the study (Section 5.2). • Sites are instructed that before any administration of study intervention, appropriately trained personnel and medications (eg, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. In addition, all participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, itching, hives) (Section 8.2.8). • 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

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		status that may indicate a possible malignancy. • Participants who develop a malignancy during the study (with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from study intervention (Section 7.1).
Liver injury	An SAE of 'toxic hepatitis' was reported in a participant in a Phase 2 Crohn's disease study who received guselkumab CCI IV at Weeks 0, 4, and 8, and CCI SC at Week 12. This event may represent drug-induced liver injury (DILI) possibly related to guselkumab (see Section 5.13.3 in the IB). Transaminase increases have been identified as an adverse reaction of guselkumab. In 2 Phase 3 psoriatic arthritis studies, increased ALT and/or AST was observed more frequently in patients treated with guselkumab CCI compared to patients treated with guselkumab CCI or placebo.	• During the conduct of the study, liver function tests will be monitored at regular intervals in accordance with regulatory guidance (FDA 2009). In addition, the induction doses evaluated in this clinical program will not exceed CCI • Participants with marked liver enzyme elevations or symptoms or signs of liver dysfunction (eg, jaundice), should undergo a thorough investigation for possible causes of liver injury (Appendix 9, Section 10.9). 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, or 9 mg/day of budesonide, or 5 mg/day beclomethasone, which must be tapered from Week 12 onwards. Furthermore, participants receiving AZA, 6-MP, or MTX, must have been taking them for ≥12 weeks and been on a stable dose for at

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		least 4 weeks before the baseline visit. Additionally, participants are also excluded from the study if they have received cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus, ustekinumab, or anti-TNFα therapy within 8 weeks, or vedolizumab within 12 weeks prior to the first dose of study intervention. Further detail regarding concomitant medications is provided in Sections 5.1 and 5.2. • During study participation, the use of immunomodulators other than AZA, 6-MP, and MTX (eg, cyclosporine) as well as biologic immunomodulators (eg, TNFα antagonists, vedolizumab) is prohibited. Participants initiating these treatments will be discontinued from further study intervention administration (see Section 6.8 for further details on prohibited concomitant medications).
Risks Due to Study Procedures		
Risks associated with the endoscopy procedure including bleeding and colonic perforation	These risks are well-recognized, but are rare (Arora 2009; Rabeneck 2008).	Trained and experienced endoscopists will be performing the procedure during this study.

Abbreviations: 6-MP=6-mercaptopurine; ALT=alanine transaminase; AST=aspartate transaminase; AZA=azathioprine; DILI=drug induced liver injury; FDA=Food and Drug Administration; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IB=Investigator's Brochure; IL=interleukin; IV=intravenously; MTX=methotrexate; q4w= every 4 weeks; q8w=every 8 weeks; SAE=serious adverse event; SC=subcutaneously; TB=tuberculosis; TNF=tumor necrosis factor alpha

2.3.2. Benefits for Study Participation

Available animal and human data support the critical role of IL-23 in the pathogenesis of Crohn's disease. Studies with other anti-IL-23 monoclonal antibodies suggest that selective targeting of IL-23 may achieve higher levels of efficacy than that observed with other mechanisms of action in patients with moderately to severely active Crohn's disease. Participants in the study will help in furthering development of this drug to treat Crohn's disease. The knowledge gained from this study has the potential to benefit patients suffering with Crohn's disease, and thus offers potential public health benefits.

2.3.3. Benefit-risk Assessment for Study Participation

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

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

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

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

In summary, the collective nonclinical and clinical evidence for the critical role of IL-23 in the pathogenesis of Crohn's disease, the benefit-risk profile of guselkumab established to date in psoriasis and other immune-mediated diseases, and the GALAXI 1 results provide a strong scientific and clinical rationale for pursuing development of guselkumab in patients with moderately to severely active Crohn's disease and for the investigation of guselkumab in this study. Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with guselkumab are justified by the anticipated benefits that may be afforded to participants with moderately to severely active Crohn's disease.

3. OBJECTIVES AND ENDPOINTS

The objectives of this study are to assess the effects of guselkumab SC in moderately to severely active Crohn's disease.

The endpoints at Week 12 will be based on comparisons of the combined guselkumab induction dose group (who received guselkumab CCI at Weeks 0, 4, and 8) with the placebo group. Endpoints after Week 12 will be based on comparisons of each guselkumab group (guselkumab

CCI at Weeks 0, 4, and 8, followed by guselkumab CCI every 4 weeks [q4w] in one group and CCI every 8 weeks [q8w] in the other group) with the placebo group. For more details on the treatment groups, see Section 4.1.

Objectives	Endpoints
Primary	
• To evaluate the efficacy, including clinical remission and endoscopic response, of guselkumab SC induction	• Clinical remission (CDAI score <150) at Week 12 • Endoscopic response (≥50% improvement from baseline in the SES-CD score) at Week 12
Secondary	
• To evaluate the efficacy of guselkumab SC across a range of outcome measures	• Clinical remission at Week 24 • PRO-2 remission (an AP mean daily score ≤1 and SF mean daily score ≤3 and no worsening of AP or SF from baseline) at Week 12 • Clinical response (decrease from baseline in CDAI ≥100 points or clinical remission) at Week 12
• To evaluate the safety of guselkumab SC	• Summary of AEs, such as SAEs and AEs leading to discontinuation of study intervention
Tertiary (analyses at applicable time points through Week 24, Week 48, and Week 96)	
• To evaluate the efficacy of guselkumab SC across a range of outcome measures	• Clinical remission • PRO-2 remission • Clinical response • Corticosteroid-free clinical remission • Change in CDAI score from baseline • AP and SF score, and change in AP and SF score from baseline • Change in SES-CD score from baseline • Endoscopic response • Endoscopic remission • Endoscopic healing • Change in histologic assessments from baseline
• To evaluate the impact of guselkumab SC on biomarkers	• Change in CRP and fecal calprotectin from baseline • Clinical-biomarker response
• To evaluate the PK and immunogenicity of guselkumab SC	• Serum concentrations of guselkumab

Objectives	Endpoints
	• Incidence and titers of antibodies to guselkumab
• To evaluate the impact of guselkumab SC on PROs	• Endpoints based on IBDQ, PROMIS-29, AP-NRS, and BSFS

Abbreviations: AE=adverse event; AP=abdominal pain; AP-NRS=Abdominal Pain-Numerical Rating Scale; BSFS=Bristol Stool Form Scale; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; IBDQ=Inflammatory Bowel Disease Questionnaire; PK=pharmacokinetic(s); PRO=Patient-reported Outcome; PROMIS=Patient-reported Outcomes Measurement Information System; SAE=serious adverse event; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; SF=stool frequency

Refer to Section 8 for evaluations related to endpoints and Section 9 for further details on the analyses of the endpoints. The tertiary endpoints include but are not limited to the endpoints specified above. Analyses will be performed at applicable timepoints through Week 24, Week 48, and Week 96 at the corresponding database locks (DBLs). Refer to the Statistical Analysis Plan (SAP) for further details.

HYPOTHESIS

The co-primary hypotheses of this study are that guselkumab is superior to placebo in inducing clinical remission at Week 12 and guselkumab is superior to placebo in inducing endoscopic response at Week 12 among participants with moderately to severely active Crohn's disease.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC induction dosing. The target population is adult participants with moderately to severely active Crohn's disease (of at least 3 months duration) with colitis, ileitis, or ileocolitis previously confirmed by radiography, histology, and/or endoscopy. To be eligible for the study, participants must also have endoscopic evidence of active Crohn's disease, and have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy.

The two groups based on prior therapies comprising the target population are briefly described below. Detailed eligibility criteria for prior exposure to conventional therapy or biologic therapy are described in Section 5.1 and Section 10 (Appendix 2 [Section 10.2] and Appendix 3 [Section 10.3]).

- **Conventional therapy failure or intolerance (CON-Failure)**
  - Participants must have demonstrated an inadequate response to, or have failed to tolerate, at least 1 of the following conventional Crohn's disease therapies: oral corticosteroids (including prednisone, budesonide, and beclomethasone dipropionate) or the immunomodulators azathioprine (AZA), 6-mercaptopurine (6-MP) or methotrexate (MTX).

  - Participants who have demonstrated corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of Crohn's disease) are also eligible.
  - Participants may either be naïve to biologic therapy (ie, infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars for these agents) or may have been exposed to biologic therapy and have not demonstrated inadequate response or intolerance.

- **Biologic therapy failure or intolerance (BIO-Failure)**
  - Participants must have demonstrated an inadequate response to, or have failed to tolerate, at least 1 or more biologic therapies (ie, infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars for these agents) at a dose that is, at minimum, a locally approved dose for the treatment of Crohn's disease.

    Inadequate response is defined as: primary nonresponse (ie, no initial response) or secondary nonresponse (ie, response initially but subsequently lost response).

  - Participants with prior exposure to IL-12/23 or IL-23 agents are ineligible for this study.

A diagram of the study design is provided in Section 1.2. Study intervention will be administered as presented in Figure 2 and Figure 3.

The target sample size is 318 participants. Participants who had an inadequate response or failure to tolerate biologic therapy will comprise approximately 35% to 65% of the population. Eligible participants will be randomly assigned in a 1:1:1 ratio to one of the following SC treatments:

- 106 participants to guselkumab CCI at Weeks 0, 4, and 8 followed by guselkumab CCI q4w through Week 24
- 106 participants to guselkumab CCI at Weeks 0, 4, and 8 followed by guselkumab CCI q8w through Week 24
- 106 participants to placebo SC q4w from Week 0 through Week 24

The randomization will be stratified by baseline Crohn's Disease Activity Index (CDAI) score (≤300 or >300), baseline Simple Endoscopic Score for Crohn's Disease (SES-CD) score (≤12 or >12), and BIO-Failure status (Yes or No) at baseline (Week 0).

All participants in the placebo group who meet at least 1 of the rescue criteria at Weeks 12 and 16 will receive rescue treatment, ie, guselkumab CCI at Weeks 16, 20, and 24 followed by guselkumab CCI q8w. To maintain the blind, participants randomized to guselkumab who meet at least 1 of the rescue criteria will continue their assigned treatment regimen and receive blinded sham rescue matching placebo SC injection. For more details, refer to Section 6.5.1. Each active study intervention and its matching placebo will be identical in appearance (Figure 2).

At Week 24, all participants will enter the extension phase and receive the same treatment regimen that they were receiving at Week 24.

The study will be unblinded after the last participant completes the Week 48 evaluations and the Week 48 DBL is completed. Upon study unblinding, placebo participants who have not been rescued with guselkumab will be discontinued from study intervention and have a final efficacy and safety (FES) visit. All other participants will continue on guselkumab treatment through Week 248.

In general, participants who are receiving oral 5-aminosalicylic acid (5-ASA) compounds, oral corticosteroids, conventional immunomodulators (AZA, 6-MP, or MTX), antibiotics, and/or enteral nutrition for the treatment of Crohn's disease at baseline should maintain a stable dose for the specified period before baseline, as defined in the inclusion criteria (Section 5.1), and through Week 48, with the exception of oral corticosteroids (Section 6.8.1). Starting at Week 12, all participants who were taking corticosteroids at Week 0 must begin tapering their corticosteroid dose (for additional details, see Section 6.8.1.1; Table 6). This tapering is mandatory, unless not medically feasible.

Participants who discontinue study intervention early should return for a study intervention discontinuation (SID) visit. All randomized participants should complete the FES follow-up visit approximately 12 weeks after the last dose of study intervention.

The overall study duration is up to 265 weeks. The study comprises of the following phases:

1. Screening phase: up to 5 weeks
2. Main treatment phase: 24 weeks
3. Extension treatment phase: 224 weeks
4. Post-treatment phase (FES follow-up visit): until approximately 12 weeks after the last dose of study intervention

Efficacy, safety, PK, immunogenicity, and biomarkers will be assessed according to the Schedule of Activities (SoA; Section 1.3). Key efficacy assessments include CDAI, Patient-reported Outcome (PRO)-2 (based on 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 SES-CD, histologic assessments, inflammatory PD markers including C-reactive protein (CRP) and fecal calprotectin, fistula assessment, PRO measures such as Inflammatory Bowel Disease Questionnaire (IBDQ) and Patient-reported Outcomes Measurement Information System (PROMIS)-29 and patient-reported symptom measures such Bristol Stool Form Scale (BSFS) and Abdominal Pain-Numerical Rating Scale (AP-NRS).

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

Key safety assessments include adverse events (AEs), clinical laboratory tests (hematology and chemistry), vital signs, physical examinations, screening electrocardiogram (ECG), monitoring for hypersensitivity reactions, injection-site reactions, and early detection of active tuberculosis (TB).

Database locks are planned for Week 24, Week 48, Week 96 and when the last participant completes the last scheduled assessment as shown in the SoA (Section 1.3). Additional DBLs may be added as necessary.

4.2. Scientific Rationale for Study Design

This SC induction study is intended to provide clinical evidence to support the efficacy and safety of guselkumab SC induction dosing, compared to placebo. The safety and efficacy endpoints in this study are similar to those in the ongoing guselkumab Phase 3 Crohn's disease program (GALAXI 2 and 3) designed to demonstrate the efficacy and safety of guselkumab IV induction, and therefore, will enable cross-study comparison of guselkumab IV induction versus SC induction treatment.

The study population is generally consistent with the population in the ongoing guselkumab Phase 3 GALAXI program, which evaluates participants with moderately to severely active Crohn's disease who demonstrated an inadequate response or failure to tolerate conventional or biologic therapies. This population reflects the high unmet need in Crohn's disease as many patients experience primary or secondary nonresponse to existing treatments.

With an estimated bioavailability of approximately 50% for guselkumab SC (TREMFYA® SmPC 2021; TREMFYA® USPI 2020), a CCI dose of guselkumab is expected to result in systemic guselkumab exposure (area under the curve [AUC]) comparable with that from a CCI the confirmatory Phase 3 studies GALAXI 2 and 3 (see Section 4.3 for more details), and for the guselkumab Phase 3 Ulcerative Colitis program (QUASAR).

The optimal maintenance dose regimen is yet to be determined from the GALAXI Phase 3 studies; therefore, after guselkumab SC induction, participants in this study will receive 1 of the 2 maintenance dose regimens of guselkumab (ie, CCI q8w or CCI q4w) also being evaluated in the GALAXI studies.

Blinding, Control, Study Phase/Periods, Intervention Groups

Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints. A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. To minimize risk to participants, they will be evaluated for rescue treatment and participants in the placebo group who meet the rescue criteria will receive guselkumab CCI at Weeks 16, 20, and 24 followed by guselkumab CCI q8w (see Section 6.5.1).

In the maintenance study of the ustekinumab Phase 3 Crohn's disease program (IM-UNITI), the sponsor assessed the effect of a single dose adjustment of ustekinumab (an IL-12/23 antagonist) in participants with Crohn's disease. Participants were randomized to receive placebo, ustekinumab 90 mg q12w, or ustekinumab 90 mg q8w (approved dose). In the ustekinumab 90 mg q8w group, 28 participants met pre-specified loss of response criteria and received a sham dose adjustment. After 16 weeks, 32.1% were in clinical remission and 46.4% were in clinical response

16 weeks later (Sands 2016). These results demonstrate that some participants with inadequate/loss of clinical response might benefit from continuing on the same dose regimen over time. Therefore, the guselkumab groups in this study will not receive a dose adjustment, but will receive a blinded sham rescue.

Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. In addition, to minimize imbalance between intervention groups, randomization will be stratified by factors that influence prognosis or treatment response (ie, stratified at baseline, by baseline CDAI score, SES-CD score, and BIO-Failure status).

A study duration of 24 weeks is thought to be sufficient to evaluate efficacy and safety of SC induction followed by SC maintenance of guselkumab in Crohn's disease. The guselkumab dose regimen after Week 8 in this study is identical to that in the ongoing guselkumab Phase 3 Crohn's studies (GALAXI 2 and 3). After Week 24, no differences in guselkumab concentrations and exposures are expected between CCI induction (in this study) and CCI induction (GALAXI) dose regimens (see Section 4.3 for more details). Consequently, this study is a 24-week study with a 224-week extension. The extension will give participants who, in the opinion of the investigator are benefiting from study intervention, access to treatment for approximately 5 years. The follow-up phase (approximately 12 weeks after the last dose of study intervention) is designed to assess the FES data as well as to collect samples for determination of PK and antibodies to guselkumab, as specified in the SoA (Section 1.3).

Biomarker and DNA Collection

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

An optional pharmacogenomic substudy is planned. It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of guselkumab and to identify genetic factors associated with Crohn's disease or the response to guselkumab treatment. The focus of this

analysis will be the evaluation of genetic single nucleic polymorphisms associated with Crohn's disease and response to treatment with guselkumab.

Biomarker and DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Patient-reported Outcomes on Health-related Quality of Life

Patient-reported outcome evaluations (ie, IBDQ, PROMIS-29) will be used to assess the benefits of guselkumab treatment on disease-specific and general health-related quality of life (HRQOL). Patient-reported outcome evaluations are only being collected in countries where translations of the evaluations are available. See Section 8.1 for more details.

Oral Corticosteroids Tapering

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

4.2.1. Study-specific Ethical Design Considerations

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

The primary ethical concern is that one third of the participants in this study with moderately to severely active Crohn's disease will receive placebo; however, these participants will have the option to be rescued upon meeting the rescue criteria (see Section 6.5.1). The use of placebo in participants with active disease is considered clinically acceptable in support of scientific research, and is still considered necessary in IBD clinical trials (Danese 2016). A placebo-control period facilitates the evaluation of the efficacy and safety of a new treatment compared with placebo.

The total blood volume to be collected from each participant in this study (approximately 328 mL over approximately 265 weeks) is far less than the American Red Cross standard limit for whole blood donation (approximately 475 mL every 8 weeks) and is, therefore, considered to be an acceptable amount of blood to be collected over this time period. For more details regarding blood collection, see Blood Sample Collection in Section 8.

4.3. Justification for Dose

This section provides the rationale for the guselkumab dose regimens that will be evaluated in this study.

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

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

A single SC induction guselkumab dose regimen CCI at Weeks 0, 4, and 8) was selected for this study based on data from the Phase 2 dose-ranging study of guselkumab IV in Crohn's disease (GALAXI 1). The GALAXI 1 Week 12 analyses demonstrated similar efficacy with guselkumab induction doses of CCI administered IV at Weeks 0, 4, and 8, respectively. There was no clear dose/exposure-response within the range of guselkumab IV induction doses tested (Danese 2021; Sandborn 2020b). As a result, the CCI IV induction dose regimen was selected for confirmatory evaluation in the guselkumab Phase 3 studies (GALAXI 2 and 3).

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

Two guselkumab maintenance dose regimens CCI q4w and CCI q8w) will be evaluated in this study. These are the same doses being evaluated in the ongoing Phase 3 GALAXI studies. The selection of the same maintenance dose regimens will enable cross-study comparison of SC induction followed by SC maintenance regimen (in this study) versus IV induction followed by SC maintenance regimen (in GALAXI studies). Overall, the 2 guselkumab maintenance dose regimens (ie, CCI q4w and CCI q8w) would provide an approximately 4-fold dose range of exposure that should support dose/exposure-response assessment of maintenance therapy in the treatment of Crohn's disease.

4.4. End of Study Definition

End of Study Definition

The study is considered completed when the last participant completes the last scheduled study assessment shown in the SoA (Section 1.3) or if a decision has been made by the sponsor not to pursue an indication in Crohn's disease and appropriate follow-up has been completed. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the main treatment phase if he or she has completed assessments at Week 24 and completed the FES follow-up visit if applicable.

A participant will be considered to have completed the extension treatment phase if he or she has completed assessments at Week 248 and completed the FES follow-up visit.

Participants who prematurely discontinue study intervention for any reason before completion of the Week 24 visit can be considered to have completed the main treatment phase if they have completed the FES follow-up visit assessments as indicated in the SoA (Section 1.3). Similarly, participants who prematurely discontinue study intervention for any reason after Week 24 and before completion of the Week 248 visit can be considered to have completed the extension treatment phase if they have completed the FES follow-up visit assessments as indicated in the SoA (Section 1.3).

5. STUDY POPULATION

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

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

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

5.1. Inclusion Criteria

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

1. Man or woman (according to their reproductive organs and functions assigned by chromosomal complement) of ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).

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

3. Have clinically active Crohn's disease, defined as a baseline CDAI score ≥220 but ≤450 and either:

    a. Mean daily SF count ≥4, based on the unweighted CDAI component of the number of liquid or very soft stools

    OR

    b. Mean daily AP score ≥2, based on the unweighted CDAI component of AP

4. Have endoscopic evidence of active ileocolonic Crohn's disease as assessed by central endoscopy reading at the screening endoscopy (SoA [Section 1.3]) 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"

5. A participant who has had extensive colitis for ≥8 years, or disease limited to a segment of the colon for ≥10 years, must:

    a. Have had a full colonoscopy to assess for the presence of dysplasia within 1 year before the first dose of study intervention

    OR

    b. Have a full colonoscopy with biopsy surveillance for dysplasia as the baseline endoscopy during the screening period. Results from these surveillance biopsies must be negative for dysplasia (low-grade, high-grade, or "indefinite dysplasia in reactive atypia") prior to the first dose of study intervention

Concomitant or Previous Medical Therapies Received

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

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

    OR

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

OR

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

OR

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

Note: Participants meeting criteria 6a-c may either be naïve to biologic therapy (ie, infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars for these agents) or may have been exposed to these biologic therapies and did not demonstrate an inadequate response or intolerance.

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

   a. Oral 5-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, or 5 mg/day beclomethasone dipropionate, and on stable dosing for at least 2 weeks; or if recently discontinued, must have been stopped for at least 2 weeks.

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

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

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

Screening Laboratory Tests

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

   a. Hemoglobin ≥8.0 g/dL

b. White blood cells (WBCs) ≥3.0 x 10^3/μL

c. Neutrophils ≥1.5 x 10^3/μL

d. Platelets ≥100 x 10^3/μL

e. Serum creatinine ≤1.5 mg/dL

f. Alanine transaminase (ALT) (or aspartate transaminase [AST]) ≤2 x upper limit of normal (ULN)

g. Total bilirubin (TBili) ≤1.5 x ULN (Isolated total bilirubin >1.5 x ULN is allowed for those participants with known Gilbert's syndrome. Gilbert's syndrome is suggested by direct bilirubin <30% [Palmer 2020].)

Tuberculosis

9. A potential participant is considered eligible if the participant meets all of the following TB screening criteria:

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

a. Have no history of active TB or show signs or symptoms suggestive of active TB upon medical history and/or physical examination at screening.

b. Have no history of latent 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:

1) Currently receiving treatment for latent TB

OR

2) Will initiate treatment for latent TB prior to the first administration of study intervention

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

c. Have had no recent close contact with a person with active TB. If there has been contact, such participants are referred to a physician specializing in TB to determine if treatment is warranted or not. This evaluation must be adequately documented and, if treatment is recommended, the participant must be receiving appropriate treatment prior to the first administration of study intervention.

d. Have a negative IGRA test result within 2 months prior to the first administration of study intervention, or who:

- Have a history of adequately treated latent TB described above.

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

Note: Indeterminate/borderline results should be handled as outlined in Section 8.2.10.

e. Have a chest radiograph (both posterior-anterior and lateral views, or per local/country regulations where applicable), or chest computed tomography (CT) within 3 months prior to the first administration of study intervention that shows no abnormalities suggestive of active or inactive TB.

Contraception

10. A woman of childbearing potential must have a negative serum pregnancy test result at screening.

11. Before randomization, a woman must be (as defined in Appendix 7 [Section 10.7])

a. Not of childbearing potential (refer to Section 10.7 for instances when a screening follicle stimulating hormone (FSH) test should be considered)

OR

b. Of childbearing potential and

- If heterosexually active, practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 12 weeks after last dose – the end of relevant systemic exposure. Note: 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.

12. 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.

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

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

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

General

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

    Note: In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the participant and his or her legally acceptable representative.

15. Must sign a separate ICF if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study.

    Note: In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the participant and his or her legally acceptable representative.

16. Be willing and able to adhere to all specified requirements, including but not limited to completion of assessments, adherence to visit schedule, and compliance with the lifestyle restrictions.

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

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. Has had any kind of bowel resection within 24 weeks, or any other intra-abdominal or other major surgery within 12 weeks, before first dose of study intervention.

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

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

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

   Note: Treatment and repeat testing can occur in the current screening period.

Concomitant or Previous Medical Therapies Received

7. 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-TNFα therapy (eg, infliximab, etanercept, certolizumab pegol, adalimumab, golimumab) received within 8 weeks of baseline
      2) Vedolizumab received within 12 weeks of baseline

3) 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 7.d.3 for investigational biologic agents).

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

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

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

Infections or Predisposition to Infections:

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

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

11. Chest radiograph must be obtained within 12 weeks before the first dose of study intervention. Results that shows an abnormality suggestive of an undiagnosed pulmonary pathology including but not limited to a malignancy, a previously unrecognized pulmonary pathology, as well as active or latent infections from TB, histoplasmosis, or coccidiomycosis would be exclusionary. A chest CT scan obtained outside of the protocol instead of a chest radiograph is also acceptable. Refer to inclusion criteria 9 for information regarding eligibility with a history of latent TB.

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

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

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

OR

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

14. Tests positive for hepatitis B virus (HBV) infection (Appendix 4 [Section 10.4]).

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

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

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

17. Has had a clinically significant infection (ie, hepatitis, sepsis, pneumonia, or pyelonephritis), has been hospitalized for an infection, or has been treated with parenteral antibiotics for an infection within 8 weeks before the first dose of study intervention. Treated and resolved infections not considered clinically significant at the discretion of the investigator need not be exclusionary (ie, acute upper respiratory tract infection, uncomplicated urinary tract infection).

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

19. Has evidence of a herpes zoster infection within 8 weeks before the first dose of study intervention.

20. During the 6 weeks prior to baseline, have had ANY of (a) confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Coronavirus Disease 2019 [COVID-19]) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection

Exception: May be included with a documented negative result from a validated SARS-CoV-2 test

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

AND

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

Note on COVID-19-related exclusion:

- The field of COVID-19-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/standards of care.
- Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

Malignancy or Increased Potential for Malignancy:

21. 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 dose of study intervention or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first dose of study intervention).

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

Coexisting Medical Conditions or Past Medical History

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

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

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

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

27. Has unstable suicidal ideation or suicidal behavior in the last 6 months that may be defined as a Columbia-Suicide Severity Rating Scale (C-SSRS) rating at screening of: suicidal ideation with intention to act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt,

interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt), and is considered to be at risk by the investigator based on an evaluation by a mental health professional. In addition, participants with C-SSRS ratings of wish to be dead ("Ideation level 1"), non-specific active suicidal thoughts ("Ideation level 2"), active suicidal ideation with any methods (not plan) without intent to act ("Ideation level 3") or non-suicidal self-injurious behavior who are determined to be at risk by the investigator may not be randomized.

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

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

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

General

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

32. 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.

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

Note: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4 describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 5 (Section 10.5).

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 6.8 for details regarding prohibited and restricted therapy during the study.

   It is recommended that participants are up-to-date on appropriate vaccinations prior to screening per routine local medical guidelines. For study participants who received locally-approved (including emergency use-authorized) COVID-19 vaccines recently prior to study entry, consider study eligibility and follow applicable local vaccine labelling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.8.3).

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 SID visit before he or she terminates study participation.

4. 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.

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

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

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

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made.

All reports and communications relating to the study will identify participants by participant identification and date of birth (as allowed by local regulations). In cases where the participant is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

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

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

Additional criteria for retesting and rescreening are outlined below.

Retesting

Retesting of abnormal screening laboratory values that may lead to exclusion will be allowed once. A second retest of an abnormal screening laboratory test may be allowed upon consultation with and approval by the sponsor's medical monitor. Retesting can occur at an unscheduled visit during the screening phase, as long as this is done within the specified screening window of approximately 5 weeks.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. A second retest of an abnormal screening laboratory test may be allowed (see above).

Rescreened participants 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 an IGRA test and chest imaging) and stool study results, and ileocolonoscopy results from the first screening event may be used if they meet the specified protocol criteria as described in Section 5.1. Medical monitor approval is required prior to the study site obtaining a new informed consent for rescreening.

5.5. Criteria for Temporarily Delaying Enrollment, Randomization or Administration of Study Intervention

Not applicable.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Study intervention will be administered as presented in Figure 2 and Figure 3.

Description of Study Interventions

Intervention Name	Guselkumab	Guselkumab	Placebo
Dose Formulation	Active guselkumab [redacted] in a single-dose PFS-Y	Active guselkumab [redacted] in a single-dose PFS-U	Matching placebo for each dose and device [redacted] PFS-Y and [redacted] PFS-U)
Unit Dose Strength(s)	[redacted]	[redacted]	Matching placebo for each dose and device
Frequency	q4w	q8w	Placebo will be administered at the same frequency as the active groups.
Route of Administration	[redacted]	[redacted]	SC
Storage	Must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. The sterile product does not contain preservatives and is designed for single use only. It should be clear to slightly yellow and may contain tiny white or clear particles. Do not use if the liquid is cloudy or discolored or has large particles. Protection from light is not required during the preparation and administration of the study intervention material. Aseptic procedures must be used during the preparation and administration of the study intervention material.	Must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. The sterile product does not contain preservatives and is designed for single use only. It should be clear to slightly yellow and may contain tiny white or clear particles. Do not use if the liquid is cloudy or discolored or has large particles. Protection from light is not required during the preparation and administration of the study intervention material. Aseptic procedures must be used during the preparation and administration of the study intervention material.	Must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. The sterile product does not contain preservatives and is designed for single use only. It should be clear to slightly yellow and may contain tiny white or clear particles. Do not use if the liquid is cloudy or discolored or has large particles. Protection from light is not required during the preparation and administration of the study intervention material. Aseptic procedures must be used during the preparation and administration of the study intervention material.
Use	Experimental	Experimental	Placebo comparator
IMP	Yes	Yes	Yes
NIMP	No	No	No

Abbreviations: IMP=Investigational Medicinal Product; NIMP=Non-investigational Medicinal Product; PFS-U= prefilled syringe with an UltraSafe Plus™ Passive Needle Guard; PFS-Y=prefilled syringe with YpsoMate autoinjector; q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous

Figure 2: Dose Regimens for the Treatment Phases From Week 0 Through Week 96

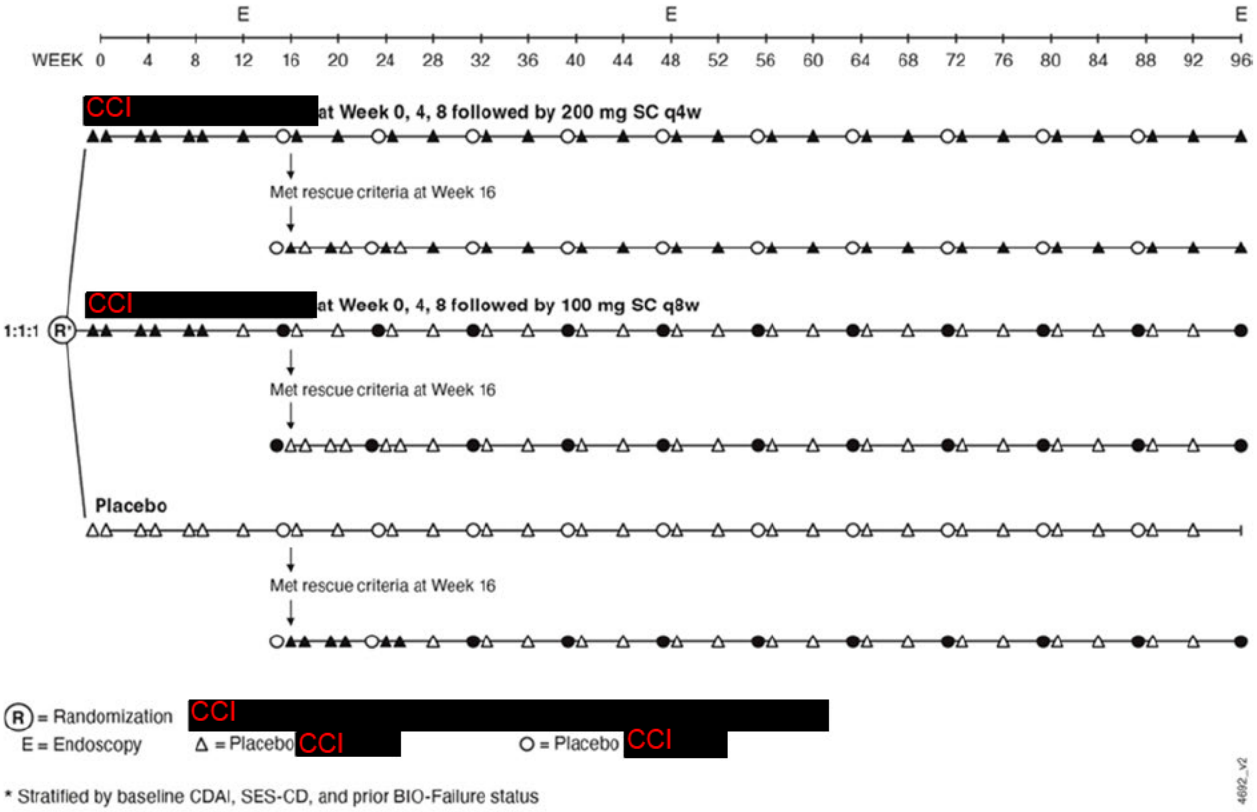
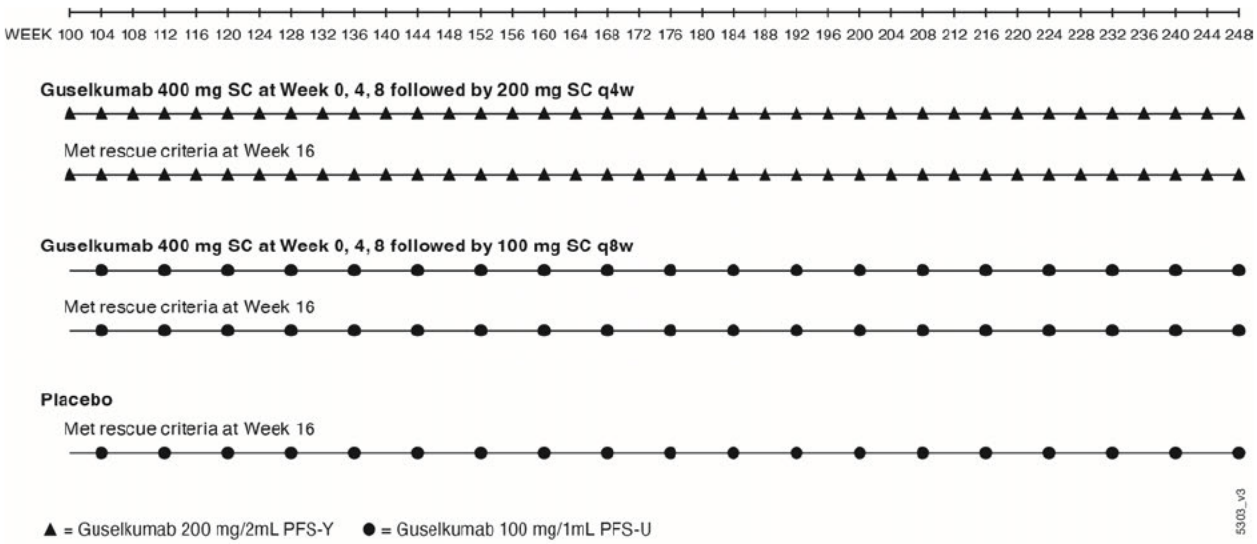


Figure 3: Dose Regimens for the Extension Treatment Phase From Week 100 Through Week 248



When multiple SC injections are administered at a visit, each injection of study intervention should be given at a different location of the body.

Study intervention administration must be captured in the source documents and/or the electronic case report form (eCRF). Study site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

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

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

For a definition of study intervention overdose, refer to Section 6.7.

Self-administration of Study Interventions (or Administration by Caregiver) at Home

Beginning at Week 36, at the discretion of the investigator and participant, and after appropriate and documented training at Weeks 28 and 32, participants may self-administer study intervention at the investigative site. A caregiver may also be trained to administer study intervention. The self-administrations of study intervention on-site should be done in the presence of study site staff. If needed, participants (or their caregivers) can be trained at later time points. Note that at Week 96 (or at the next visit if after Week 96), all participants continuing in the study who were not previously trained should be trained to self-administer study intervention using the device (either PFS-Y or PFS-U) based on their assigned treatment regimen, if allowed per local regulation. The training with the correct device based on assigned treatment regimen must be documented prior to starting at-home administration after Week 96.

Starting from Week 52 up to Week 92, participants may self-administer (or their caregivers may administer) study intervention at home every 8 weeks, at the visits where only a single injection is required, if allowed per local regulation.

Starting from Week 96 up to Week 244, participants may self-administer (or their caregivers may administer) study intervention at home every 4 or 8 weeks based on their treatment assignment, if allowed per local regulation. On-site visits are required every 16 weeks after Week 96 and at Week 248 (the last dosing visit) for all participants allowed to self-administer at home. Participants who are unable or unwilling to have study injections administered at home will be required to return to the site for administration of study intervention injection every 4 or 8 weeks, based on their treatment assignment.

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

6.1.1. Combination Products

The sponsor-manufactured combination products provided for use in this study are the CCI prefilled syringe (PFS) with YpsoMate Autoinjector (hereafter referred to as CCI

The sponsor manufactures the CCI The sponsor also assembles the CCI

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

All combination product deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the study. For studies in combination products, these deficiencies will be reported as Product Quality Complaints (PQC) (see Appendix 6 [Section 10.6]) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Storage

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

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

Study personnel will instruct participants on how to transport, store, and administer study intervention for at-home use.

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

Handling/Accountability

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

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention and used study intervention with the empty outer box/carton must be available for verification by the sponsor's or designee's study site monitor during on-site monitoring visits for study intervention accountability.

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

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. At Week 0, participants will be randomly assigned to 1 of 3 intervention groups in a 1:1:1 ratio (see Section 4.1) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-Failure status (Yes or No) at baseline (Week 0). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then be given the relevant participant details to uniquely identify the participant.

Blinding

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

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

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

The full sponsor unblinding will occur at the Week 48 DBL. However, at the Week 24 DBL, data will be unblinded for analysis to a limited number of sponsor personnel only. Identification of sponsor personnel who will have access to the unblinded participant-level data at the time of the Week 24 DBL will be documented before unblinding. The method by which the study integrity will be maintained will be described in the SAP.

Treatment assignment will remain blinded to the study sites and participants until the last participant completes the Week 48 evaluations, and the Week 48 DBL is completed. Upon study unblinding, placebo participants who have not been rescued with guselkumab will be discontinued from study intervention and have an FES follow-up visit. All other participants will continue on guselkumab treatment through Week 248.

Under normal circumstances, the investigator blind should not be broken until the Week 48 DBL is completed, unless specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant. In such case, the investigator may in an emergency determine the identity of the intervention by contacting the IWRS. It is recommended that the investigator contacts the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and/or in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

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

6.4. Study Intervention Compliance

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

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

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

6.5. Dose Modification

6.5.1. Rescue Medication

All participants in the placebo group who meet at least 1 of the following rescue criteria will receive rescue medication:

- CDAI score >220 and <70-point reduction from baseline CDAI at both Week 12 and Week 16

  OR

- SES-CD score increase by at least 50% from baseline at Week 12

Upon meeting at least 1 of the rescue criteria, participants in the placebo group will receive guselkumab CCI at Weeks 16, 20, and 24 followed by guselkumab CCI q8w.

To maintain the blind, participants randomized to guselkumab who meet at least 1 of the rescue criteria will continue their assigned treatment regimen and receive blinded sham rescue matching placebo SC injection at Weeks 16, 20, and 24. Each active study intervention and its matching

placebo are identical in appearance. Details regarding the analysis rules for placebo participants receiving rescue medication will be included in the SAP.

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

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

6.7. Treatment of Overdose

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

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

- Contact the medical monitor immediately.
- Closely monitor the participant for AEs/serious adverse events (SAEs) and laboratory abnormalities.
- Document the quantity of the excess dose in the eCRF.

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

6.8. Concomitant Therapy

Prestudy therapies administered up to 30 days before the first dose of study intervention must be recorded on the eCRF. Any COVID-19 vaccines administered, regardless of timing, must be recorded on the eCRF.

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

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

6.8.1. Concomitant Medications

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

Week 0 Through Week 48

In general, participants who are receiving these medications for Crohn's disease 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 in the judgement of the investigator it is required 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 6.8.1.1).

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

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

If the above medical therapies are initiated or medication doses are changed based on medical necessity as assessed by the investigator, participants should continue to attend all study visits and have all assessments. This does not represent a deviation from the study protocol and the participants may remain on their assigned therapy (guselkumab or placebo). Details regarding the analysis rules for participants who initiate any of the above concomitant Crohn's disease-specific medical therapies will be included 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 Crohn's disease (eg, stress doses of corticosteroids for surgery, asthma, adrenocortical insufficiency).

After Week 48

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

6.8.1.1. 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 6. 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 6: 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.	

6.8.2. Prohibited Concomitant Medications

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

- Immunomodulatory agents other than AZA, 6-MP, or MTX (including, but not limited to 6-thioguanine, cyclosporine, mycophenolate mofetil, tacrolimus, and sirolimus)
- Immunomodulatory biologic agents (including, but not limited to, TNFα antagonists, natalizumab, ustekinumab, rituximab, vedolizumab)
- Experimental Crohn's disease medications (including, but not limited to upadacitinib, filgotinib, etrasimod, ozanimod, etrolizumab, brazikumab, mirikizumab, risankizumab, and andecaliximab)
- Thalidomide or related agents

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

As protection of human research participants is paramount, it is recognized that initiating such therapies may rarely be required due to medical necessity. However, initiation of these prohibited medications should be documented as a deviation from the study protocol, and participants will be discontinued from receiving further study intervention. Participants who discontinue study intervention administration should complete a SID visit and an FES follow-up visit as described in Section 1.3.

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

6.8.3. Vaccinations (Including COVID-19)

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

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

Participants must not receive live viral, live bacterial, or BCG vaccinations during the study and for 12 weeks after receiving the last dose of study intervention (Section 5.3).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant discontinues study intervention or withdraws from the study before the end of the study, assessments should be obtained as specified in the SoA (Section 1.3).

7.1. Discontinuation of Study Intervention

A participant who discontinues study intervention will not be automatically withdrawn from the study (see Section 7.2).

A participant's study intervention must be discontinued if:

1. The participant initiates treatment with prohibited therapies for Crohn's disease (Section 6.8).
2. The participant has a Crohn's disease-related surgery that represents a lack of efficacy of study intervention or that will preclude the future ability to assess efficacy using the CDAI or other instruments required for demonstration of efficacy endpoints.

   Note: Other permitted Crohn's disease-related surgeries (eg, to resolve long-standing complications such as strictures or for symptomatic nonhealing fistulas, in participants experiencing improvement on study intervention) other than minor procedures (eg, placement of a seton or cutaneous drainage of an abscess) should be postponed until after the FES follow-up visit, unless necessary to ensure participant well-being and/or safety.
3. The participant becomes pregnant or plans a pregnancy within the study period (Section 8.3.5).
4. The participant (or the participant's representative) withdraws consent to receive study intervention.
5. The participant develops a systemic opportunistic infection.
6. The participant meets **ANY** of the following TB-related conditions:
   - A diagnosis of active TB is made.

- A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.
- A participant undergoing evaluation has a chest imaging with evidence of current active TB and/or a positive IGRA test result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study intervention and continued to completion (see also Section 8.2.10). Indeterminate/borderline results should be handled as outlined in Section 8.2.10.
- 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, including an injection-site 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 mmHg or blood pressure <90/60 mmHg.
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 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.
10. The participant has severe liver test abnormalities that are not transient and are not explained by other etiologies, as described in Section 8.2.4 and Appendix 9 (Section 10.9).
11. The investigator believes that for safety reasons or tolerability reasons (eg, AE), it is in the best interest of the participant to discontinue study intervention.

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

12. Persistent inadequate response or worsening of Crohn's disease:
    a. The participant has a CDAI score >220 and <70-point reduction from baseline CDAI at both Week 20 and Week 24.

       OR

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

    These events must be evaluated by the investigator. A consultation with the study medical monitor may also be considered, at the investigator's discretion. Discontinuation of study intervention must be considered in participants with clinically significant worsening of Crohn's disease where continuation of the study intervention is not in the best interest of the participant.
13. The participant develops a serious infection, including but not limited to sepsis or pneumonia.

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

If a participant discontinues study intervention for any reason before the end of the treatment period, then the assessments as specified in the SoA (Section 1.3) should be obtained. 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. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. Participants who terminate study participation will not be required to return for any follow-up assessments; however, these participants should complete the safety and efficacy evaluations specified in the SoA (Section 1.3) at the time they terminate study participation. 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.

7.2.1. Withdrawal From the Use of Research Samples

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

- The collected samples will be retained and used for research activities in accordance with the participant's original separate informed consent for optional research samples.

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

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

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

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-term Retention of Samples for Additional Future Research in Appendix 5 [Section 10.5.5]). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and may be in the separate ICF for optional research samples.

7.3. Lost to Follow-up

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

A participant will be considered lost to follow-up if 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 (Section 1.3) summarizes the frequency and timing of scheduled visits, and the timing of efficacy, safety, PK, immunogenicity, PRO, and other assessments applicable to this study.

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

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

The C-SSRS should be completed after all PRO assessments and before any other tests, procedures, or other consultations to prevent influencing participant perceptions.

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

For women of childbearing potential only, additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

Screening Phase

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

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

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

Women of childbearing potential must have a negative serum pregnancy test result at screening. Participants must be reminded that they are required to use a highly effective method of contraception during the study (as described in Inclusion Criterion 11) and must continue taking such precautions for 12 weeks after receiving the last administration of study intervention. The method(s) of contraception used by each participant must be documented.

Participants must undergo testing for TB (Section 8.2.10) 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 imaging results and responses to tuberculin skin or other TB testing. A participant's eligibility according to TB screening criteria is described in Inclusion Criterion 9.

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/immunogenicity, efficacy, biomarker, and pharmacogenomic evaluations at the same time point, the order of blood draws will be samples for CRP, chemistry/lipids, hematology, PK/immunogenicity, serum biomarkers, pharmacogenomics, and whole blood RNA.

The total blood volume to be collected from each participant will be approximately 328 mL over approximately 265 weeks (Table 7). This total may vary due to:

- Whether or not the participant consents to take part in the optional pharmacogenomics study (6 mL).
- Repeat or unscheduled samples taken for safety reasons or technical issues with the samples.
- Regional or country-specific variation in blood collection systems.

Table 7: Volume of Blood to be Collected From Each Participant

Study Period or Type of Sample	Approximate Total Volume of Blood (mL)
Screening through Week 248	307.5
Final visit (FES)	14.5
Pharmacogenomics sample[a]	6
Approximate Total	**328**

a. Sample to be collected only from participants who have consented to provide an optional pharmacogenomics (DNA) sample for research.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the SoA (Section 1.3) for the timing and frequency of all sample collections.

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

Study-specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IB)
- ICF
- IFU
- IPPM
- IWRS manual
- Study medication diary
- Symptom and Health Diary cards
- eCRF completion instructions
- Central laboratory manual
- Laboratory kits
- Biopsy manual
- Endoscopy kit
- Imaging manual
- Electronic patient-reported outcome equipment
- Patient recruitment materials

8.1. Efficacy Assessments

Efficacy evaluations will include the following:

- CDAI
- PRO-2 (the unweighted CDAI components of the total number of liquid or very soft stools and the AP score)
- Endoscopic assessments of the intestinal mucosa based on the presence and absence of mucosal ulcerations and the SES-CD
- Histologic assessments
- Inflammatory PD markers including CRP and fecal calprotectin
- Fistula assessment
- PRO measures to assess HRQOL outcomes including IBDQ and PROMIS-29

- Patient-reported symptom measures including BSFS and AP-NRS

The **CDAI** (Appendix 8 [Section 10.8]) will be assessed by collecting information on 8 different Crohn's disease-related variables (Best 1976): extraintestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid or very soft stools, AP/cramping, use of antidiarrheal drug(s) and/or opiates, and general well-being. 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 abdominal mass is assessed through physical examination. The **PRO-2** includes the unweighted CDAI components of the total number of liquid or very soft stools and the AP score.

Endoscopic assessments of the intestinal mucosa will be evaluated during ileocolonoscopy in all participants. A video ileocolonoscopic examination will be performed at the time points specified in the SoA (Section 1.3). Video endoscopies will be assessed by a central facility that will be blinded to treatment group and visit. A complete video endoscopic examination does not require assessment of the terminal ileum if it cannot be visualized. The **SES-CD** score will be used to evaluate **Endoscopic Improvement** (Daperno 2004). The SES-CD is based on the evaluation of 4 endoscopic components (presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions, and presence/type of narrowing/strictures) across 5 ileocolonic segments. Each endoscopic component is scored from 0 to 3 for each segment, resulting in a total score of up to 15 for each component, except for the narrowing component which can only attain a maximum total score of 11 because by definition, the presence of a narrowing that cannot be passed can be only observed once. In summary, an overall total SES-CD score is derived from the sum of all the component scores and can range from 0 to 56. **Endoscopic healing**, which is traditionally defined as the resolution (absence) of mucosal ulcers in response to a therapeutic intervention, will also be assessed.

Histologic assessments will be performed using biopsy samples collected during ileocolonoscopy. Biopsy samples will be collected at the time points specified in the SoA (Section 1.3) from the predefined anatomic locations as described in the biopsy manual. The biopsy samples collected post-baseline will be obtained near where the screening biopsy samples were collected, as clinically feasible. Refer to the biopsy manual for details on the biopsy sample collection.

Histologic assessments will be conducted by a central reader who is blinded to treatment group, participant number, and visit. Type of histology analyses will be specified in the SAP.

C-reactive protein has been demonstrated to be useful as a marker of inflammation in patients with IBD. In Crohn's disease, elevated CRP concentrations have been associated with severe clinical activity, elevated sedimentation rate, and active disease as detected by colonoscopy (Solem 2005). Blood samples for the measurement of CRP will be collected from all participants at the time points specified in the SoA (Section 1.3). CRP will be evaluated using a validated, high-sensitivity assay.

Fecal calprotectin has been demonstrated to be a sensitive and specific marker in identifying intestinal inflammation and response to treatment in patients with IBD (Costa 2005). Stool samples for fecal calprotectin concentration will be collected from all participants at the time points

specified in the SoA (Section 1.3) through on-site or at-home collection. The assay for fecal calprotectin concentration will be performed using a validated method.

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

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

- The **IBDQ** is a validated, 32-item, self-reported questionnaire for participants with IBD to assess disease-specific HRQOL by evaluating PROs across 4 dimensions: bowel symptoms (loose stools, AP), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability) (Irvine 1994). Scores range from 32 to 224, with higher scores indicating better outcomes. Participants will complete the IBDQ on site.
- The **PROMIS-29** is a validated general health profile instrument that is not disease-specific. It is a collection of short forms containing 4 items for each of 7 domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities). PROMIS-29 also includes an overall average pain intensity 0-10 numeric rating scale. Participants will complete the PROMIS-29 forms on site.

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

- The **BSFS** is a medical aid to classify the form (or consistency) of human feces into 7 categories (Lewis 1997). It has been used as a research tool to evaluate the effectiveness of treatments for various diseases of the bowel (eg, irritable bowel syndrome). Participants will complete the BSFS as a daily diary entry from Week 0 through Week 48.
- The **AP-NRS** is an 11-point (0-10) scale that will be used to evaluate AP. The score of 0 represents “no AP” and the score of 10 represents the “worst possible AP” with greater scores indicating greater pain severity and intensity. Participants will complete the AP-NRS as a daily diary entry from Week 0 through Week 48, selecting only one number that best reflects their pain at its worst.

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

The PRO instrument must be available for regulators and for Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) submissions.

The PRO and AE data will not be reconciled with one another.

8.2. Safety Assessments

Safety assessments will include the monitoring of AEs, injection-site reactions, symptoms of a hypersensitivity reaction, CD-related surgeries and procedures, and any signs or symptoms of infection or TB. In addition, physical examinations, vital signs, ECGs, clinical safety laboratory tests, and C-SSRS will be performed, as well as review of concomitant medication.

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and Appendix 6 (Section 10.6).

Any clinically relevant changes occurring during the study must be recorded in the AE section of the eCRF.

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

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

8.2.1. Physical Examinations

Physical examinations, including height and weight, will be performed as specified in the SoA (Section 1.3). 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 should be performed at the screening visit for study eligibility assessment. Participants should be instructed to remove shoes and outdoor apparel and gear prior to measurements for height and weight.

8.2.2. Vital Signs

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

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

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

Vital signs must be obtained prior to and approximately 30 minutes after the SC injection.

8.2.3. Electrocardiogram

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), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

  A medical monitor or delegate and the clinical site will be notified if prespecified abnormal laboratory values defined in the laboratory manual are identified in any participant during the conduct of the study.
- **Serology**: HIV antibody, HBV antibodies and surface antigen, and HCV antibody. For participants who are eligible with hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (anti-HBc) and/or hepatitis B surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines. Additional details are provided in Appendix 4 (Section 10.4).
- **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, ALP, and TBili should be confirmed by a retest within 24 hours if possible, but no later than 72 hours following notification of test results. Additional clinical and laboratory studies may be performed to evaluate the underlying etiology of abnormal findings. See Appendix 9 (Section 10.9) for additional information on monitoring and assessment of abnormal liver function tests.
- **Pregnancy testing:** Female participants of childbearing potential will undergo a serum pregnancy test at screening. Urine pregnancy tests will be performed before each study intervention administration on-site, at the SID visit, and at the FES follow-up visit, except for visits performed via telemedicine contact (if allowed per local regulation and per investigator discretion) as specified in the SoA (Table 3 and Table 4).
- **FSH**: Refer to Section 10.7 for instances when a screening FSH test should be considered.

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

8.2.5. Columbia-Suicide Severity Rating Scale

The C-SSRS defines 5 subtypes of suicidal ideation and 4 possible suicidal behaviors, as well as non-suicidal self-injurious behavior and completed suicide. It will be used as a screening tool to prospectively evaluate suicidal ideation and behavior in this study, as part of a comprehensive

evaluation of safety. The C-SSRS is an investigator-administered questionnaire (Mundt 2013; Posner 2011). Two versions of it will be used in this study: the 'Baseline/Screening' version of the C-SSRS will be conducted during the screening visit and the 'Since Last Visit' version of the C-SSRS will be completed at all other visits through the end of the study.

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

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

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

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

Participants with C-SSRS ratings of wish to be dead ("Ideation level 1"), non-specific active suicidal thoughts ("Ideation level 2"), active suicidal ideation with any methods (not plan) without intent to act ("Ideation level 3") or non-suicidal self-injurious behavior must be determined not to be at risk by the investigator in order to be randomized. Any questions regarding eligibility of such participants should be discussed with the medical monitor or designee.

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

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

Interruption or the discontinuation of study treatment should be considered for any participant who reports suicidal ideation with intention to act ("Ideation level 4"), suicidal ideation with specific

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

Any C-SSRS finding, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (see Appendix 6 [Section 10.6]).

8.2.6. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

8.2.7. Injection-site Reactions

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.

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

8.2.8. Hypersensitivity Reactions

Before any administration of study intervention at the study site, appropriately trained personnel and medications must be available to treat hypersensitivity reactions, including anaphylaxis. All participants must be observed carefully for symptoms of a hypersensitivity reaction (eg, urticaria, itching, hives). If a mild or moderate hypersensitivity reaction is observed, acetaminophen, nonsteroidal anti-inflammatory drugs, and/or diphenhydramine may be administered.

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

Participants who experience serious adverse reactions related to an injection should be discontinued from further study intervention administrations (see Section 7.1).

Participants who experience reactions following an injection 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 mmHg or blood pressure <90/60 mmHg will not be permitted to receive additional study intervention (see Section 7.1).

Participants who experience reactions suggestive of serum sickness (resulting in symptoms such as myalgia and/or arthralgia with fever and/or rash that are not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an 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 (see Section 7.1).

8.2.9. Infections

Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits (see SoA, Section 1.3). Study intervention administration should not be given to a participant with a clinically important, active infection. If a participant develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study intervention must be strongly considered (Section 7.1). Any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

8.2.10. Tuberculosis Evaluation

8.2.10.1. Initial Tuberculosis Evaluation

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

Participants with a negative IGRA are eligible to continue with pre-randomization procedures. Participants with a newly identified positive IGRA test result must undergo an evaluation for active or latent TB, or suspected false-positive initial testing, and initiate appropriate treatment if needed (see Section 5.1). Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, United States (US) guidelines should be followed.

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

8.2.10.2. Ongoing Tuberculosis Evaluation

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

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

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

Note:

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

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

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

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

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

Further details on AEs, SAEs, and PQC can be found in Appendix 6 (Section 10.6).

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

All Adverse Events

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

Serious Adverse Events

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

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

A **possible Hy's law Case** is defined by the occurrence of ALT/AST ≥3 x ULN together with TBili ≥2 x ULN or international normalized ratio (INR) >1.5 (if measured). Any possible Hy's law case is considered an important medical event and should be reported to the sponsor in an expedited manner, even before all other possible causes of liver injury have been excluded.

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

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made per sponsor reporting process.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

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

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 6 (Section 10.6).

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

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

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events:

- Adverse events related to symptoms of Crohn's disease
- Adverse events related to worsening or progression of Crohn's disease

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention (see Section 7.1).

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required (see Appendix 6 [Section 10.6] and Appendix 7 [Section 10.7]).

8.3.6. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study intervention must be reported by the investigator according to the procedures in Appendix 6 (Section 10.6). 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. Pharmacokinetics

Serum samples will be used to evaluate the PK of guselkumab at the time points presented in the SoA (Section 1.3). Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, or for the evaluation of relevant biomarkers. Participant confidentiality will be maintained.

8.4.1. Evaluations

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

At visits where serum concentration of guselkumab and antibodies to guselkumab will be evaluated, 1 venous blood sample of sufficient volume should be collected. Each serum sample will be divided into 3 aliquots: 1 for serum concentration of guselkumab, 1 for antibodies to guselkumab, and a back-up.

The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

8.4.2. Analytical Procedures

Pharmacokinetics

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

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

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

Pharmacokinetic/Pharmacodynamic Evaluations

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

8.5. Pharmacogenomics

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

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

DNA samples will be analyzed for identification of genetic factors that may be associated with clinical response. This research may consist of the analysis of 1 or more candidate genes or assessment of single nucleic polymorphisms in relation to guselkumab intervention and/or Crohn's disease. Whole blood samples of approximately 6 mL will be collected for genetic analyses as specified in the SoA (Section 1.3).

8.6. Biomarkers

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

Data collected from these samples will be used for exploratory research that will include the following objectives:

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

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

8.6.1. Serum-based Biomarkers

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

8.6.2. Whole Blood-based Biomarkers

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

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

8.6.3. Biopsy-based Biomarkers

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

8.6.4. Pharmacodynamics

Inflammatory PD markers will be evaluated using blood and fecal samples collected at visits as indicated in the SoA (Section 1.3). Post-baseline PD test results, with the exception of CRP and fecal calprotectin (Section 8.1), will not be released to the investigators by the central laboratory.

8.7. Immunogenicity Assessments

Antibodies to guselkumab will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the SID and FES visits. These samples will be tested by the sponsor or sponsor's designee.

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

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Participant confidentiality will be maintained.

Analytical Procedures

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

8.8. Medical Resource Utilization and Health Economics

Crohn's disease related surgeries and procedures are collected and reviewed in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Refer to the SAP for further details.

9.1. Statistical Hypotheses

Refer to Section 3 for the hypotheses.

9.2. Sample Size Determination

Sample sizes were determined by the power to detect a significant difference in clinical remission at Week 12 and in endoscopic response at Week 12 (co-primary endpoints) between the combined guselkumab group and the placebo group, using a 2-sided chi-square test with 0.05 significance level. The assumed rates are 50% versus 15% (guselkumab versus placebo) for clinical remission and 30% versus 13% for endoscopic response. The study is sized such that the guselkumab therapy achieves >90% power for the co-primary endpoints compared with placebo. This sample size also provides >90% power for all secondary endpoints.

Clinical Remission at Week 12

Assumptions for clinical remission at Week 12 were based on the Phase 2 data from the CNTO1959CRD3001 Phase 2/3 program. In the Phase 2 study (GALAXI 1), the proportions of participants who met the eligibility requirement for the GRAVITI study and who were in clinical remission at Week 12, were 12.0%, 59.2%, 55.6% and 42.9% for placebo, guselkumab CCI IV, guselkumab CCI IV and guselkumab CCI IV, respectively, for a treatment difference of 31% to 47%. Of note, in GALAXI 1, approximately 50% of the participants were BIO-Failure.

Note that the eligibility criterion on SES-CD for this study is relatively new and not many historical studies have this requirement, hence the actual placebo rate could vary. Based on these considerations and the data above, the clinical remission rates are assumed to be 15% for placebo

and 50% for guselkumab CCI (treatment difference of 35%), assuming about 50% of the participants will be BIO-Failure in this study.

Endoscopic Response at Week 12

Assumptions for endoscopic response at Week 12 were also based on GALAXI 1. The proportions of participants who met the eligibility requirement for this current study and who were in endoscopic response at Week 12, were 12.0%, 34.7%, 35.6% and 22.4% for placebo, guselkumab CCI IV, guselkumab CCI IV and guselkumab CCI IV, respectively, for a treatment difference of 10% to 24%.

Based on these data, the endoscopic response rates are assumed to be 13% for placebo and 30% for guselkumab CCI (treatment difference of 17%), assuming about 50% of the participants will be BIO-Failure in this study.

In this study, 212 participants in the combined guselkumab group and 106 participants in the placebo group will provide at least 90% power for achieving the co-primary endpoints of clinical remission at Week 12 and endoscopic response at Week 12 (Table 8), based on the assumptions above.

Table 8: Power to Detect a Treatment Effect of Guselkumab Based on Proportion of Participants Achieving Clinical Remission at Week 12 or Endoscopic Response at Week 12

Co-primary Endpoint of Clinical Remission at Week 12		
Placebo (N=106)	**Guselkumab SC (N=212)**	**Power**
15%	45%	>99%
15%	**50%**	**>99%**
15%	55%	>99%
Co-primary Endpoint of Endoscopic Response at Week 12		
10%	25%	91%
13%	**30%**	**94%**
13%	35%	>99%
Abbreviations: SC=subcutaneous		

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

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

9.4. Statistical Analyses

9.4.1. General Considerations

The SAP will be finalized prior to the first DBL (ie, Week 24), and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. Any modifications and/or clarifications to protocol-specified statistical analyses or any other statistical analyses will be described in the SAP.

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

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

Statistical testing will be performed at a significance level of 0.05 (2-sided). The Type I error will be controlled over the co-primary, secondary, and selected Week 48 tertiary endpoints (Section 9.4.4) in the multiplicity-controlled testing procedure. For endpoints that are not multiplicity-controlled, nominal p-values will be presented.

The co-primary and secondary endpoints (as well as all endpoints through Week 24) will be evaluated at the Week 24 DBL. The evaluation of the Week 48 endpoints, including the Week 48 tertiary endpoints that are included in the testing procedure, will be evaluated at the subsequent Week 48 DBL.

9.4.2. Primary Endpoints

The co-primary endpoints are:

- **Clinical remission** (CDAI score <150) at Week 12
- **Endoscopic response** (≥50% improvement from baseline in SES-CD score) at Week 12

Estimands and Estimators

Two co-primary estimands, ie, a precise definition of the primary targeted treatment effect, are defined by the following 5 attributes: treatment by Week 12, population, intercurrent events (ICEs) and corresponding strategies, variable (endpoint), and population-level summary.

Primary Estimand of Clinical Remission at Week 12

i. Treatment by Week 12:

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

Control: Placebo SC q4w (Weeks 0, 4, and 8)

ii. Population: Participants with moderately to severely active Crohn's disease

iii. Variable (endpoint):

A binary response variable (response/non-response) where response is defined as achieving CDAI score <150 at Week 12 without experiencing any of the ICEs in categories 1 to 3 as outlined below prior to the Week 12 visit.

iv. Intercurrent events and corresponding strategies:

The following are the ICEs considered for this study:

1) A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)
2) A prohibited change in Crohn's disease medication
3) Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease
4) Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)
5) Discontinuation of study intervention due to COVID-19 infection, for reasons other than lack of efficacy or an AE of worsening Crohn's disease, or any other COVID-19 related reasons

Intercurrent events in categories 1 to 3 will be handled by the composite strategy, ICE category 4 will be handled by the hypothetical strategy, and ICE category 5 will be handled by treatment policy strategy. The composite strategy assesses the treatment effects not only based on the variable measurements, but also based on ICEs. This estimand acknowledges that having an ICE in categories 1 to 3 is an unfavorable outcome. For participants experiencing ICE 4, the hypothetical strategy envisages a scenario in which ICE category 4 would not occur and data points after the occurrence of ICE category 4 and onward will not be used. For participants experiencing ICE category 5, the treatment policy strategy considers the occurrence of ICE category 5 is irrelevant in defining the treatment effect and so observed values of the variable will be used, if available, regardless of the occurrence of ICE category 5.

v. Population-level summary:

Difference in proportions of responders (according to the variable defined in **iii** above) between the combined guselkumab group and the placebo group.

Primary Estimand of Endoscopic Response at Week 12

i. Treatment by Week 12:

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

Control: Placebo SC q4w (Weeks 0, 4, and 8)

ii. Population: Participants with moderately to severely active Crohn's disease

iii. Variable (endpoint):

A binary response variable (response/non-response) where response is defined as achieving endoscopic response (≥50% improvement from baseline in SES-CD score) at Week 12 without experiencing any of the ICEs in categories 1 to 3 as outlined above prior to the Week 12 visit.

iv. Intercurrent events and corresponding strategies:

The same ICEs and corresponding strategies that are specified for the co-primary endpoint of clinical remission at Week 12 will be used.

v. Population-level summary:

Difference in proportions of responders (according to the variable defined in **iii** above) between the combined guselkumab group and the placebo group.

Estimators

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

The CDAI score will be calculated for a visit if at least 4 of the 8 components are available at that visit. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last available components. If the CDAI score cannot be calculated (ie, <4 components available) at a visit, the CDAI score will be considered missing for that visit. The total SES-CD score at a visit will be calculated based on all segments scored at the visit. If the total SES-CD score cannot be calculated (ie, no segment is scored) at a visit, the total SES-CD score will be considered missing.

After accounting for the ICE strategies, participants whose responder status is missing for a co-primary endpoint will be considered to be a non-responder for that co-primary endpoint. To examine the robustness of the co-primary endpoint analyses, sensitivity analyses using alternative missing data handling rules may be performed and will be specified in the SAP.

To control the Type I error, a fixed sequence testing approach will be used for the co-primary endpoints. In particular, clinical remission at Week 12 will be tested first, followed by the testing of endoscopic response at Week 12.

For testing of the co-primary endpoints, the efficacy of the induction dose of guselkumab versus the placebo group will be compared. As such, the two guselkumab groups that are randomized to

receive an identical guselkumab induction dose regimen through Week 12 will be combined for these comparisons.

To compare the induction dose regimen of guselkumab versus placebo for the co-primary endpoints, the CMH chi-square test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-Failure status (Yes or No) at baseline will be used. The study will be considered successful if both tests of the co-primary endpoints are positive.

In addition, subgroup analyses of the co-primary endpoints will be performed based on demographic and baseline disease characteristics, and baseline and previous use of medications for Crohn's disease (including BIO-Failure status).

9.4.3. Secondary Endpoints

The analyses of the 3 secondary endpoints listed below will be performed after the tests of the co-primary endpoints. For the endpoint of clinical remission at Week 24, the test between the high dose group (CCI q4w) and the placebo group will be performed first, followed by the test between the low dose group (CCI q8w) and the placebo group. The testing sequence will continue for the next 2 endpoints in the order listed below. If any test in the sequence, including the tests of the co-primary endpoints, does not achieve significance at the 2-sided 0.05 level, all the p-values for the subsequent endpoints will be considered nominal.

- Clinical remission (CDAI score <150) at Week 24
- PRO-2 remission at Week 12 (defined as an AP mean daily score at or below 1 and SF mean daily score at or below 3, ie, AP ≤1 and SF ≤3, and no worsening of AP or SF from baseline)
- Clinical response (decrease from baseline in CDAI ≥100 points or clinical remission) at Week 12

Estimands and Estimators

Secondary Estimand of Clinical Remission at Week 24

i. Treatment by Week 24:

Experimental: Guselkumab CCI q4w (Weeks 0, 4, and 8) followed by guselkumab CCI q4w (Weeks 12, 16, and 20)

Experimental: Guselkumab CCI q4w (Weeks 0, 4, and 8) followed by guselkumab CCI q8w at Week 16

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

ii. Population: Participants with moderately to severely active Crohn's disease

iii. Variable (endpoint):

A binary response variable (response/non-response) where response is defined as achieving CDAI score <150 at Week 24 without experiencing any of the ICEs in categories 1 to 3 and 6 as outlined below prior to the Week 24 visit.

iv. Intercurrent events and corresponding strategies:

1) A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)
2) A prohibited change in Crohn's disease medication
3) Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease
4) Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)
5) Discontinuation of study intervention due to COVID-19 infection, for reasons other than lack of efficacy or an AE of worsening Crohn's disease, or any other COVID-19 related reasons
6) Meet rescue criteria (see Section 6.5.1)

Intercurrent events in categories 1 to 5 will be handled in the same way as for the primary estimands. Intercurrent events in categories 1 to 3 and 6 will be handled by the composite strategy. This estimand acknowledges that having an ICE in categories 1 to 3 and 6 is an unfavorable outcome. For participants experiencing ICE category 4, the data points after the occurrence of ICE category 4 and onward will not be used. For participants experiencing ICE category 5, the observed values of the variable will be used, if available, regardless of the occurrence of ICE category 5.

v. Population-level summary:

Difference in proportions of responders (according to the variable defined in **iii** above) between each guselkumab group and the placebo group.

Secondary Estimand of PRO-2 Remission at Week 12

The same estimand (except for the "variable" attribute) that is specified for the co-primary endpoint analyses will be used.

Variable (endpoint):

A binary response variable (response/non-response) where response is defined as achieving PRO-2 remission (defined as AP ≤1 and SF ≤3, and no worsening of AP or SF from baseline) at Week 12 without experiencing any of the ICEs in categories 1 to 3 as outlined above, prior to the Week 12 visit.

Secondary Estimand of Clinical Response at Week 12

The same estimand (except for the "variable" attribute) that is specified for the co-primary endpoint analyses will be used.

Variable (endpoint):

A binary response variable (response/non-response) where response is defined as achieving clinical response (decrease in CDAI score ≥100 points or clinical remission) at Week 12 without experiencing any of the ICEs in categories 1 to 3 as outlined above, prior to the Week 12 visit.

Estimators

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

For the secondary endpoints, the CMH chi-square test (2-sided) stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-Failure status (Yes or No) at baseline will be used to compare guselkumab dose regimens versus placebo.

After accounting for the ICE strategies, participants whose responder status is missing for a secondary endpoint will be considered to be a non-responder for that secondary endpoint.

9.4.4. Tertiary Endpoints

The tertiary endpoints are evaluated at applicable timepoints through Week 96; they include but are not limited to the endpoints described in Section 3. A complete list of the tertiary endpoints will be provided in the SAP. Two tertiary endpoints (clinical remission at Week 48, endoscopic response at Week 48) will be controlled for multiplicity. These endpoints will be added at the end of the multiplicity-controlled testing procedure described in Section 9.4.3; the full testing procedure will be specified in the SAP. The testing of other tertiary endpoints will not be controlled for multiplicity, and nominal p-values will be provided.

9.4.5. Safety Analyses

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

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 12 weeks is considered to be treatment-emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

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

Clinical Laboratory Tests

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

Suicidal Ideation and Behavior

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

9.4.6. Other Analyses

Pharmacokinetic Analyses

The analyses are based on PK Analysis Set.

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

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database or data presentations. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

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

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

Immunogenicity Analyses

The analyses are based on Immunogenicity Analysis Set.

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

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

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

Biomarkers Analyses

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

Changes in serum protein analytes and whole blood RNA obtained over time will be summarized by intervention group where local regulations permit. Associations between baseline levels and changes from baseline in select biomarkers and response to treatment will be explored. RNA analyses will be summarized in a separate technical report.

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

Pharmacokinetic/Pharmacodynamic Analyses

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

Pharmacogenomic Analyses

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

9.5. Interim Analysis

No interim analysis is planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AP	abdominal pain
AP-NRS	Abdominal Pain-Numerical Rating Scale
AST	aspartate transaminase
AUC	area under the curve
AZA	azathioprine
BCG	Bacille Calmette-Guérin
BSFS	Bristol Stool Form Scale
CDAI	Crohn's Disease Activity Index
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DBL	database lock
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
eSource	electronic source
EU	European Union
EU-CTR	European Union Clinical Trials Regulation
FDA	Food and Drug Administration
FES	final efficacy and safety
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GPSP	Good Post-marketing Study Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICE	intercurrent event
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFU	Instructions for Use
Ig	immunoglobulin
IGRA	interferon gamma release assay

IL	interleukin
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
IPPM	Investigational Product Procedures Manual
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LT	liver tests
MRI	magnetic resonance imaging
MTX	methotrexate
NIMP	Non-investigational Medicinal Product
PD	pharmacodynamic(s)
PFS	prefilled syringe
PFS-U	prefilled syringe with an UltraSafe Plus™ Passive Needle Guard
PFS-Y	prefilled syringe with YpsoMate autoinjector
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	Patient-reported Outcome
PROMIS	Patient-reported Outcomes Measurement Information System
q4w	every 4 weeks
q8w	every 8 weeks
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SC	subcutaneous
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SID	study intervention discontinuation
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBili	total bilirubin
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
WBC	white blood cell

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in an eCRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Definitions of Inadequate Response to or Intolerance of Corticosteroids or 6-Mercaptopurine/Azathioprine/Methotrexate and Corticosteroid Dependence

CORTICOSTEROIDS

Participants have failed to respond to corticosteroids if they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving at least 0.75 mg/kg/day or ≥40 mg/day of prednisone (or corticosteroid equivalent, given orally or intravenously) for 2 weeks; or ≥9 mg/day of budesonide or ≥5 mg/day of beclomethasone dipropionate given orally for at least 4 weeks. Evidence of CON-Failure must be documented in the participant's source documentation.

Participants are intolerant of corticosteroids if:

- They have developed clinically significant AEs (eg, osteonecrosis or osteoporosis, psychosis, uncontrolled diabetes) unresponsive to dose reduction that, in the judgment of the investigator, precluded the use of corticosteroids to treat Crohn's disease.

  OR

- They have a medical condition that precludes the use of corticosteroids as a treatment for Crohn's disease.

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

6-MERCAPTOPURINE, AZATHIOPRINE, OR METHOTREXATE

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

- At least 3 months of therapy with 1 mg/kg/day of 6-MP, 2 mg/kg/day of AZA, or 25 mg/week (intramuscular or subcutaneous) of MTX.

  OR

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

  OR

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

  OR

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

Participants are intolerant of 6-MP, AZA, or MTX if:

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

  OR

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

10.3. Appendix 3: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to Tumor Necrosis Factor Antagonist Therapies (Infliximab, Adalimumab, or Certolizumab Pegol), Vedolizumab, or Approved Biosimilars

The criteria for inadequate initial response, response followed by loss of response, or intolerance to infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars are described in items 1, 2, and 3, below.

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

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

a. Have received, at minimum, a locally approved induction dose, for example:

1) Infliximab (2 or 3 doses of ≥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) Certolizumab pegol (2 or 3 doses of ≥400 mg)

OR

4) Vedolizumab (at least 2 and up to 4 doses of 300 mg IV)

AND

b. Did not initially respond to these induction doses of infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of Crohn's disease, as assessed by a treating physician:

1) Lack of improvement or worsening in stool frequency

2) Lack of improvement or worsening in daily abdominal pain

3) Occurrence, lack of improvement, or worsening of fever thought to be related to Crohn's disease

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

5) Lack of improvement or worsening in rectal bleeding

6) Initiation or increase in antidiarrheal medication

These signs and symptoms of Crohn's disease must have occurred ≥2 weeks after receiving the last induction dose of infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having had an inadequate initial response to infliximab, adalimumab, certolizumab pegol, vedolizumab,

or approved biosimilars. 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, etc, and/or evidence of disease flare based on clinical imaging modalities including but not limited to ileocolonoscopy, CT, and magnetic resonance imaging [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 as described in Section 5.1 to be eligible for enrollment.

AND

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

   1) Provide the dates and doses of the failed induction therapy with infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars.

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

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

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

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

a. Initially responded to induction therapy

AND

b. Have received, at minimum, 2 doses of a locally approved maintenance dose, for example:

   1) Infliximab (at a dose of ≥5 mg/kg)

      or

   2) Adalimumab (at a dose of ≥40 mg)

      or

   3) Certolizumab pegol (at a dose of ≥400 mg)

      or

   4) Vedolizumab (at a dose of ≥300 mg IV or ≥108 mg SC)

AND

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

1) Worsening in stool frequency
2) Worsening in daily abdominal pain
3) Occurrence or worsening in fever thought to be related to Crohn's disease
4) Recurring drainage from a previously nondraining fistula or development of a new draining fistula
5) Worsening in rectal bleeding
6) Initiation or increase in antidiarrheal medication

These signs and symptoms of Crohn's disease must have occurred ≥2 weeks after receiving the last maintenance dose of infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having lost response to infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars. 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 maintenance therapy with infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars.
   2) Documents that the participant had recurrence of disease activity despite maintenance therapy with infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars.

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

3. Current or prior intolerance to therapy with infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars

Eligible participants must satisfy criteria a and b.

a. Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum sickness-like reaction); or 3) significant injection-site reaction. Definitions of these 3 criteria are provided below. Adverse reactions also must have followed ≥1 dose of infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars and, in the treating physician's opinion, precluded continued use of the therapy.
   1) A significant acute infusion/administration reaction is defined as an adverse reaction that was:
      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 mmHg systolic and 60 mmHg diastolic, or a systemic or orthostatic drop in systolic blood pressure of greater than 20 mmHg

AND

b) Occurred ≤24 hours after infusion/administration of infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars.

AND

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

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

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

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

AND

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

AND

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

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, certolizumab pegol, or approved biosimilars.

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, certolizumab pegol, vedolizumab, or approved biosimilars.

2) Documents that the participant had intolerance to infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars.

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

10.4. Appendix 4: Hepatitis B Virus (HBV) Screening With HBV DNA Testing

Participants must undergo screening for HBV. At a minimum, this includes testing for HBsAg, anti-HBs, and anti-HBc total:

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

These eligibility criteria based on HBV test results are also represented in Table 9 below. For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines.

Table 9: Eligibility Based on Hepatitis B Virus Test Results

Hepatitis B Test Result			
HBsAg	**Anti-HBs**	**Anti-HBc total**	**Status**
negative	negative	negative	**Eligible**
negative	(+)	negative	
negative	(+)	(+)	
(+)	negative or (+)	negative or (+)	**Not eligible**
negative	negative	(+)	**(Require testing for presence of HBV DNA*)**

***** If HBV DNA is detectable, the participant is not eligible for this protocol. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, the participant is not eligible for the protocol.
Abbreviations: DNA=deoxyribonucleic acid; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; anti-HBs=hepatitis B surface antibody; anti-HBc=hepatitis B core antibody

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

10.5. Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

10.5.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [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.

Post-marketing Study

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

Protocol Amendments

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

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

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

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

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

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

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

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

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

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1.

Other Ethical Considerations

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

10.5.2. Financial Disclosure

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

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

10.5.3. Informed Consent Process

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

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

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

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

10.5.4. Data Protection

Privacy of Personal Data

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

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

The informed consent obtained from the participant (or his or her legally designated representative) includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. 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 or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

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

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

10.5.5. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand guselkumab, to understand Crohn’s disease, to understand differential intervention responders, and to develop diagnostic tests to identify Crohn’s disease populations that may be responsive or non-responsive to treatment with guselkumab. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1).

10.5.6. Committees Structure

No Data Monitoring Committee is planned for this study.

10.5.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker

research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

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

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

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

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

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

Registration of Clinical Studies and Disclosure of Results

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

10.5.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. 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 the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.5.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the 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 an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

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

10.5.10. Source Documents

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

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

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

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

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

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

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

10.5.11. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor 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.

10.5.12. On-Site Audits

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

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

10.5.13. Record Retention

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

investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. For trials performed under Regulation [EU] No. 536/2014, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

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

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

10.5.14. 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/Site Termination

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

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

10.6. Appendix 6: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.6.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, for time of last AE recording).

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

Serious Adverse Event

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

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

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may

require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

10.6.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator. The following selection should be used to assess all AEs.

Related

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

Not Related

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

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

10.6.3. Severity Criteria

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

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

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

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

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

10.6.4. Special Reporting Situations

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

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, 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 and/or applicable source documents. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

10.6.5. Procedures

All Adverse Events

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

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

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

- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

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

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

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

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

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

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

10.6.6. Product Quality Complaint Handling

Definition

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

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

Procedures

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

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

10.6.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.7. Appendix 7: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.3.5 and Appendix 6 (Section 10.6).

Definitions

Woman of Childbearing Potential

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 FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

  If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.

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

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

Contraceptive (birth control) use by men or women 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.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device
• Intrauterine hormone-releasing system
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

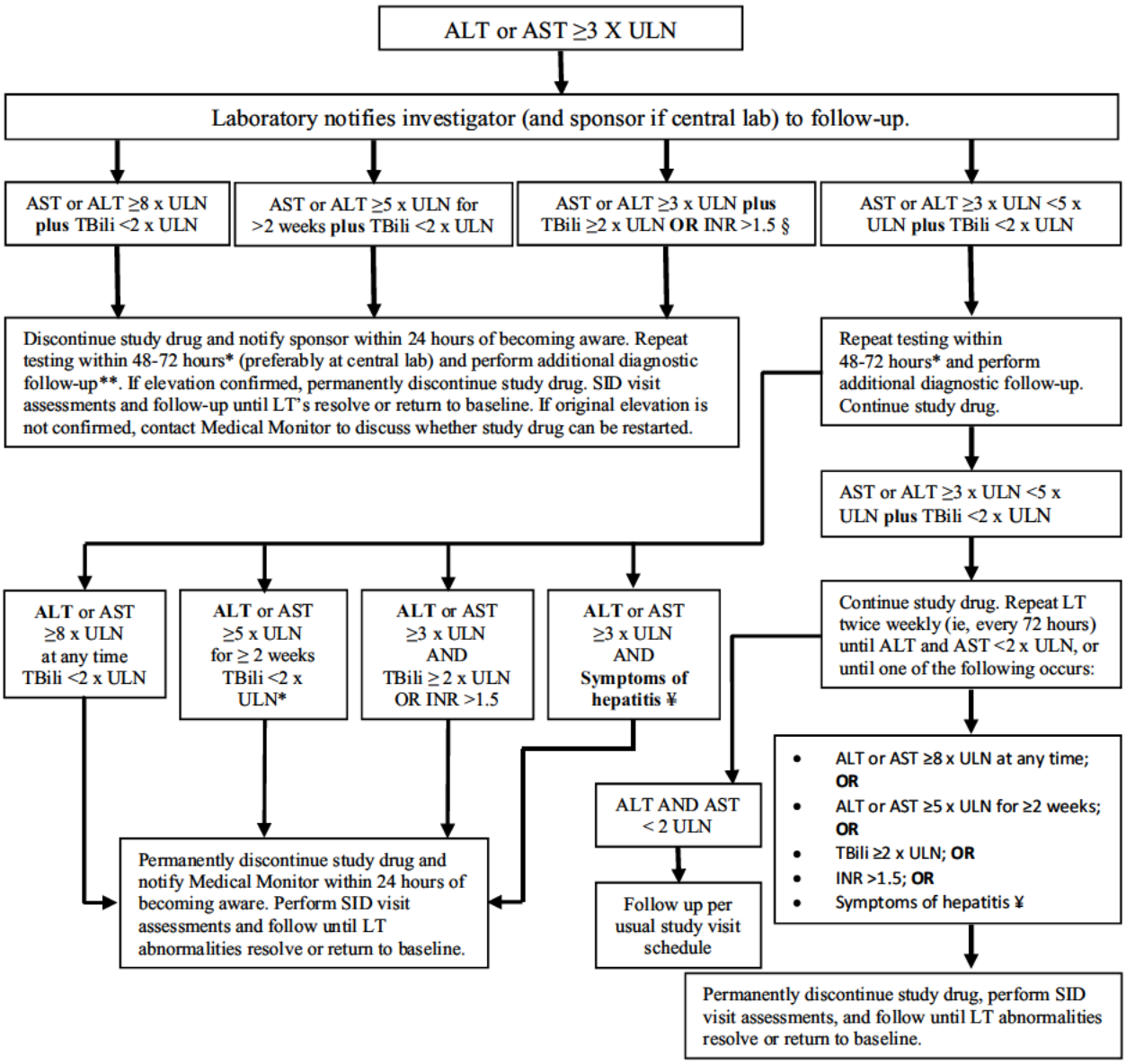
10.8. Appendix 8: Crohn's Disease Activity Index

DISEASE ACTIVITY INDEX	SUM	X FACTOR	SUBTOTAL
Total number of liquid or very soft stools in the previous 7 days		x 2 =	
Sum abdominal pain/cramps ratings (total for previous 7 days): 0 = none 2 = moderate 1 = mild 3 = severe		x 5 =	
General well-being (total for previous 7 days): 0 = generally well 3 = very poor 1 = slightly under par 4 = terrible 2 = poor		x 7 =	
Categories currently present and presumed to be related to Crohn's disease: 0 = no; 1 = yes			
ϒ = arthritis/arthralgia		x 20 =	
ϒ = iritis/uveitis		x 20 =	
ϒ = erythema nodosum/pyoderma gangrenosum/aphthous stomatitis		x 20 =	
ϒ = anal fissure, fistula or abscess		x 20 =	
ϒ = other fistula		x 20 =	
ϒ = fever over 100° F (37.8° C) during the previous 7 days.		x 20 =	
During the previous 7 days has subject received antidiarrheal therapy at least once: **OR** During the previous 7 days has subject received opiate therapy on each of the 7 days: 0 = no 1 = yes		x 30 =	
Abdominal mass: 0 = none 2 = questionable 5 = definite		x 10 =	
Hematocrit: Males: (47-Hct) = SUM Females: (42-Hct) = SUM	(add or subtract by sign)	x 6 =	
(Standard Weight - Actual Body Weight) / Standard Weight x 100 =	*	x 1 =	(add or subtract by sign, round to 3 decimal places)

* If this value is less than -10 then enter -10 here.
Standard weight and actual weight must be in same units (kg or lb)

TOTAL = _____
(round total to integer)

10.9. Appendix 9: Guideline Algorithm for Monitoring, Assessment and Evaluation of Abnormal Liver Tests



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

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

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

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

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

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

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

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

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

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

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

7. Based on potential baseline confounders of the disease target population consider (optionally): gamma-glutamyl transferase (to confirm the liver origin of elevated ALP levels), serum creatine phosphokinase (to confirm the liver origin of elevated AST levels], lactate dehydrogenase (to help exclude hemolysis), glutamate dehydrogenase (if muscle injury is suspected or if muscle disease is target population).
8. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: antinuclear antibody, anti-liver kidney microsomal antibody type 1, anti-liver-kidney microsomal antibodies, anti-smooth muscle antibodies (to screen for additional immune-related etiologies), erythrocyte sedimentation rate, and CRP (to screen for potential systemic inflammatory causes).
9. If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in Table 10), then gamma-glutamyl transferase, anti-mitochondrial antibody and anti-neutrophil cytoplasmic antibody should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/total iron binding capacity and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If patient is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings

and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.

Table 10: Patterns of DILI Based on Elevations of Liver Tests

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

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

    A liver biopsy may be considered:

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

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

10.10. Appendix 10: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the COVID-19 pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
  - Remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures, eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration (including training where pertinent)
  - Procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at-home administration (including the potential for self-administration of study intervention)
  - Laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
  - Other procedures may be conducted at an appropriate facility
- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix “COVID-19-related” in the eCRF.
  - Other relevant study data elements impacted by the pandemic should also be documented / labeled as “COVID-19-related” in eCRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP.

10.11. Appendix 11: Protocol Amendment History

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

Amendment 1 (13 September 2023)

Overall Rationale for the Amendment To address a CCI [redacted]

The changes made to the clinical protocol CNTO1959CRD3004 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
CCI [redacted]	CCI [redacted]	CCI [redacted]
Section 1.3 Schedule of Activities, Table 4	Removed "additional study visits."	To clarify that there are no additional visits.
Section 2.3.1 Risks for Study Participation	Participants who have received a live viral or bacterial vaccination within 4 weeks prior to screening will be excluded from the study.	For clarification and alignment with Exclusion Criterion #15.
Section 6.1 Study Intervention(s) Administered, Figure 2	Schema modified to add blinded sham rescue arms for the guselkumab treatment groups.	To clarify the rescue treatment for participants randomized to guselkumab.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	The full sponsor unblinding will occur at the Week 48 DBL. At the Week 24 DBL, data will be unblinded for analysis to a limited number of sponsor personnel only. Identification of sponsor personnel who will have access to the unblinded participant-level data at the time of the Week 24 DBL will be documented before unblinding. The method by which the study integrity will be maintained will be described in the SAP.	To clarify that only a limited number of sponsor personnel will be unblinded at Week 24.
Section 8.6.4 Pharmacodynamics	Test results for CRP and fecal calprotectin are accessible to investigators through the central laboratory as previously outlined in a protocol clarification communication.	To clarify laboratory results accessible to investigators.
Section 9.4.1 General Considerations	The SAP will be finalized prior to the first DBL (ie, Week 24). Any modifications and/or clarifications to protocol-specified statistical analyses or any other statistical analyses will be described in the SAP. Clarification provided for analyses of key endpoints at the Week 24 and Week 48 DBLs.	To clarify that the SAP contains all planned analyses and supersedes the protocol analyses and to clarify the timing of the evaluation of the endpoints with respect to the DBLs.

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol	Minor grammatical, formatting, and spelling changes, and changes to ensure consistency across the document were made.	Minor errors were noted.

11. REFERENCES

Arora G, Mannalithara A, Singh G, Gerson LB, Triadafilopoulos G. Risk of perforation from a colonoscopy in adults: a large population-based study. Gastrointest Endosc. 2009;69(3 Pt 2):654-664.

Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70(3):439-444.

Bittner B, Richter W, and Schmidt J. Subcutaneous administration of biotherapeutics: An overview of current challenges and opportunities. BioDrugs. 2018;32(5):425-440.

Costa F, Mumolo MG, Ceccarelli L, et al. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. Gut. 2005;54:364-368.

Danese S et al. The effect of guselkumab induction therapy on early clinical outcome measures in patients with moderately to severely active Crohn's disease: results from the Phase 2 GALAXI 1 study. European Crohn's Disease and Colitis Organisation (ECCO) Congress, 2021. Oral presentation.

Danese S, Schabel E, Masure J, Plevy S, Schreiber S. Are we ready to abandon placebo in randomised clinical trials for inflammatory bowel disease? Pros and cons. JCC. 2016;10(Suppl 2):S548–S552.

Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505-512.

De Cock E, Kritikou P, Sandoval M, et al. Time savings with rituximab subcutaneous injection versus rituximab intravenous infusion: A time and motion study in eight countries. PLoS One. 2016;11(6):e0157957.

D'Haens GR, Sartor RB, Silverberg MS, et al. Future directions in inflammatory bowel disease management. J Crohn's Colitis. 2014;8(8):726-734.

Food and Drug Administration. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009 Drug Safety. https://www.fda.gov/media/116737/download. Accessed 29 January 2021.

Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. BioDrugs. 2007;21(2):105-116.

Gordon JP, McEwan PC, Maguire A, et al. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. Eur J Gastroenterol Hepatol. 2015;27(7):804-812.

Investigator's Brochure: CNTO1959 (guselkumab) Edition 12. Janssen Research & Development (August 2021).

Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology. 1994;106(2):287-296.

Ji P, Nikolov N, Seymour S, et al. A novel pharmacokinetic bridging strategy to support a change in the route of administration for biologics. J. Pharm. Sci. 2019;108:2490-2499.

Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997; 32(9):920-924.

Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in adults. Am J Gastroenterol. 2018;113(4):481-517. Erratum in: Am J Gastroenterol. 2018;113(7):1101.

Mundt JC, Greist JH, Jefferson JW, et al. Prediction of suicidal behavior in clinical research by lifetime suicidal ideation and behavior ascertained by the electronic Columbia-Suicide Severity Rating Scale. J Clin Psych. 2013; 74(9):887-893.

Nielsen OH and Ainsworth MA. Tumor necrosis inhibitors for inflammatory bowel disease. N Engl J Med. 2013;369(8):754-762.

Palmer M, Regev A, Lindor K. Consensus guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury occurring during clinical trials in adults with chronic cholestatic liver disease. Aliment Pharmacol Ther. 2020;51:90-109.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-1277.

Rabeneck L, Paszat LF, Hilsden RJ, et al. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. Gastroenterology. 2008;135(6):1899-1906.

Rutgeerts P, Feagan BG, Marano CW, et al. Randomised clinical trial: a placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis. Aliment Pharmacol Ther. 2015;42:504-514.

Sandborn WJ. The present and future of inflammatory bowel disease treatment. Gastroenterol Hepatol. 2016;12(7):438-441.

Sandborn WJ (2020a), Baert F, Danese S, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. Gastroenterology. 2020;158:562-572.

Sandborn WJ (2020b), Chan D, Johanns J, et al. The efficacy and safety of guselkumab induction therapy in patients with moderately to severely active Crohn's disease: Week 12 interim analyses from the Phase 2 GALAXI 1 Study. United European Gastroenterology Week, 2020. Abstract #OP089.

Sands BE, Gasink C, Jacobstein D, et al. Efficacy and safety of dose adjustment and delayed response to ustekinumab in moderate-severe Crohn's disease: results from the IM-UNITI maintenance study. United European Gastroenterology Week, 2016. Oral presentation.

Solem CA, Loftus EV, Tremaine WJ, et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(8):707-12.

Tetteh EK, Morris S. Evaluating the administration costs of biologic drugs: development of a cost algorithm. Health Econ Rev. 2014;4(1):26.

Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: Medical treatment. J Crohn's Colitis. 2020;14(1):4-22.

TREMFYA® SmPC. https://www.ema.europa.eu/en/medicines/human/EPAR/tremfya#product-information-section. Accessed on 11 August 2021.

TREMFYA® USPI. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TREMFYA-pi.pdf. Accessed on 13 January 2021.

Usmani SZ, Mateos MV, Hungria V, et al. Greater treatment satisfaction in patients receiving daratumumab subcutaneous vs. intravenous for relapsed or refractory multiple myeloma: COLUMBA clinical trial results. J Cancer Res Clin Oncol. 2021;147(2):619-631.

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: 04 October 2024

(Day Month Year)

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

Signature

User	Date	Reason
PPD	04-Oct-2024 21:48:44 (GMT)	Document Approval