**Janssen Research & Development**

# Statistical Analysis Plan

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

**Protocol CNTO1959CRD3007; Phase 3**

**CNTO1959 (guselkumab)**


| | |
|---|---|
| **Status:** | Approved |
| **Date:** | 30 November 2023 |
| **Prepared by:** | Janssen Research & Development, LLC |
| **Document No.:** | EDMS-RIM-1164638, 3.0 |


**Compliance:** The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

# TABLE OF CONTENTS

# VERSION HISTORY

**SAP Version History Summary**

| SAP Version | Approval Date | Change | Rationale |
|---|---|---|---|
| 1.0 | 10/27/2023 | Not Applicable | Initial release |
| 2.0 | 11/14/2023 | Include pharmacokinetics and immunogenicity | Include additional data points for CSR |
| 3.0 | 11/30/2023 | Administrative | Correction to version number (internal) |
| | | | |
| | | | |

# 1. INTRODUCTION

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

Janssen made an internal business decision to discontinue the PROGRESS study. This decision is not related to any efficacy or safety concerns. Only four subjects were enrolled, and the originally planned statistical analyses are no longer applicable.

We will report data collected on those four patients including:

- Baseline characteristics: demographics, medical history of interest, date of CD diagnosis, Montreal classification, prior gastrointestinal surgeries, prior CD medications, qualifying surgery information, corticosteroid use
- Efficacy assessments: Rutgeerts score, CDAI score, fistula assessment, fecal calprotectin, CRP, medical resource utilization
- Safety assessments: adverse events, concomitant and prohibited medications, hematology, clinical chemistry
- Pharmacokinetics and immunogenicity: serum guselkumab concentration, antibody status (titer and neutralizing antibodies status)

Below are the originally planned statistical analyses for reference.

This SAP contains definitions of the analysis sets, derived variables, and statistical methods for all planned analyses for the main study period database lock and the Week 156 database lock. The term "study intervention" throughout this SAP refers to placebo and guselkumab.

## 1.1. Objectives and Endpoints

The primary and secondary objectives and endpoints are listed below.

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the efficacy of guselkumab treatment versus placebo in preventing endoscopic recurrence of CD in participants after surgery | • Endoscopic recurrence prior to or at Week 48 (as defined by modified Rutgeerts score ≥ i2a in the neo-terminal ileum, anastomotic site, or its equivalent elsewhere in the gastrointestinal (GI) tract [eg colonic ulceration]) |
| **Secondary** | |
| • To evaluate clinical remission without disease recurrence in participants treated with guselkumab versus placebo after surgery | • Clinical remission (CDAI < 150) without disease recurrence at Week 48 (as defined in Section 5.4.1.1) |
| • To evaluate disease recurrence in participants treated with guselkumab versus placebo after surgery | • Time-to-disease recurrence (as defined by CDAI/event driven criteria as described in Section 5.4.1.1) at the main study database lock, which will incorporate all available follow-up of enrolled participants at the time that the last participant dosed has completed the Week 48 study procedures, including the ileocolonoscopy |

| Objectives | Endpoints |
|---|---|
| • To evaluate symptoms such as stool frequency and abdominal pain scores in guselkumab versus placebo after surgery | • Abdominal pain free (abdominal pain [AP] score = 0) at Week 48<br>• Time-to-recurrence of symptoms, defined as time to attaining an AP mean daily score >1 (and also >1 point higher than baseline) along with stool frequency (SF) mean daily score >3 (and also >3 higher per day than baseline) for 2 consecutive weeks through Week 48 |
| • To evaluate the safety and PK of guselkumab in participants with CD in the postoperative period | • Frequency and type of AEs and serious adverse events (SAEs)<br>• Describe serum guselkumab concentrations over time |
| • The evaluate the efficacy of guselkumab in limiting steroid use and maintaining remission in the postoperative period | • Steroid free clinical remission at Week 48, defined as CDAI <150 and no corticosteroids within 30 days |
| **Other** | |
| • To evaluate fatigue and other patient reported outcomes in guselkumab versus placebo after surgery | • Change in Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue Short Form 7a score over 48 weeks<br>• Change in PROMIS-Fatigue SF 7a at each post baseline visit through Week 152<br>• Change in PROMIS-29 score, both overall score and individual domain scores at each post baseline visit through Week 152<br>• Change from baseline in the WPAI at each post baseline visit through Week 152<br>• Abdominal pain (AP score = 0) at each post baseline visit through Week 152 |
| • To evaluate steroid use and healthcare utilization in participants within the postoperative period | • The number of participants not on corticosteroids and without disease recurrence at each post baseline visit through Week 152<br>• The number of participants not on corticosteroids and who have not experienced endoscopic or disease recurrence at each post baseline visit through Week 152 |
| • To evaluate histologic status in CD patients after surgery | • Histologic score (as measured by Geboes scale/RHI/GHAS) at Week 48 ileocolonoscopy<br>• The number of participants with Geboes score of 2.0 or less at Week 48 ileocolonoscopy<br>• The number of participants with Geboes score over 3.1 at Week 48 ileocolonoscopy |
| • To evaluate the efficacy and safety of open-label guselkumab SC induction and maintenance treatment in the cross over population after postoperative endoscopic or disease recurrence of CD has occurred | • Clinical remission (CDAI < 150) at 24 weeks after initiation of guselkumab SC induction<br>• Clinical response (CDAI decrease of <100 points or CDAI <150) at 24 weeks after initiation of guselkumab SC induction<br>• Endoscopic remission (SES-CD of 3 or less) at 24 weeks after guselkumab SC induction |

| Objectives | Endpoints |
|---|---|
| | • Endoscopic remission (modified Rutgeerts score <i2a) at 24 weeks after guselkumab SC induction |
| • To evaluate the efficacy of guselkumab treatment versus placebo in changes to inflammatory biomarkers after surgery | • The change from baseline in CRP concentration at all postbaseline visits through Week 152<br>• The change from baseline in fecal calprotectin concentration at all postbaseline visits through Week 152<br>• Fecal calprotectin recurrence, defined by calprotectin of >200 µg/g with a 100 µg/g increase over baseline |
| • To evaluate the clinical efficacy of guselkumab treatment | • Disease recurrence (using CDAI/Event-driven definition as described in Section 9.4.3) at Week 152<br>• Clinical remission (CDAI <150) at each post baseline visit<br>• Time to a flare of abdominal pain |
| • To evaluate the endoscopic efficacy of guselkumab treatment | • Endoscopic remission (SES-CD of 3 or less) at Week 24, Week 48, Week 152<br>• Endoscopic recurrence (modified Rutgeerts score >i2a) at Week 24, Week 152 |

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

Efficacy endpoints definitions are as follows:

- **Endoscopic Recurrence prior to or at Week 48:** modified Rutgeerts score ≥ i2a in the neo-terminal ileum, anastomotic site, or its equivalent elsewhere in the gastrointestinal (GI) tract [eg colonic ulceration].
- **Clinical remission without disease recurrence at Week 48:** Clinical remission without disease recurrence is a composite endpoint defined by the following:
  - CDAI < 150 at Week 48 and.
  - No endoscopic recurrence as defined by Rutgeerts score < i2 by Week 48 and
  - Have not experienced a disease recurrence as defined below.
- **Disease recurrence:** Disease Recurrence is a composite endpoint defined by the following:
  - A ≥ 70-point increase from baseline in CDAI score at beyond 8 weeks after randomization; and a CDAI score of ≥ 200 **and** evidence of endoscopic recurrence. Endoscopic recurrence is defined as a modified Rutgeerts score of ≥ i2a at the anastomotic site or its equivalent elsewhere in the GI tract, unless a stool test for C. difficile toxin or other enteric pathogen is positive.
  - In event of a positive test for enteric pathogen including C. difficile toxin, the underlying infection should be treated and if ileocolonoscopy has not yet been performed, it should only be done when the infection has resolved, and if disease recurrence threshold is still met.

- OR initiation of a physician-prescribed corticosteroids, or an increase in the dose of steroids already being taken (by greater than 5 mg/day), for over one week for the treatment of CD **and** evidence of endoscopic recurrence as described above, unless a stool test for C. difficile toxin or other enteric pathogen is positive.
- OR a new draining external fistula.
- OR the reopening and draining of a previously existing external fistula.
- OR developing a new internal fistula.
- OR developing a new perianal abscess.
- OR developing a new intra-abdominal abscess more than three months after the date of the index surgery.

Participants who have confirmed endoscopic recurrence at Week 24 or Week 48 and cross over to open-label guselkumab treatment will be censored at cross over for the time to disease recurrence endpoint.

Time-to-disease recurrence at the main study database lock, which will incorporate all available follow-up of enrolled participants at the time that the last participant dosed has completed the Week 48 study procedures, including the ileocolonoscopy.

- **Abdominal pain free at Week 48**: abdominal pain [AP] score = 0.
- **Time-to-recurrence of symptoms**: defined as time to attaining an AP mean daily score >1 (and also >1 point higher than baseline) along with stool frequency (SF) mean daily score >3 (and also >3 higher per day than baseline) for 2 consecutive weeks through Week 48.
- **Steroid free clinical remission at Week 48**: defined as CDAI <150 and no corticosteroids within 30 days.

Specific primary, secondary, and exploratory endpoints, along with definitions, are provided in Section 5, Statistical Analyses, and the study protocol.

## 1.2. Study Design

### 1.2.1. Overall Design

This is a Phase 3, multicenter, randomized, placebo-controlled, prospective double-blind study designed to evaluate the efficacy and safety of CC guselkumab in preventing the recurrence of active CD in patients who have recently undergone a surgical resection for CD. A diagram of the study design is provided in Section 1.2.2, Schema.

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

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

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

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

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

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

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

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

**Database Locks and Maintenance of the Blind**

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

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

**Study Length**

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

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

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

It is recognized that some participants will have been steroid dependent prior to their surgery and may be unable to safely complete tapering of their steroid therapy prior to randomization. However, as participants enter the study without residual active CD, participants who enter the study on steroids should initiate, or continue, tapering of corticosteroids for CD without any delay upon study entry at Week 0, unless medically inappropriate. Corticosteroid tapering should follow the below-recommended schedule (Table 1), without exceeding the prescribed magnitude or rate of tapering unless due to medical necessity (eg, participant experiencing corticosteroid-related side effects).

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

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

If medically necessary (due to worsening disease or symptoms), participants may initiate oral corticosteroids if needed to manage their disease, but these should be discontinued and/or tapered off, as described above, as soon as clinically possible. The initiation of a physician-prescribed corticosteroid, or an increase in the dose of steroids already being taken (by greater than 5 mg/day), for over one week for the treatment of CD warrants further evaluation for disease recurrence as described in Section 5.4.1.1.

In contrast to the concomitant medications described above, initiation of any of the following medications is prohibited (until the last study intervention administration at Week 144) and if initiated, should result in discontinuation from further study intervention, although such participants should not terminate study participation (unless enrolling in an interventional CD study or initiating a commercial anti-IL23 as further described below), and are encouraged to complete all visits through the next 12 weeks, at which point the mandatory early termination visit should be performed.

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

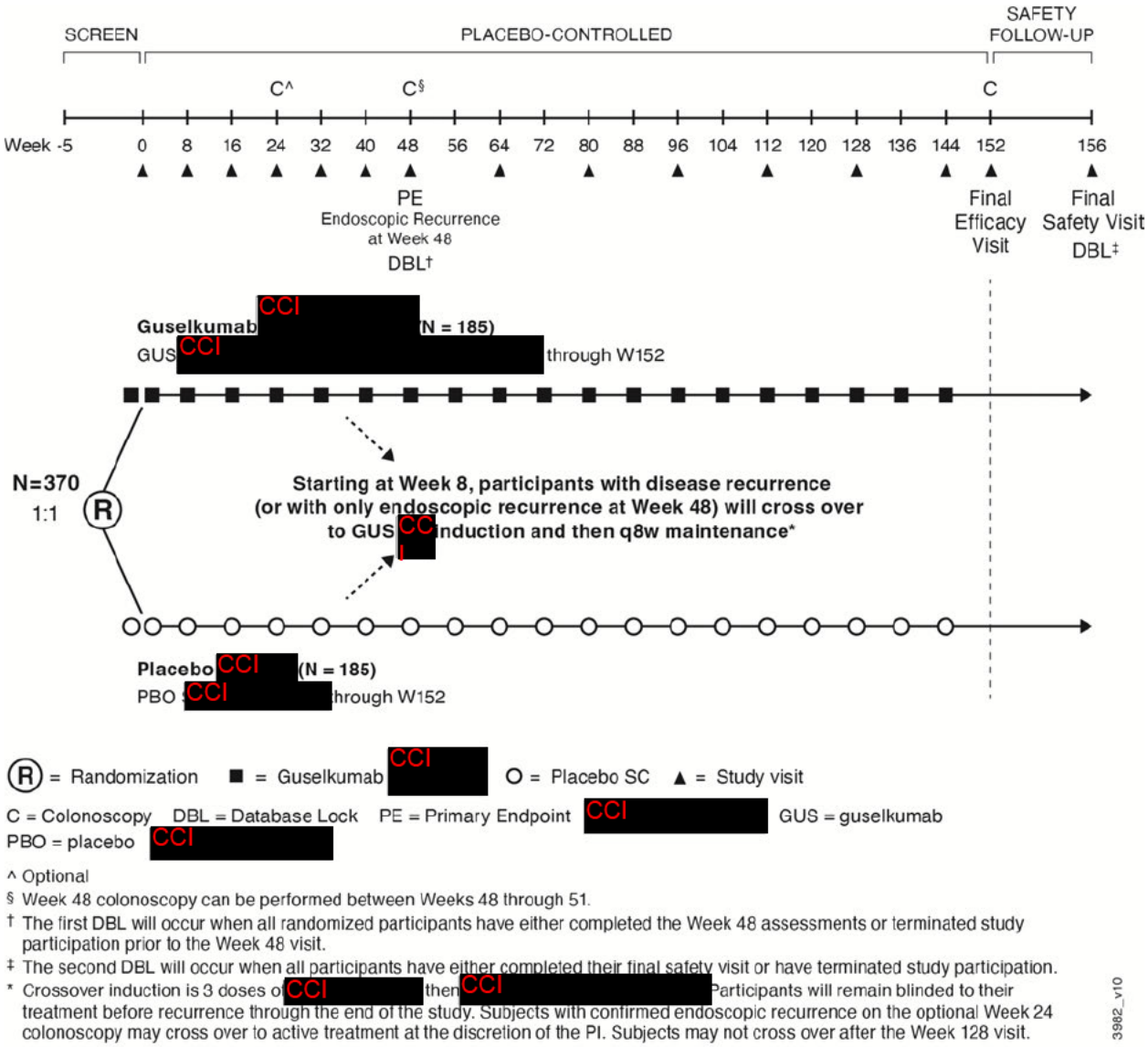
  Note: AZA, 6-MP, MTX and corticosteroids may be initiated if medically necessary for rescue therapy, so their initiation does NOT necessitate discontinuation of study intervention.
- Immunosuppressant biologic agents, including but not limited to commercial TNF-antagonists (eg, infliximab, adalimumab, certolizumab), IL 12-23 inhibitors (ie, ustekinumab), IL-23 inhibitors (eg, risankizumab), integrin inhibitors (eg, natalizumab, vedolizumab), and abatacept
- Experimental or investigational CD medications

Note: Until the study treatment period is completed (ie, Week 152), participants must not receive commercial anti-IL23 agents outside of the protocol or participate in any other CD clinical study with an investigational agent while in this study. Further, participants must discontinue any further study intervention and also terminate study participation in these circumstances, with performance of the early termination visit prior to initiating these drugs. If the decision or realization that this is about to occur coincides with a scheduled visit, then the early termination visit should be

performed in place of the scheduled visit, with the scheduling and performance of the follow-up ileocolonoscopy occurring as soon as possible. The rationale for handling initiation of these agents in this way is that subsequent efficacy and safety data in the context of the study would be uninterpretable.

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

### 1.2.2. Schematic Overview of the Study



### 1.2.3. Randomization and Blinding

Randomization will be used to minimize bias in the initial 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, stratification by known potentially relevant baseline characteristics that may affect study outcomes will also be used to avoid chance imbalance of these relevant variables among treatment groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

**Intervention Allocation**

**Procedures for Randomization and Stratification**

Central randomization will be implemented in this study. At Week 0, participants will be randomly assigned to 1 of 2 intervention groups in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery). The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant.

**Blinding**

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

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

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

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

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

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

## 2. STATISTICAL HYPOTHESES

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

## 3. SAMPLE SIZE DETERMINATION

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

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

### Endoscopic Recurrence

Assumptions for endoscopic recurrence prior to or at Week 48 were based on previous studies, as described in Table 2.

**Table 2: Endoscopic Recurrence, Placebo Group**

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

* References are provided in the protocol.

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

To accommodate other potential scenarios, power was calculated based on different assumptions as listed in Table 3.

**Table 3: Power to Detect a Treatment Effect Based on Different Scenarios in Endoscopic Recurrence**

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

## Clinical Remission without Disease Recurrence

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

To accommodate other potential scenarios, power was calculated based on different assumptions as listed in Table 4:

**Table 4: Power to Detect a Treatment Effect Based on Different Scenarios in Clinical Remission without Disease Recurrence**

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

### Disease Recurrence

Assumptions for disease recurrence were based on previous studies, as described in Table 5.

**Table 5: Disease Recurrence, Placebo Group**

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

* References are provided in the protocol.

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

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

**Table 6: Power to Detect a Treatment Effect Based on Different Scenarios in Disease Recurrence**

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

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

# 4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

| Analysis Sets | Description |
|---|---|
| Randomized | The randomized analysis set includes all participants who were randomized in the study. |
| Full Analysis Set (FAS) | All randomized participants.<br><br>Participants in the FAS will be analyzed according to their randomized study intervention regardless of the study intervention they actually received. |
| Safety Analysis Set | All randomized participants who receive at least 1 dose of study intervention.<br><br>Participants in the Safety Analysis Set will be analyzed according to the study intervention they actually received. |
| Pharmacokinetics Analysis Set | All randomized participants who receive at least 1 dose of study intervention and have at least one valid blood sample drawn postbaseline for PK analysis.<br><br>Participants in the PK Analysis Set will be analyzed according to the study intervention they actually received. |
| Immunogenicity Analysis Set | All participants who received at least 1 dose of study intervention and have appropriate samples for anti-drug antibody detection.<br><br>Participants in the Immunogenicity Analysis Set will be analyzed according to the study intervention they actually received. |

# 5. STATISTICAL ANALYSES

## 5.1. General Considerations

- Unless otherwise specified, for each study, data from all investigational centers/sites will be pooled for analysis
- Study Day 1 refers to the day of the first study intervention administration. All efficacy and safety assessments at all visits will be assigned a day relative to this day.

  Study day for a visit is defined as:

  – Visit date - (date of Study Day 1) +1, if visit date is ≥ date of Study Day 1

  – Visit date - date of Study Day 1, if visit date < date of Study Day 1

  There is no 'Study Day 0'.
- Baseline assessment is defined as the last available assessment collected prior to the first study intervention.
- Descriptive statistics (ie, N, mean, median, SD, IQ range, minimum and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphical data displays (eg, line plots) may also be used to summarize the data.

- The following conventions will be applied for reporting descriptive statistics of all continuous parameters. For presentation, the mean and median will be presented to 1 decimal greater than the original data, SD will be 2 decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.
- The following intervention groups will be presented through Week 48, unless otherwise stated:
  - Placebo
  - Guselkumab

Partial dates for adverse events will be imputed as described in Appendix 11.

### 5.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. All post-baseline visits up to and including Week 56 will have a visit window of ± 10 days counting from Week 0 as Day 1. If a study visit occurs outside this window, the Sponsor should be consulted about how the participant should resume his or her normal dose schedule. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint.

## 5.2. Participant Disposition

The number of participants screened, the number of participants screen failed, primary reason for screen failure and the number of participants re-screened will be presented. In addition, the number of participants who were randomized will be given.

The number of participants included in the analysis sets by intervention group will be presented. Percentages will be based on the number of participants in the RAS. In addition, the distribution of participants by region, country and site ID will be presented for the Full Analysis Set.

The number and frequency of participants in the following disposition categories will be summarized by the intervention group based on the Full Analysis Set:

- Participants who received study intervention
- Participants who completed the study intervention through Week 48
- Participants discontinuing study intervention prior to Week 48 and reasons for discontinuation
- Participants discontinuing study intervention prior to Week 156 and reasons for discontinuation
- Participants who terminated study participation prior to Week 156 and reasons for termination

A listing of participants who prematurely discontinued study intervention or prematurely discontinued the study and the primary reason for discontinuation will be presented. The listing will identify the visits completed and when the study intervention or study was discontinued.

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention prior to Week 48
- Participants who terminated study participation
- Participants who were randomized yet did not receive study intervention
- Participants who were unblinded prior to Week 48

Study assessment of compliance will be summarized and listed by randomized treatment group. This will include the number of participants who missed at least one scheduled CDAI assessment, at least one scheduled endoscopy assessment, or at least one missed study agent administration due to any reason or due to COVID-19-related events.

## 5.3. Primary Endpoint(s) Analysis

### 5.3.1. Definition of Endpoint

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

Rutgeerts score

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

### 5.3.2. Estimand

#### 5.3.2.1. Primary Estimand

An estimand is a precise definition of the primary targeted treatment effect defined by the following 5 attributes: Study Intervention, population, variable (endpoint), intercurrent events (ICEs) and corresponding strategies, and population-level summary.

**Primary Trial Objective:** To evaluate the efficacy of guselkumab treatment prior to or at Week 48 compared with placebo in preventing endoscopic recurrence of CD in participants after surgery.

**Estimand Scientific Question of Interest:** What is the proportion of participants developing endoscopic recurrence prior to or at Week 48, and thus considered to have benefited from guselkumab versus placebo?

**Study intervention:**

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

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

**Variable:** A binary recurrence variable (recurrence/no recurrence) where recurrence is defined as Endoscopic Recurrence prior to or at Week 48 (as defined by modified Rutgeerts score greater than or equal to i2a in the neo-terminal ileum, anastomotic site, or its equivalent elsewhere in the GI tract (eg, colonic ulceration)) or experiencing intercurrent events (ICEs) 1-4 presented below.

**Summary Measure (Population-level summary):** Difference in proportions of the binary recurrence variable of endoscopic recurrence, as described above, between guselkumab group and the placebo group.

**Intercurrent events and their corresponding strategies:**

The ICEs considered for this study are listed in Table 7:

**Table 7: Intercurrent Events and Corresponding Analysis Strategies for Endoscopic Recurrence prior to or at Week 48**

| **Intercurrent Events** (between baseline and Week 48) | **Analysis Strategy for Intercurrent Events** |
|---|---|
| 1. A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)<br>2. A prohibited change in CD medication<br>3. Discontinuation of study intervention due to lack of efficacy or an AE of worsening CD<br>4. Cross over to open-label guselkumab | **Composite Strategy:** Participants are considered endoscopic recurrence if they experience any of these ICEs, prior to Week 48, as reflected in the variable definition. |
| 5. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)<br>6. Discontinuation of study intervention due to reasons other than those in ICE 3 or 5 | **Treatment Policy:** ICE5 and ICE6 will be ignored, and any data observed after the associated ICE event will be used for the analysis. |

Abbreviation: AE=adverse event; CD=Crohn's disease; COVID-19= Coronavirus disease 2019; ICE=intercurrent event

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

#### 5.3.2.2. Supplementary Estimands for the Primary Endpoint

##### 5.3.2.2.1. All ICEs Composite

In this supplementary estimand, all ICEs defined above for the primary estimand are addressed by the **composite strategy**. The supplementary estimand for the primary endpoint acknowledges that having an ICE is an unfavorable outcome. Besides the strategy change, other components of the supplementary estimand are the same as those for the primary estimand with the exception of the Variable, which is described as follows:

***Supplementary Estimand of Endoscopic Recurrence prior to or at Week 48***

**Variable (endpoint)**: A binary recurrence variable (recurrence/no recurrence) where recurrence is defined as Endoscopic Recurrence prior to or at Week 48 (as defined by modified Rutgeerts score greater than or equal to i2a in the neo-terminal ileum, anastomotic site, or its equivalent elsewhere in the GI tract (eg, colonic ulceration)) or experiencing intercurrent events (ICEs) 1-6 presented in Table 7.

### 5.3.3. Analysis Methods

#### 5.3.3.1. Estimator (Analysis) of the Primary Estimand

The analyses will be based on the Full Analysis Set (FAS), which includes all randomized participants. Participants will be analyzed according to the intervention group to which they were randomized regardless of the study intervention they actually received.

To compare the guselkumab versus placebo group for the primary endpoint, the Cochran Mantel Haenszel chi-square test (2-sided) will be used with stratification of clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery). The study will be considered successful if the test of the primary endpoint is positive at the 0.05 significance level.

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

Multiple imputation will be used for imputing missing data under the assumption that the data are MAR. The analysis will impute the missing Rutgeerts score at Week 48 using the analysis method and ancillary variables as described in Table 8. The responses at Week 48 will be derived from the imputed datasets and combined for analysis.

**Table 8: Multiple Imputation Methods for Rutgeerts Score at Week 48**

| Variable | MI specification | Analysis method/Summary statistics |
|---|---|---|
| Rutgeerts score at Week 48 | Multiple imputation with monotone regression of total scores | MIdataset1 (N=200, Seed=5748941)<br>• Imputation variables: Rutgeerts score at Week 48<br>• Ancillary variables: Treatment group, and history of primary non-response to at least one approved ADT (Yes, No), clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery) |

The number and percentage of participants who experienced any ICE prior to Week 48 will be summarized by the type of ICE.

#### 5.3.3.2. Estimator (Analysis) for the Supplementary Estimands of the Primary Endpoint

##### 5.3.3.2.1. All ICEs Composite

The same estimator used for the primary estimand will be used for the supplementary estimand, with the exception that the treatment policy no longer applies to ICE5 and ICE6, as all ICEs are addressed by the composite strategy. After accounting for the ICE strategies, participants whose endoscopic recurrence status is missing for the primary endpoint will be considered to having endoscopic recurrence.

### 5.3.4. Subgroup Analyses

To evaluate the consistency of the primary analyses, subgroup analyses based on demographics (eg, age, sex, race, body weight, region), baseline characteristics (CD duration, involved gastrointestinal areas, number of CD related prior surgeries, CDAI score), baseline CD-related concomitant medication usage and biologic history (oral corticosteroids, oral 5-ASA compounds, immunomodulators(6-MP, AZA, or MTX), oral corticosteroids and immunomodulators, oral corticosteroids or immunomodulators prior biologic use), and potential risk factors for recurrence of active CD (number of risk factors for recurrence of active CD, the qualifying surgery was the patient's second intra-abdominal operation for CD in the past 10 years, the qualifying surgery was the patient's third (or more) intra-abdominal operation for CD, the qualifying surgery was performed for a penetrating complication of CD (ie, an intra-abdominal abscess, internal fistula, sinus tracts or intestinal perforation), the patient has any history of perianal fistulizing CD provided that this has not been active in the 3 months prior to study start, the patient is a cigarette smoker), the patient has Kono-S (antimesenteric functional end-to-end handsewn), the patient has mesenterectomy will be performed if sufficient data are available in the subgroup.

For subgroup analyses, the analysis sets are based on the **FAS.** Subgroup analyses will be performed when the number of participants in each subgroup permits. The following subgroup analyses will be performed:

1. The consistency of treatment effect for the primary endpoint will be evaluated for the subgroups defined in Section 5.8.5, using the **primary estimand**:

   For each of the subgroups identified in Section 5.8.5, the rate (risk) difference of guselkumab vs placebo group and the associated p-values and 95% confidence intervals will be provided using forest plots. The difference in proportions, p-values and confidence intervals will be provided based on the same model specified in Section 5.3.3.1.

2. Using the primary estimand, an analysis of the primary endpoint will be performed for each region, country, and investigator site. This analysis will be descriptive and statistical testing will not be applied.

### 5.3.5. Sensitivity Analyses

The following sensitivity analyses will be based on varying assumptions of the missing data, and different definition for the primary endpoint of endoscopic recurrence.

#### 5.3.5.1. Tipping Point Analysis

Tipping point sensitivity analyses will be conducted to explore the potential impact of missing data and to show the robustness of the conclusion based on the primary analysis. The analysis finds a (tipping) point in this spectrum of assumptions, at which conclusions change from being favorable to the experimental intervention to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. The tipping point can be identified when the result is no longer statistically significant.

The Tipping Point Analysis will be applied to primary endpoint and will use the primary estimand, after accounting for ICEs. For participants with missing data for the endpoint, the endoscopic recurrence (recurrence/no recurrence) will be imputed in an increasing manner by participant level for each intervention group. Specifically, for each participant, a recurrence/no recurrence status will be imputed starting with the scenario where all participants have recurrence up to the scenario where all participants have no recurrence. This would include all possible scenarios of recurrence status for all missing data allowing assumptions about the missing outcomes to vary independently, including scenarios where participants randomized to the Guselkumab group have worse outcomes than participants on placebo. For each scenario, the adjusted intervention difference (with CMH weight) in proportion of participants achieving the primary endpoint between the Guselkumab group and placebo group and the corresponding p-values will be provided.

#### 5.3.5.2. Modified Endoscopic Recurrence

This sensitivity analysis will evaluate the primary endpoint in a similar fashion. Same ICE strategy and similar estimand and estimators will be used, with exception that

- The definition of endoscopic recurrence: endoscopic recurrence prior to or at Week 48 as defined by modified Rutgeerts score i2b or above in the neo-terminal ileum, anastomotic site, or its equivalent elsewhere in the GI tract (eg, colonic ulceration).
- Variable (endpoint): A binary recurrence variable (recurrence/no recurrence) where recurrence is defined as Endoscopic Recurrence prior to or at Week 48 (as defined by modified Rutgeerts score greater than i3) or experiencing intercurrent events (ICEs) 1-4.

## 5.4. Secondary Endpoint(s) Analysis

### 5.4.1. Key Confirmatory Secondary Endpoint(s)

The following are the first secondary endpoint and second secondary endpoint:

- Clinical remission without disease recurrence at Week 48
- Time to disease recurrence

The analyses of the first secondary endpoint will be performed after the test of the primary endpoint. The analyses of second secondary endpoint will be performed after the test of the primary endpoint and the first secondary endpoint.

#### 5.4.1.1. Definition of Endpoint(s)

Clinical remission without disease recurrence is a composite endpoint defined by the following:

- CDAI < 150 at Week 48 and
- No endoscopic recurrence as defined by Rutgeerts score < i2a by Week 48 and
- Have not experienced a disease recurrence as defined below

Disease recurrence is a composite endpoint defined by the following:

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

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

Abdominal pain free at Week 48 is defined as abdominal pain (AP) score = 0 at Week 48

Time-to-recurrence of symptoms is defined as time to attaining an AP mean daily score >1 (and also >1 point higher than baseline) along with stool frequency (SF) mean daily score >3 (and also >3 higher per day than baseline) for 2 consecutive weeks through Week 48. Participants who cross over to open-label guselkumab treatment and do not have recurrence of symptoms will be censored at cross over for the time to recurrence of symptoms endpoint.

Steroid free clinical remission at Week 48 is defined as CDAI <150 and no corticosteroids within 30 days.

#### 5.4.1.2. Estimand(s)

##### 5.4.1.2.1. Estimand of Clinical Remission without Disease Recurrence at Week 48

**Objective:** To evaluate clinical remission without disease recurrence in participants treated with guselkumab versus placebo after surgery.

**Estimand Scientific Question of Interest:** What is the proportion of participants achieving clinical remission without disease recurrence at Week 48, and thus considered to have benefited from guselkumab versus placebo?

**Study intervention:**

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

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

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

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

**Intercurrent events and their corresponding strategies:**

The ICEs considered for this study are listed in Table 9:

**Table 9: Intercurrent Events and Corresponding Analysis Strategies for Clinical Remission without Disease Recurrence at Week 48**

| **Intercurrent Events** (between baseline and Week 48) | **Analysis Strategy for Intercurrent Events** |
|---|---|
| 1. A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)<br>2. A prohibited change in CD medication (details in Appendix 9 Medications of Special Interest)<br>3. Discontinuation of study intervention due to lack of efficacy or an AE of worsening CD<br>4. Cross over to open-label guselkumab | **Composite Strategy:** Participants are considered not achieving clinical remission without disease recurrence if they experience any of these ICEs, prior to Week 48, as reflected in the variable definition. |
| 5. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)<br>6. Discontinuation of study intervention due to reasons other than those in ICE 3 or 5 | **Treatment Policy:** ICE5 and ICE6 will be ignored, and any data observed after the associated ICE event will be used for the analysis. |

Abbreviation: AE=adverse event; CD=Crohn's disease; COVID-19= Coronavirus disease 2019; ICE=intercurrent event

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

#### 5.4.1.2.2. Estimand of Time to Disease Recurrence

**Objective:** To evaluate disease recurrence in participants treated with guselkumab versus placebo after surgery

**Estimand Scientific Question of Interest:** What is the difference in time to disease recurrence at the main database lock, and thus considered to have benefited from guselkumab versus placebo?

**Study intervention:**

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

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

**Variable:** The time to disease recurrence (as defined above) or experiencing ICE 1-3 presented below.

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

**Intercurrent events and their corresponding strategies:**

The following are the ICEs considered for this study:

**Table 10: Intercurrent Events and Corresponding Analysis Strategies for Disease Recurrence at Main Database Lock**

| **Intercurrent Events** (between baseline and main database lock) | **Analysis Strategy for Intercurrent Events** |
|---|---|
| 1. A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)<br>2. A prohibited change in CD medication (details in Appendix 9 Medications of Special Interest)<br>3. Discontinuation of study intervention due to lack of efficacy or an AE of worsening CD | **Composite Strategy:** Participants are considered having disease recurrence if they experience any of these ICEs, prior to main database lock, as reflected in the variable definition. |
| 4. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection)<br>5. Discontinuation of study intervention due to reasons other than those in ICE 3 or 4 | **Treatment Policy:** ICE4 and ICE5 will be ignored, and any data observed after the associated ICE event will be used for the analysis. |

Abbreviation: AE=adverse event; CD=Crohn's disease; COVID-19= Coronavirus disease 2019; ICE=intercurrent event

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

#### 5.4.1.2.3. Estimand of Abdominal Pain Free at Week 48

**Objective:** To evaluate abdominal pain scores in guselkumab versus placebo after surgery.

**Estimand Scientific Question of Interest:** What is the proportion of participants achieving abdominal pain free at Week 48, and thus considered to have benefited from guselkumab versus placebo?

**Study intervention:**

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

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

**Variable:** A binary variable of abdominal pain free at Week 48 (abdominal pain [AP] score = 0) or experiencing ICEs 1-4 in Table 9.

**Summary Measure (Population-level summary):** Difference in proportions of the binary variable of abdominal pain free, as described above, between guselkumab group and the placebo group.

**Intercurrent events and their corresponding strategies:**

The same ICEs and corresponding strategies that are specified for primary endpoint of endoscopic recurrence prior to or at Week 48 will be used.

#### 5.4.1.2.4. Estimand of Time-to-Recurrence of Symptoms

**Objective:** To evaluate symptoms such as stool frequency and abdominal pain scores in guselkumab versus placebo after surgery.

**Estimand Scientific Question of Interest:** What is the difference in time to symptoms at the main database lock, and thus considered to have benefited from guselkumab versus placebo?

**Study intervention:**

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

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

**Variable:** The time to symptoms (defined as time to attaining an AP mean daily score >1 (and also >1 point higher than baseline) along with stool frequency (SF) mean daily score >3 (and also >3 higher per day than baseline) for 2 consecutive weeks through Week 48) or experiencing ICE 1-3 in Table 10.

**Summary Measure (Population-level summary):** Difference in the time to symptoms (as defined above) or experiencing ICE 1-3 presented in Table 10 between guselkumab group and the placebo group.

**Intercurrent events and their corresponding strategies:**

The same ICEs and corresponding strategies that are specified for second secondary endpoint of time to disease recurrence will be used.

#### 5.4.1.2.5. Estimand of Steroid Free Clinical Remission at Week 48

**Objective:** To evaluate the efficacy of guselkumab treatment at Week 48 compared with placebo in limiting steroid use and maintaining remission in the postoperative period.

**Estimand Scientific Question of Interest:** What is the proportion of participants achieving steroid free clinical remission at Week 48, and thus considered to have benefited from guselkumab versus placebo?

**Study intervention:**

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

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

**Variable:** A binary variable of steroid free clinical remission at Week 48 (defined as CDAI <150 and no corticosteroids within 30 days) or experiencing ICEs 1-4 in Table 9.

**Summary Measure (Population-level summary):** Difference in proportions of the binary variable of steroid free clinical remission, as described above, between guselkumab group and the placebo group.

**Intercurrent events and their corresponding strategies:**

The same ICEs and corresponding strategies that are specified for primary endpoint of endoscopic recurrence prior to or at Week 48 will be used.

### 5.4.1.3. Analysis Methods

The analyses of the secondary endpoints will be based on the Full Analysis Set (FAS), which includes all randomized participants. Participants will be analyzed according to the intervention group to which they were randomized regardless of the study intervention they actually received.

**Estimators of Clinical Remission at Week 48 without Disease Recurrence**

Summaries of the proportion of participants that achieve clinical remission without disease recurrence by treatment group will be provided. To compare the guselkumab versus placebo group for the first secondary endpoint, the CMH chi-square test (2-sided) will be used with stratification of clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery).

After accounting for the ICE strategies, missing data will be imputed by multiple imputation. Multiple imputation will be used for imputing missing data under the assumption that the data are MAR. The analysis will impute the missing Rutgeerts score at Week 48 using the analysis method

and ancillary variables as described in Table 11. The responses at Weeks 48 will be derived from the imputed datasets and combined for analysis.

**Table 11: Multiple Imputation Methods for CDAI at Weeks 48**

| Variable | MI specification | Analysis method/Summary statistics |
|---|---|---|
| CDAI score at Week 48 | Multiple imputation with monotone regression of total scores | MIdataset1 (N=200, Seed=5748941)<br>• Imputation variables: CDAI at Week 48<br>• Ancillary variables: Treatment group, baseline Rutgeerts score, history of primary non-response to at least one approved ADT (Yes, No), clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery) |

### Estimators of Disease Recurrence

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

### Estimators of Abdominal Pain Free at Week 48

Summaries of the proportion of participants that achieve abdominal pain free by treatment group will be provided. To compare the guselkumab versus placebo group for the first secondary endpoint, the CMH chi-square test (2-sided) will be used with stratification of clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery).

After accounting for the ICE strategies, missing data will be imputed by multiple imputation. Multiple imputation will be used for imputing missing data under the assumption that the data are MAR. The analysis will impute the missing Rutgeerts score at Week 48 using the analysis method and ancillary variables as described in Table 12. The responses at Weeks 48 will be derived from the imputed datasets and combined for analysis.

**Table 12: Multiple Imputation Methods for AP Score at Weeks 48**

| Variable | MI specification | Analysis method/Summary statistics |
|---|---|---|
| AP score at Week 48 | Multiple imputation with monotone regression of total scores | MIdataset1 (N=200, Seed=5748941)<br>• Imputation variables: AP score at Week 48<br>• Ancillary variables: Treatment group, baseline Rutgeerts score, history of primary non-response to at least one approved ADT (Yes, No), clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery) |

### Estimators of Recurrence of Symptoms

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

### Estimators of Steroid Free Clinical Remission at Week 48

Summaries of the proportion of participants that achieve steroid free clinical remission by treatment group will be provided. To compare the guselkumab versus placebo group for the first secondary endpoint, the CMH chi-square test (2-sided) will be used with stratification of clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery).

After accounting for the ICE strategies, missing data will be imputed by multiple imputation. Multiple imputation will be used for imputing missing data under the assumption that the data are MAR. The analysis will impute the missing Rutgeerts score at Week 48 using the analysis method and ancillary variables as described in Table 13. The responses at Weeks 48 will be derived from the imputed datasets and combined for analysis.

**Table 13: Multiple Imputation Methods for CDAI at Weeks 48**

| Variable | MI specification | Analysis method/Summary statistics |
|---|---|---|
| CDAI score at Week 48 | Multiple imputation with monotone regression of total scores | MIdataset1 (N=200, Seed=5748941)<br>• Imputation variables: CDAI at Week 48<br>• Ancillary variables: Treatment group, baseline Rutgeerts score, history of primary non-response to at least one approved ADT (Yes, No), clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery) |

Type I error will be controlled over the primary and secondary endpoints hierarchically. The sequence of tests will be:

1. Endoscopic recurrence prior to or at Week 48
2. Clinical remission without disease recurrence at Week 48
3. Time-to-disease recurrence
4. Abdominal pain free at Week 48
5. Time-to-recurrence of symptoms
6. Steroid free clinical remission at Week 48

## 5.5. Other Endpoint(s) Analysis

### 5.5.1. Definition of Endpoints

- Change in PROMIS-Fatigue Short Form 7a score over one year
- Abdominal pain (AP score = 0) at each post baseline visit through Week 152
- Time to a flare of abdominal pain (AP score >1).
- Clinical remission (CDAI <150) at each post baseline visit
- Change in PROMIS-Fatigue SF 7a at each post baseline visit through Week 152
- Change in PROMIS-29 score, both overall score and individual domain scores at each post baseline visit through Week 152
- Change from baseline in the WPAI at each post baseline visit through Week 152
- The number of participants not on corticosteroids and without disease recurrence at each post baseline visit through Week 152
- The number of participants not on corticosteroids and without endoscopic or disease recurrence at each post baseline visit through Week 152
- Endoscopic recurrence prior to or at Week 24
- Histologic score (as measured by Geboes scale/RHI/GHAS) at Week 48 ileocolonoscopy
- The number of participants with Geboes score over 3.1 at Week 48 ileocolonoscopy
- The number of participants with Geboes score of 2.0 or less at Week 48 ileocolonoscopy
- Clinical remission (CDAI <150) at Week 24 after initiation of guselkumab CCI induction
- Clinical response (CDAI decrease of <100 points or CDAI <150) 24 weeks after initiation of guselkumab SC induction
- Disease recurrence (using definition described in Section 5.4.1) at Week 152
- Fecal calprotectin recurrence, defined by calprotectin of >200 with a 100 µg/g increase over baseline
- The change from baseline in fecal calprotectin concentration at all postbaseline visits through Week 152

- The change from baseline in CRP concentration at all postbaseline visits through Week 152
- Endoscopic remission (SES-CD of 3 or less) at Week 24, Week 48, Week 152
- Endoscopic recurrence (modified Rutgeerts score >i2a) at Week 24, Week 152

**PRO Instruments**

- **PROMIS-29**

  The Patient-Reported Outcomes Measurement Information System (PROMIS)-29 is a validated general health profile instrument that is not disease-specific (Hayes 2018). It is a collection of short forms containing 4 items for each of 7 domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles an activities). They assess all domains over the past seven days except for Physical Function which has no timeframe specified. PROMIS-29 also includes an overall average pain intensity 0-10 numeric rating scale. The raw score of each domain is converted into a standardized score with a mean of 50 and a standard deviation (SD) of 10 (T-Score). The standardized T-score is reported as the final score for each participant. Pain Intensity is presented as raw responses (0-10). Norm-based scores have been calculated for each domain on the PROMIS measures, with a score of 50 representing the mean or average of the reference population. On symptom-oriented domains of PROMIS-29 (anxiety, depression, fatigue, pain interference, and sleep disturbance), higher scores represent worse symptomatology. On the function-oriented domains (physical functioning and social role), higher scores represent better functioning.

- **PROMIS Fatigue-7a**

  The PROMIS Fatigue 7-items Short Form (PROMIS Fatigue Short Form 7a) contains 7 items evaluating fatigue-related symptoms (ie, tiredness, exhaustion, mental tiredness, and lack of energy) and associated impacts on daily activities (ie, activity limitations related to work, selfcare, and exercise) (Ameringer 2016). PROMIS Fatigue Short Form 7a has a recall period of past 7 days. Compared to the fatigue scale of PROMIS-29, PROMIS Fatigue Short Form 7a provides additional information to evaluate severity of fatigue. The raw total score is converted into a standardized score with a mean of 50 and a SD of 10 (T-Score). The standardized T-score is reported as the final score for each participant.

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

  The WPAI-CD is a validated instrument created as a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to CD (Reilly 2008). The WPAI-CD consists of 6 questions to determine employment status, hours missed from work due to CD, hours missed from work for other reasons, hours worked, the degree to which CD affected work productivity while at work, and the degree to which CD affected activities outside of work. Higher scores indicate greater impairment.

### 5.5.2. Analysis Methods

Unless otherwise specified, the exploratory endpoints listed and defined in Section 5.5.1 will be analyzed based on the FAS according to the randomized intervention group regardless of the intervention actually received.

All exploratory endpoints will be tested regardless of the significance of the primary and secondary endpoints; the testing of these endpoints will not be controlled for multiplicity. Nominal p-values will be presented.

Descriptive statistics (ie, N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Frequency counts and percentages will be used to summarize categorical variables. Graphical data displays (eg, line plots) may also be used to summarize the data.

**Binary Endpoints**

The intercurrent events captured for binary endpoints specified in Section 5.3.2 will be applied to each of the above binary endpoints. Participants with ICEs in categories 1-4 will be considered to have unfavored outcome. For participants experiencing an ICE 5 and ICE 6, their observed values will be used, if available.

Participants with any missing data for an endpoint after accounting for the ICEs will be imputed as having unfavored outcome. Binary endpoints will be summarized with the number and frequency of participants who achieve the endpoint by treatment group. Treatment comparisons will be performed using CMH chi-square test stratified by clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery). In case of rare events, the Fisher's exact test will be used for treatment comparisons.

**Time-to-event Endpoints**

The ICEs captured for time-to-event endpoints specified in Section 5.4.1 will be applied to each of the above time-to-event endpoints. Participants with ICEs in categories 1-3 will be considered to have unfavored outcome. For participants experiencing an ICE 4 and ICE 5, their observed values will be used, if available.

Time-to-event endpoints will be summarized with median survival time and interquartile range of survival time by treatment group. Kaplan-Meier curves will be provided for time-to-event endpoints as well. Treatment comparisons will be performed using the log-rank test stratified by clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery).

**Continuous Endpoints**

The ICEs specified as following will be applied to each of the above continuous endpoints, ie, if a participant has an ICE in categories 1-4, last available values will be assigned from the point of ICE onward (i.e., no change from baseline). For participants experiencing an ICE 5 or ICE 6, their observed values will be used, if available. Note that the application of ICE categories 1-4 overrides that of ICE 6 and ICE 6. This means that for a participant with an ICE in categories 1-4 baseline values will be assigned from the point of ICE onward (ie, no change from baseline), regardless of whether the participant has had an ICE 5 or ICE 6.

To account for the missing data for continuous endpoints of change from baseline measured at more than one post-baseline visit (after applying the ICEs), a Mixed-Effect Model Repeated Measures (MMRM) will be used, under the assumption of missing at random (MAR), to test the difference between treatment groups. In MMRM, missing data will not be imputed, but rather missing data will be accounted for through correlation of repeated measures in the model. Additionally, if the MMRM normality assumption is in question, an appropriate transformation may be implemented before fitting the MMRM model.

The explanatory variables of the MMRM model will include treatment group, visit, applicable baseline score, clinical remission status at baseline (CDAI < 150, CDAI ≥ 150), region (North America, Western Europe, rest of world) and number of prior surgeries (1 surgery versus > 1 surgery, with the qualifying surgery counting as 1 surgery), an interaction term of visit with treatment group, and an interaction term of visit with applicable baseline score.

An unstructured covariance matrix for repeated measures within a participant will be used. The F test will use Kenward-Roger's approximation for degree of freedom. In case of lack of convergence, empirical structured covariances will be used in the following order until convergence is reached: 1) Toeplitz, 2) first order Autoregressive Moving Average.

The treatment difference between treatment groups will be estimated by the difference in the least squares means (LSmeans). The 95% 2-sided CI for the differences in LSmeans and p-values will be calculated based on the MMRM.

## 5.6. Other Exploratory Analyses

### 5.6.1. Risk Factor of Endoscopic Recurrence and Disease Recurrence

The analyses to identify risk factor of endoscopic recurrence and disease recurrence will be based on safety analysis set (based on actual intervention received).

All variables in interest will be included in univariate analysis. Univariate logistic regression model will be applied for endoscopic recurrence and univariate Cox proportional regression model will be applied for disease recurrence. The variables that are significantly (p value < 0.1) associated with each endpoint will be included in a full multivariable model for each endpoint. Stepwise selection, based on AIC, will be used to find the subset of variables to form a reduced multivariable model with only significant variable for each endpoint.

Variables in interest are listed as below:

- Second intra-abdominal operation for CD in the past 10 years
- Qualifying surgery was the patient's ≥3 intra-abdominal operation for CD
- Qualifying surgery was performed for a penetrating complication of CD
- Any history of perianal fistulizing CD provided that this has not been active in the 3 months before study start

- Cigarette smoker
- Kono-S anastomosis
- Mesenteric resection
- CD duration before first surgery (< 1 year, 1-10 yrs, > 10 years)
- Location of CD (Montreal L1 vs L2 vs L3 v L4)
- Crohn's phenotype: B3 (penetrating) vs other phenotypes

### 5.6.2. Cross over

The testing of these endpoints will not be controlled for multiplicity and nominal p-values will be provided.

#### 5.6.2.1. Definition of Endpoints

- Clinical remission (CDAI < 150) at 24 weeks after initiation of guselkumab SC induction
- Clinical response (CDAI decrease of <100 points or CDAI <150) at 24 weeks after initiation of guselkumab SC induction
- Endoscopic remission (SES-CD of 3 or less) at 24 weeks after guselkumab SC induction
- Endoscopic remission (modified Rutgeerts score <i2a) at 24 weeks after guselkumab SC induction

#### 5.6.2.2. Analysis Methods

Unless otherwise specified, the exploratory endpoints listed and defined in Section 5.6.2 will be analyzed based on the cross over participants.

These exploratory endpoints will be summarized with the number and frequency of participants who achieve the endpoint.

Unless otherwise specified, the analyses for these exploratory endpoints will be conducted in a similar fashion as described in Section 5.5.2.

## 5.7. Safety Analyses

All safety analyses will be based on the safety analysis set based on actual intervention received, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

### 5.7.1. Extent of Exposure

The exposure data will be summarized through Week 48 and Week 152. The number and percentage of subjects who receive study agents will be summarized by treatment group for the safety analysis set. Descriptive statistics will be presented for the following parameters:

- Number of study agent CCI [redacted] through Week 48.
- Number of study agent CCI [redacted] through Week 152.

For cross over population, additional descriptive statistic will be presented for the following parameter:

- Number of study agent CCI [redacted] from cross over through cross over + Week 24.

### 5.7.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through Week 48 and Week 156, is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered as treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. Average duration of study participation follow-up in weeks will be presented for each summary of AEs. The duration of follow-up in weeks will be defined as [(study discontinuation) – (date of first study intervention) + 1]/7 (including the SFU period after the last study intervention), if participants discontinued study intervention prematurely. The duration of follow-up in weeks will be defined as [(date of Visit 48) – (date of first study intervention) + 1]/7, if participants completed study intervention through Week 48. The duration of follow-up in weeks will be defined as [(date of Visit 156) – (date of first study intervention) + 1]/7, if participants completed study intervention through Week 156. To account for differences in follow-up times, adverse events will also be summarized using events per 100 participant years of follow-up.

The following summaries will be provided for treatment-emergent adverse events:

- Overall summary of AEs, presenting frequencies and types of AEs
- Summary of AEs by system organ class (SOC) and preferred term (PT)
- Summary of SAEs by SOC and PT
- Summary of related to study intervention AEs (as assessed by the investigator) by system organ class and preferred term
  - A related AE is defined as any event with a relationship to study intervention of ‘related’ on the AE eCRF page or if the relationship to study intervention is missing.
- Summary of AEs leading to discontinuation of study intervention by SOC and PT
- Frequency and type of AEs associated with the SMQ Opportunistic Infections (narrow)

- Frequency and type of AE of special interest (AESI):
  - active tuberculosis (TB)
  - newly identified malignancy
- Frequency and type of AEs associated with major adverse cardiovascular events (MACE)
  - Adverse events included as a component of MACE will be death related to cardiovascular event, nonfatal myocardial infraction, nonfatal stroke
- Venous thromboembolism (VTE)
- Frequency and type of AEs associated with drug-related hepatic disorders (refer to Appendix 8)
- Frequency and type of AEs associated with anaphylaxis/serum sickness (refer to Appendix 8)
- Frequency and type of AEs associated with malignancies (refer to Appendix 8)
- Summary of CCI -site reactions as recorded as an CCI -site reaction by the investigator on the eCRF

In addition to the summary tables, listings of participants with SAEs, AEs leading to discontinuation of study intervention, AEs related to study intervention and COVID-19 related AEs will be provided.

Deaths will be listed by actual intervention received, including cause of death and relationship to study intervention.

### 5.7.3. Additional Safety Assessments

#### 5.7.3.1. Clinical Laboratory Tests

The following laboratory tests will be performed during the study and summaries will be provided:

**Protocol-Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | | |
|---|---|---|---|
| Hematology | Platelet count<br>Red blood cell count<br>Hemoglobin<br>Hematocrit | <u>RBC Indices:</u><br>MCV<br>MCH<br>% Reticulocytes | <u>White Blood Cell (WBC) count with Differential:</u><br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| | Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported. | | |

| Laboratory Assessments | Parameters | |
|---|---|---|
| Clinical Chemistry | Sodium<br>Potassium<br>Chloride<br>Bicarbonate<br>Blood urea nitrogen (BUN)<br>Creatinine<br>Glucose [nonfasting]<br>Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic<br>Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic<br>Gamma-glutamyltransferase (GGT) | Total bilirubin<br>Alkaline phosphatase<br>Calcium<br>Phosphate<br>Albumin<br>Total protein<br>Magnesium |
| | Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Appendix 13: Liver Safety.<br><br>A possible Hy's law Case is defined by the occurrence of ALT/AST ≥3 x ULN, alkaline phosphatase (ALP) <2 x ULN together with total bilirubin ≥2 x ULN or International Normalized Ratio (INR) >1.5 (if measured). Any possible Hy's Law case is considered an important medical event and must be reported to the sponsor in an expedited manner, even before all other possible causes of liver injury have been excluded. A confirmed Hy's law case must be reported as a SAE. | |
| Other Screening Tests | • Serum (at screening) and urine Pregnancy Testing (for women of childbearing potential only)<br>• Serology (at screening; HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody, hepatitis B surface antibody [antiHBs], hepatitis B core antibody total [anti-HBc])<br>• TB evaluation (QuantiFERON-Gold) | |

Clinical laboratory test values are to be graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 (Protocol Attachment 10). The laboratory tests not included in NCI-CTCAE tables in Attachment 10 will not be presented in the corresponding tables or listings.

Summaries of clinical laboratory tests by study intervention group over time will be provided for participants in the Safety Analysis Set:

- Summary of maximum NCI-CTCAE toxicity grade for post-baseline laboratory values through Week 48 and through Week 156.
- Shift tables for maximum NCI-CTCAE toxicity grade from baseline through Week 48 and through Week 156 will be summarized for the following lab parameters:
  - Hematology: hemoglobin, platelets, total WBC, absolute lymphocytes, and absolute neutrophils;
  - Chemistry: ALT, AST, alkaline phosphatase, and total bilirubin.
- Summary of maximum post-baseline measurement through Week 48 and through Week 156 for ALT, AST, alkaline phosphatase, and total bilirubin relative to ULN.

- Summary of maximum post-baseline measurement through Week 48 and through Week 156 for ALT, AST, alkaline phosphatase, and total bilirubin relative to ULN among participants taking immunomodulators at baseline.
- Summary of maximum post-baseline elevated liver function tests through Week 48 and through Week 156 by the following categories for ALT, AST, alkaline phosphatase, and total bilirubin relative to ULN:
  - > 1 to ≤ 3 x ULN
  - > 3 to ≤ 5 x ULN
  - > 5 to ≤ 10 x ULN
  - > 10 to ≤ 20 x ULN
  - > 20 x ULN
- Summary of potential Hy's Law case (ALT or AST ≥3 x ULN and total bilirubin ≥2 x ULN or INR >1.5) through Week 48 and through Week 156.
- Box plots of observed laboratory values and change from baseline in laboratory parameters (hematology and chemistry) through Week 48 and through Week 156 will be provided.

Listings of participants with any abnormal post-baseline laboratory values of NCI-CTCAE grade ≥ 2, participants with maximum post-baseline elevated liver function tests (AST or ALT >5xULN) and participants with potential Hy's Law case (ALT or AST ≥3 x ULN and total bilirubin ≥2 x ULN or INR >1.5), will also be provided by study intervention group, participant, and visit.

There will be no imputation for missing laboratory values.

Any laboratory values given as <X.X in the database will be imputed with the value of the number without the sign for the descriptive statistics and the calculation of changes from baseline, eg. a value of <2.2 will be imputed as 2.2 for the calculations.

#### 5.7.3.2. Other Safety Parameters

##### 5.7.3.2.1. The Columbia Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) 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 that defines five subtypes of suicidal ideation and 4 possible suicidal behaviors, as well as non-suicidal self-injurious behavior and completed suicide.

The baseline is defined as the most severe/maximum score at screening and Week 0. Suicidal ideation and behavior based on the electronic Clinical Outcome Assessment (eCoA) C-SSRS findings ≥ 1 and on any C-SSRS finding reported on the AE CRF, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, will be summarized. Number of participants with treatment-emergent events of suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent by worst severity through Week 48 and through Week 156 by ideation/ behavior level will be presented. In addition, summary of change from

baseline to postbaseline worst severity in suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent through Week 48 and through Week 156 will be included. Furthermore, participants with positive postbaseline (C-SSRS findings > 0) ideation and behavior through Week 48 and through Week 156 will be presented in a data listing.

## 5.8. Other Analyses

### 5.8.1. Pharmacokinetics

PK analyses will be performed on the PK Analysis Set.

#### 5.8.1.1. Serum Guselkumab Concentrations

Blood samples for determining the serum guselkumab concentration will be drawn from all participants according to the Schedule of Activities in the Protocol.

Descriptive statistics of the serum guselkumab concentrations will be calculated by intervention group at each visit, including n, arithmetic mean, SD, median, coefficient of variation (%CV), interquartile range, range (minimum and maximum).

The following analyses will be performed:

- Summary of serum guselkumab concentrations by visit through Week 48 (or up to the time of cross over if applicable)
- Summary of serum guselkumab concentrations by visit through Week 152 (or up to the time of cross over if applicable)
- Proportion of participants without detectable serum guselkumab concentration (below the lower limit of quantification) at each visit through Week 48 (or up to the time of cross over if applicable)
- Proportion of participants without detectable serum guselkumab concentration (below the lower limit of quantification) at each visit through Week 152 (or up to the time of cross over if applicable)
- Summary of serum guselkumab concentrations at each visit by baseline body weight (using quartiles) through Week 48 (or up to the time of cross over if applicable)
- Summary of serum guselkumab concentrations at each visit by baseline body weight (using quartiles) through Week 152 (or up to the time of cross over if applicable)

For patients who had a cross over, additional analyses will be performed:

- Summary of serum guselkumab concentrations by visit from cross over through the end of study (including the PK at cross over visit)
- Proportion of participants without detectable serum guselkumab concentration (below the lower limit of quantification) at each visit from cross over through the end of study (including the PK at cross over visit)
- Summary of serum guselkumab concentrations at each visit by baseline body weight (using quartiles) from cross over through the end of study (including the PK at cross over visit)

#### 5.8.1.2. Pharmacokinetic Data Handling Rules

Unless otherwise specified, the following data handling rules will apply to PK analyses:

- Participants will be analyzed according to the intervention that they actually received.
- All serum concentration summaries for a particular time point will include data obtained from treated participants at the timepoint of interest without imputing any missing data.
- A concentration not quantifiable (below the lower limit of quantification) will be treated as 0 in the summary statistics and shown as the lower limit of quantification (< LLOQ) in the data listings.
- The data from a participant who meets any of the following dosing deviation criteria will be excluded from the by-visit data analyses from that point onwards:
  - Discontinued study intervention.
  - Skipped a study intervention administration.
  - Received an incomplete / incorrect dose.
  - Received an incorrect study intervention.
  - Received an additional dose.

Additional samples excluded from the analysis are described as follows:

- Pre-dose samples collected after the study intervention administration at the time of visit
- Pre-dose samples collected before the study intervention administration at Week 0, 4, and 8 that were outside of the visit window +/- 4 days
- Samples collected before the study intervention administration after Week 8 through Week 48 that were outside of the visit window +/- 7 days.

#### 5.8.1.3. Relationship between Pharmacokinetic Concentration and Efficacy

To explore the relationship between guselkumab serum concentrations and the efficacy endpoints, the analyses of the primary and secondary efficacy endpoints by trough concentrations, using quartiles, at Week 16, Week 24 and Week 48 will be presented graphically.

Additional relationships between the serum concentrations and the exploratory efficacy endpoints may be explored graphically.

#### 5.8.1.4. Population Pharmacokinetic Analysis

If sufficient data are available, then population PK analysis using serum concentration-time data of guselkumab will be performed using nonlinear mixed-effects modeling. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

### 5.8.2. Immunogenicity

#### 5.8.2.1. Immunogenicity Analysis

Unless otherwise mentioned, summaries of immunogenicity to guselkumab will be provided based on the Immunogenicity Analysis Set.

Serum samples will be screened for antibodies binding to guselkumab and the titer of confirmed positive samples will be reported.

The incidence and titers of antibodies to guselkumab will be summarized through Week 48 and through Week 152 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 study intervention). The maximum titers of antibodies to guselkumab will be provided for participants who are positive for antibodies to guselkumab. These analyses will also be performed by baseline immunomodulator use (Yes, No).

Separate listings of participants who are positive for antibodies to guselkumab will be provided. The listing will contain intervention group, visit, serum guselkumab concentration at the visit, dose administered, baseline immunomodulators use (Yes or No), CDAI score at the visit, modified Rutgeerts score, SES-CD score at the visit, CCI -site reactions, and antibody status (titer and neutralizing antibodies status) for all visits, and cross over status (Yes or No). In addition, a list of antibodies to guselkumab status in participants who discontinued study intervention early will be provided.

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

#### 5.8.2.2. Other Immunogenicity Analyses

To explore the relationship of antibodies to guselkumab status with serum guselkumab concentrations, and efficacy and safety, the following analyses may be performed as appropriate:

- Summary of median trough serum guselkumab concentrations over time by antibodies to guselkumab status
- Summary of primary and secondary efficacy endpoints by antibodies to guselkumab if sufficient participants have antibodies to guselkumab
- Summary of CCI -site reactions by antibodies to guselkumab status

### 5.8.3. Pharmacodynamics and Biomarkers

Changes in serum protein analytes and whole blood ribonucleic acid (RNA) obtained over time will be summarized by study intervention group. Associations between baseline levels and changes from baseline in select markers and response to study intervention will be explored. The biomarker analyses will characterize the effects of guselkumab to identify biomarkers relevant to study intervention, and to determine if these biomarkers can predict response to guselkumab.

Inflammatory pharmacodynamics markers (CRP and fecal calprotectin) will be evaluated and are discussed in further detail in Appendix 6.3. Analyses of serum biomarkers, whole blood RNA, peripheral blood mononuclear cells, stool biomarkers, and endoscopic biopsy will be reported in separate technical reports.

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.

### 5.8.4. Health Economics

The data collected will be used to conduct exploratory economic analyses based on the FAS. The summaries of health economics will be performed for the main study period.

#### 5.8.4.1. Medical Resource Utilization and Health Economics Data, Associated with Medical Encounters

Medical resource utilization and health economics data associated with medical encounters, will be collected in the CRF throughout the study.

1. Proportion of participants having any CD-related ER/hospitalizations and/or surgeries through Week 48.
2. Summary of duration of CD-related medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient) (total days length of stay, including duration by wards; eg, intensive care unit)
3. Time to first CD-related ER/hospitalization and/or surgeries through Week 48.
4. Summary of duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
5. Proportion of participants having any ER/hospitalizations and/or surgeries through Week 48
6. Time to first ER/hospitalization and/or surgeries through Week 48
7. Proportion of participants with a CD-related surgery through Week 48
8. Time to first CD-related surgery through Week 48
9. Summary of diagnostic and therapeutic tests and procedure by type through Week 48

#### 5.8.4.2. Work Productivity and Activity Impairment-General Health

For the endpoints listed below, analysis will be based on the data as observed and the attributes and strategies for the ICEs will only be applied to Work Productivity and Activity Impairment

Questionnaire-General Health (WPAI-CD) endpoint:

1. Change from baseline in the WPAI at each post baseline visit through Week 152

**WPAI-CD**

The WPAI-CD is a validated instrument created as a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to Crohn's disease. The WPAI-CD consists of 6 questions:

Q1) currently employed (working for pay)? (yes, no) ***If No, skip to Q6.***

Q2) hours missed from work in the past 7 days due to Crohn's disease,

Q3) hours missed in the past 7 days from work for other reasons,

Q4) hours worked in the past 7 days,

Q5 the degree to which Crohn's disease affected work productivity while at work in the past 7 days,

Q6) the degree to which Crohn's disease affected activities outside of work in the past 7 days.

Four scores are derived.

1. percentage of absenteeism: 100*Q2/(Q2+Q4)
2. percentage of presenteeism (reduced productivity while at work): 100*Q5/10
3. an overall work impairment score that combines absenteeism and presenteeism: 100*{Q2/(Q2+Q4) + [(1-Q2/(Q2+Q4)) * (Q5/10)]}
4. percentage of impairment in activities performed outside of work: 100* Q6/10

Higher scores indicate greater impairment.

Note that for participants with answer='No' to Q1, only the 4th score (ie, percent activity impairment outside work due to CD) can be calculated.

### 5.8.5. Definition of Subgroups

The following subgroups will be evaluated for the primary endpoint in this study:

1. Demographics:
   a. Age at baseline (≤ median age, > median age)
   b. Sex (male, female)
   c. Race (Caucasian, non-Caucasian)
   d. Weight at baseline (≤ median body weight, > median body weight)
   e. Center location [Americas (Canada, USA), APAC (Australia, South Korea, Taiwan), EMEA (Austria, Belgium, Czech Republic, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, UK, Serbia, Spain), LATAM (Argentina, Brazil, Mexico)]

2. Baseline disease characteristics:
    a. CD duration (≤ 5 years, > 5 years to ≤ 15 years, or > 15 years)
    b. Involved gastrointestinal areas (ileum, colon, ileum & colon)
    c. number of CD-related prior surgeries (0, 1-2, >2)
    d. CDAI score (<150, ≥ 150)
3. Baseline CD-related concomitant medication usage and tumor necrosis factor (anti-TNF) history:
    a. Oral corticosteroids (receiving, not receiving)
    b. Oral corticosteroids and (6-MP, AZA, or MTX) (receiving, not receiving)
    c. Oral corticosteroids or (6-MP, AZA, or MTX) (receiving, not receiving)
    d. Prior biologic use (Yes, No)
4. Risk factors for recurrence of active CD:
    a. Number of risk factors for recurrence of active CD (1, >1)
    b. The qualifying surgery was the patient's second intra-abdominal operation for CD in the past 10 years (Yes, No)
    c. The qualifying surgery was the patient's third (or more) intra-abdominal operation for CD (Yes, No)
    d. The qualifying surgery was performed for a penetrating complication of CD (ie, an intra-abdominal abscess, internal fistula, sinus tracts or intestinal perforation) (Yes, No)
    e. The patient has any history of perianal fistulizing CD provided that this has not been active in the 3 months prior to study start (Yes, No)
    f. Smoking statue (Y, N)
    g. The patient has Kono-S (antimesenteric functional end-to-end handsewn) (Yes, No)
    h. The patient has mesenterectomy (Yes, No)

# 6. SUPPORTING DOCUMENTATION

## 6.1. Appendix 1 List of Abbreviations

| | |
|---|---|
| ADA | anti-drug antibody |
| AE | adverse event |
| ALT/SGPT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST/SGOT | aspartate aminotransferase |
| ATC | anatomic and therapeutic class |
| AUC | area under the curve |
| BMI | body mass index |
| BSA | body surface area |
| CI | confidence interval |
| CL | total systemic clearance |
| Cmax | maximum concentration |
| CRF | case report form |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | coefficient of variation |
| DMC | Data Monitoring Committee |
| DPS | Data Presentation Specifications |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| F (%) | absolute SC bioavailability |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| iARBM | Integrated Analytical Risk-Based Monitoring |
| ICH | International Conference on Harmonisation |
| IQ | Interquartile |
| IVRS | interactive voice response system |
| IWRS | interactive web response system |
| LLOQ | lower limit of quantification |
| LOCF | last observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRD | minimum required dilution |
| Nab | neutralizing antibodies |
| PD | pharmacodynamic(s) |
| PI | principal investigator |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| QTL | Quality Tolerance Limit |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SMQs | standardised MedDRA queries |
| TEAE | treatment-emergent adverse event |
| Tmax | time to maximum concentration |
| US NCI | United States National Cancer Institute |
| V | volume distribution |
| Vz | volume of distribution based on terminal phase |
| Vz/F | apparent volume of distribution based on terminal phase after extravascular administration |
| WHO | World Health Organization |
| WHO-DD | World Health Organization Drug Dictionary |

## 6.2. Appendix 2 Changes to Protocol-Planned Analyses

## 6.3. Appendix 3 Demographics and Baseline Characteristics

Table 14 and Table 15 present the list of the demographic and baseline Crohn's disease variables that will be summarized by treatment group, and overall for the FAS.

**Table 14: Demographic Variables**

| **Continuous Variables** | **Summary Type** |
|---|---|
| Age (years) | Frequency distribution with the number and percentage of participants in each category. |
| Weight (kg) | |
| Height (cm) | |
| BMI (kg/m$^2$) | |
| **Categorical Variables** | |
| Sex (male, female, unknown, undifferentiated) | |
| Race[a] (American Indian or Alaska Native, Asian (Japanese or Other Asian), Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple) | |
| Ethnicity (Hispanic or Latino, not Hispanic or Latino) | |
| Region (North America, Western Europe, rest of world) | |
| Tobacco or nicotine use (non-user, prior user, current user) | |
| Alcohol use (never used, current user, former user) | |

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

**Table 15: Baseline Disease Characteristic Variables**

| **Continuous Variables** | **Summary Type** |
|---|---|
| Crohn's disease duration (years) | Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range). |
| CDAI score | |
| PRO-2 score (weighted sum of AP and SF subscores of CDAI) | |
| Days from surgery to randomization | |
| IBDQ | |
| CRP | |
| Fecal Calprotectin | |
| **Categorical Variables** | Frequency distribution with the number and percentage of participants in each category. |
| Crohn's disease complications (Intra-abdominal abscess, sinus tracts/perforations, fistula, structuring complications of CD, total or sub-total colectomy, partial bowel resection, perianal surgery, other CD related surgery, total parenteral nutrition) | |
| Involved GI areas (Ileum, Colon, Ileum and Colon) | |
| Previous ADTs (1, 2, > 2) | |
| Primary nonresponse to at least one approved ADT (yes, no) | |
| Secondary nonresponse to at least one approved ADT (yes, no) | |
| Intolerance to at least one approved ADT (yes, no) | |
| PRO-2 score [Stool frequency ≥ 4 and Abdominal pain ≥ 2, Stool frequency ≥ 4 and Abdominal pain < 2, Stool frequency < 4 and Abdominal pain ≥ 2] | |
| Fecal calprotectin > 250 mg/kg | |
| CRP >3 mg/L | |
| Fecal calprotectin > 250 mg/kg and CRP >3 mg/L | |

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

## 6.4. Appendix 4 Protocol Deviations and Quality Tolerance Limits (QTL)

In general, the following list of major protocol deviations (PDs) may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock.

The following categories will be considered as major PDs:

- Received wrong treatment or incorrect dose
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Developed withdrawal criteria but not withdrawn
- Other
  - Didn't cross over when met the cross over criteria
  - Cross over when not met the cross over criteria

Participants with a major protocol deviation through Week 48 will be summarized by category based on the FAS. A listing of participants who have major protocol deviations will be provided.

Participants having irregularities in study intervention administration will be summarized in more detail using sub-categories identified prior to unblinding (eg, participant receives study intervention administration outside of protocol window). In addition, participants with study intervention administration irregularities will be listed.

A listing of participants with protocol deviations related to COVID-19 by center and by category (major PD, minor PD) will be provided.

Quality Tolerance Limit (QTL) parameters and thresholds are defined and will be monitored in this study. QTL parameters will be summarized. More details are described in the Integrated Analytical Risk-Based Monitoring (iARBM) Plan.

## 6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the [World Health Organization Drug Dictionary (WHO-DD)]. Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of CD concomitant medications will be presented by ATC term and intervention group. Prior medications will be summarized by ATC term and intervention.

Summaries of CD medication history for the FAS will be summarized by treatment group:

- Summary of Concomitant Medications for CD at Baseline
  - Participants with 1 or more concomitant medications for CD (n, %)
  - Aminosalicylates (n, %)
  - Antibiotics (n, %)
  - Corticosteroids (including budesonide and beclomethasone dipropionate) (n, %)
  - Corticosteroids P.Eq dose (excluding budesonide and beclomethasone dipropionate) (mg/day)
  - Budesonide dose (mg/day)
  - Beclomethasone dirpropionate dose (mg/day)
  - Corticosteroids (duration of use)
  - Immunomodulators (6-MP/AZA/MTX) (duration of use)
  - Biologics (Infliximab, Adalimumab, Certolizumab Pegol, Vedolizumab, Ustekinumab, Risankizumab, biosimilars of Infliximab and Adalimumab)
- Summary of TNF Antagonist Therapy History by Number of TNF Antagonists (1, 2, 3) Received
  - Participants with inadequate initial response, loss of response, or intolerance to TNF antagonist
  - Participants with inadequate initial response to TNF antagonist
  - Participants with response followed by loss of response to TNF antagonist
  - Participants with intolerance to TNF antagonist
- Summary of Biologic Therapy History by Biologic (Infliximab, Adalimumab, Certolizumab Pegol, Vedolizumab, Ustekinumab, Risankizumab, biosimilars of Infliximab and Adalimumab)
  - Participants with inadequate initial response, loss of response or intolerance to biologic therapy
  - Participants with inadequate initial response to biologic therapy

  - Participants with response followed by loss of response to biologic therapy
  - Participants with intolerance to biologic therapy
- Summary of CD-related Non-biologic Medication History (History of Response to or Intolerance of Corticosteroids or 6-MP/AZA/MTX)
  - Participants with inadequate response, intolerance, or dependence
  - Participants with inadequate response
  - Participants intolerant
  - Participants dependent
- Summary of CD-related Biologic Medication History
  - Primary response, secondary nonresponse, or intolerance to
    - At least one anti-TNF
    - ≥ 2 anti-TNFs
    - Anti-TNF only
    - Ustekinumab
    - Ustekinumab only
    - Ustekinumab and at least one other biologic
    - Vedolizumab
    - Vedolizumab only
    - Vedolizumab and at least one other biologic
    - Risa
    - Risa only
    - Risa and at least one other biologic

## 6.6. Appendix 6 Medical History

A summary of medical history of interest, as well as a summary of CD history and CD conditions of interest, and smoking status will be summarized for the FAS.

## 6.7. Appendix 7 Intervention Compliance

Randomized treatment versus actual treatment will be summarized using the FAS.

The doses in mg will be calculated based on administered volume (the actual volume administered after accounting for priming and flushing) as follows:

- For Placebo:
  - For induction dosing at Week 0:
    - CCI 1: dose [mg] = (administered volume [mL]/1 mL) x 0 mg
    - CCI 2: dose [mg] = (administered volume [mL]/1 mL) x 0 mg
  - For maintenance dosing starting at Week 8 then CCI through Week 144:
    - CCI 1: dose [mg] = (administered volume [mL]/1 mL) x 0 mg
- For Guselkumab:
  - For induction dosing at Week 0:
    - CCI 1: dose [mg] = (administered volume [mL]/1 mL) x 100 mg
    - CCI 2: dose [mg] = (administered volume [mL]/1 mL) x 100 mg
  - For maintenance dosing starting at Week 8 then CCI through Week 144:
    - CCI 1: dose [mg] = (administered volume [mL]/1 mL) x 100 mg

## 6.8. Appendix 8 Adverse Events of Special Interest

Any newly identified:

- clinically significant infection - tuberculosis (TB) events, invasive fungal infections, and hepatitis B reactivation
- newly identified malignancy
- hypersensitivity reaction
- congestive heart failure
- demyelinating disorders
- lupus-like syndrome

after the first study intervention administration are considered as AESI.

- Malignancy will be identified as AEs where the preferred perm is featured in the global Standardized MedDRA Queries (SMQ) dataset is SMQ='MALIGNANCIES (SMQ)' and SUB_SMQ1='MALIGNANT TUMOURS (SMQ)'

The following AEs will be identified and summarized as described in Section 5.7.2:

- Drug-related hepatic disorders will be identified by SMQs (narrow) MedDRA version 24.1 or current available version:
  - Select AE terms from dictionary with smq = "HEPATIC DISORDERS (SMQ)" and sub_smq1="DRUG RELATED HEPATIC DISORDERS - COMPREHENSIVE SEARCH (SMQ)" and scope="NARROW"

Identification of other AEs:

- AEs associated with anaphylaxis/serum sickness
  - AEs with one of the following dictionary-derived term in ADAE ADaM dataset, variable ADAE.AEDECOD:
    - ANAPHYLACTIC REACTION
    - ANAPHYLACTIC SHOCK
    - ANAPHYLACTOID REACTION
    - ANAPHYLACTOID SHOCK
    - TYPE I HYPERSENSITIVITY
    - "SERUM SICKNESS"
    - "SERUM SICKNESS-LIKE REACTION"

## 6.9. Appendix 9 Medications of Special Interest

The following will be considered as prohibited changes in CD medications for the ICE category 2 for all estimands:

1. Prohibited medications initiated after Week 0:

- Immunomodulatory agents except for AZA, 6-MP, or MTX (including, but not limited to, 6-thioguanine, cyclosporine, mycophenolate mofetil, tacrolimus, and sirolimus).
- Advanced therapy agents (including, but not limited to, additional TNFα antagonists, antiIL23 medications, natalizumab, ustekinumab, vedolizumab, rituximab).
- All experimental vaccines and medications, including those for CD (including, but not limited to upadacitinib, filgotinib, ozanimod, etrolizumab, and andecaliximab).
- Thalidomide or related agents.
- Total or partial parenteral nutrition
- IV and intramuscular corticosteroids
- Oral corticosteroids dose at a prednisone-equivalent dose above 20 mg/day, or 6 mg/day of budesonide, or 5 mg/day beclomethasone dipropionate.
- Live vaccines
- Participants must not receive guselkumab outside of the protocol or participate in any other clinical study with an investigational agent while in this study. Prior to termination of study participation, participants should complete evaluations for an ED visit.

2. Corticosteroids initiated or doses changed based on medical necessity as assessed by the investigator:

- Initiation of oral corticosteroids (including budesonide and beclomethasone dipropionate) due to worsening of CD.
- Increase in the dose of oral corticosteroids (including budesonide and beclomethasone dipropionate) above the baseline dose due to worsening of CD.
- Initiation of oral corticosteroids (including budesonide and beclomethasone dipropionate) due to reasons other than worsening CD for more than 28 days cumulatively between Week 0 and Week 48.
- Increase in the dose of oral corticosteroids (including budesonide and beclomethasone dipropionate) above the baseline dose due to reasons other than worsening of CD for more than 28 days cumulatively between Week 0 and Week 48.

3. Immunomodulator agents initiated from Week 0 through Week 48 or doses changed based on medical necessity as assessed by the investigator:

- Initiation of oral 6-MP/AZA due to worsening of CD.
- Initiation of oral, subcutaneous, or intramuscular MTX due to worsening of CD.
- Increase in the dose of oral 6-MP/AZA above the baseline dose due to worsening of CD.

- Increase in the dose of oral, subcutaneous, or intramuscular MTX above the baseline dose due to worsening of CD (within the same route).
- Any switch between 6-MP/AZA and MTX due to worsening of CD.

4. Antibiotics

- Initiation or change of antibiotics due to worsening CD.

## 6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Text in gray italic in the table is present in the grading scale, but is not applied by Janssen when grading lab data.

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Janssen implementation notes |
|---|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | | | |
| Anemia | Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L | Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L | Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated* | *Life-threatening consequences; urgent intervention indicated* | Clinical signs and symptoms are not taken into consideration for grading. |
| Leukocytosis | - | - | >100,000/mm3; >100 x 10e9 /L | *Clinical manifestations of leucostasis; urgent intervention indicated* | Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L) |
| **Investigations** | | | | | |
| Activated partial thromboplastin time prolonged | >ULN - 1.5 x ULN | >1.5 - 2.5 x ULN | >2.5 x ULN; *bleeding* | - | Clinical signs and symptoms are not taken into consideration for grading. |
| Alanine aminotransferase increased | >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal | >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal | >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal | Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied. |
| Alkaline phosphatase increased | >ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal | >2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal | >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal | Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied. |
| Aspartate aminotransferase increased | >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal | >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal | >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal | Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied. |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Janssen implementation notes |
|---|---|---|---|---|---|
| Blood bilirubin increased | >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal | >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal | >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal | >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal | Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied. |
| CD4 lymphocytes decreased | <LLN - 500/mm3; <LLN - 0.5 x 10e9 /L | <500 - 200/mm3; <0.5 - 0.2 x 10e9 /L | <200 - 50/mm3; <0.2 x 0.05 - 10e9 /L | <50/mm3; <0.05 x 10e9 /L | |
| Cholesterol high | >ULN - 300 mg/dL; >ULN - 7.75 mmol/L | >300 - 400 mg/dL; >7.75 - 10.34 mmol/L | >400 - 500 mg/dL; >10.34 - 12.92 mmol/L | >500 mg/dL; >12.92 mmol/L | |
| CPK increased | >ULN - 2.5 x ULN | >2.5 x ULN - 5 x ULN | >5 x ULN - 10 x ULN | >10 x ULN | |
| Creatinine increased | Creatine Kinase >ULN - 1.5 x ULN | Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN | Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN | Creatine Kinase >6.0 x ULN | |
| Fibrinogen decreased | <1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline | <0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline | <0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline | <0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL | Ranges defined for "abnormal" are applied only on values < LLN. Grade 0 will be assigned to values > ULN. |
| GGT increased | >ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal | >2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal | >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal | Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied. |
| Haptoglobin decreased | <LLN | - | - | - | |
| Hemoglobin increased | Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L | Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L | Increase in >4 g/dL; Increase in >40 g/L | - | The increase indicates the level of increase above normal (above ULN). Applied as, e.g. grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L). |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Janssen implementation notes |
|---|---|---|---|---|---|
| INR increased | >1.2 - 1.5;<br>*>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated* | >1.5 - 2.5;<br>*>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated* | >2.5;<br>*>2.5 x baseline if on anticoagulation; bleeding* | - | Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading. |
| Lipase increased | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN;<br>*>2.0 - 5.0 x ULN and asymptomatic* | >2.0 - 5.0 x ULN with signs or symptoms;<br>*>5.0 x ULN and asymptomatic* | >5.0 x ULN and with signs or symptoms | "Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied. |
| Lymphocyte count decreased | <LLN - 800/mm3;<br><LLN - 0.8 x 10e9/L | <800 - 500/mm3;<br><0.8 - 0.5 x 10e9 /L | <500 - 200/mm3;<br><0.5 - 0.2 x 10e9 /L | <200/mm3;<br><0.2 x 10e9 /L | |
| Lymphocyte count increased | - | >4000/mm3 - 20,000/mm3;<br>>4 - 20 x 10e9 /L | >20,000/mm3;<br>>20 x 10e9 /L | - | Added ranges in SI unit (x 10e9 /L). |
| Neutrophil count decreased | <LLN - 1500/mm3;<br><LLN - 1.5 x 10e9 /L | <1500 - 1000/mm3;<br><1.5 - 1.0 x 10e9 /L | <1000 - 500/mm3;<br><1.0 - 0.5 x 10e9 /L | <500/mm3;<br><0.5 x 10e9 /L | Both Neutrophils and segmented neutrophils are graded using these criteria. |
| Platelet count decreased | <LLN - 75,000/mm3;<br><LLN - 75.0 x 10e9 /L | <75,000 - 50,000/mm3;<br><75.0 - 50.0 x 10e9 /L | <50,000 - 25,000/mm3;<br><50.0 - 25.0 x 10e9 /L | <25,000/mm3;<br><25.0 x 10e9 /L | |
| Serum amylase increased | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN;<br>*>2.0 - 5.0 x ULN and asymptomatic* | >2.0 - 5.0 x ULN *with signs or symptoms;*<br>*>5.0 x ULN and asymptomatic* | >5.0 x ULN *and with signs or symptoms* | "Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied. |
| White blood cell decreased | <LLN - 3000/mm3;<br><LLN - 3.0 x 10e9 /L | <3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L | <2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L | <1000/mm3;<br><1.0 x 10e9 /L | |
| **Metabolism and nutrition disorders** | | | | | |
| Acidosis | pH <normal, but >=7.3 | - | pH <7.3 | *Life-threatening consequences* | pH <normal is implemented as pH <LLN.<br>Clinical signs and symptoms are not taken into consideration for grading. |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Janssen implementation notes |
|---|---|---|---|---|---|
| Alkalosis | pH >normal, but <=7.5 | - | pH >7.5 | *Life-threatening consequences* | pH >normal is implemented as pH >ULN.<br>Clinical signs and symptoms are not taken into consideration for grading. |
| Hypercalcemia | Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L;<br><br>Ionized calcium >ULN - 1.5 mmol/L | Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L;<br><br>Ionized calcium >1.5 - 1.6 mmol/L;<br><br>*Symptomatic* | Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L;<br><br>Ionized calcium >1.6 - 1.8 mmol/L;<br><br>*hospitalization indicated* | Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L;<br><br>Ionized calcium >1.8 mmol/L;<br><br>*life-threatening consequences* | Clinical signs and symptoms are not taken into consideration for grading.<br>Note: For Hypercalcemia or Hypocalcemia in the CTCAE Lab Toxicity grading scale, the reference ranges from serum calcium (ULN /LLN) from the local or central lab are being utilized. |
| Hyperkalemia | Potassium >ULN - 5.5 mmol/L | Potassium >5.5 - 6.0 mmol/L;<br>*intervention initiated* | Potassium >6.0 - 7.0 mmol/L;<br>*hospitalization indicated* | Potassium >7.0 mmol/L;<br>*life-threatening consequences* | Clinical signs and symptoms are not taken into consideration for grading. |
| Hypermagnesemia | Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L | - | Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L | Magnesium >8.0 mg/dL; >3.30 mmol/L;<br>*life-threatening consequences* | Clinical signs and symptoms are not taken into consideration for grading. |
| Hypernatremia | Sodium >ULN - 150 mmol/L | Sodium >150 - 155 mmol/L;<br>*intervention initiated* | Sodium >155 - 160 mmol/L;<br>*hospitalization indicated* | Sodium >160 mmol/L;<br>*life-threatening consequences* | Clinical signs and symptoms are not taken into consideration for grading. |
| Hypertriglyceridemia | Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L | Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L | Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L | Triglycerides >1000 mg/dL; >11.4 mmol/L;<br>*life-threatening consequences* | Clinical signs and symptoms are not taken into consideration for grading. |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Janssen implementation notes |
|---|---|---|---|---|---|
| Hypoalbuminemia | Albumin <LLN - 3 g/dL; <LLN - 30 g/L | Albumin <3 - 2 g/dL; <30 - 20 g/L | Albumin <2 g/dL; <20 g/L | *Life-threatening consequences; urgent intervention indicated* | Clinical signs and symptoms are not taken into consideration for grading. |
| Hypocalcemia | Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L;<br><br>Ionized calcium <LLN - 1.0 mmol/L | Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L;<br><br>Ionized calcium <1.0 - 0.9 mmol/L;<br><br>*Symptomatic* | Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L;<br><br>Ionized calcium <0.9 - 0.8 mmol/L;<br><br>*hospitalization indicated* | Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L;<br><br>Ionized calcium <0.8 mmol/L;<br><br>*life-threatening consequences* | Clinical signs and symptoms are not taken into consideration for grading.<br>Note: For Hypercalcemia or Hypocalcemia in the CTCAE Lab Toxicity grading scale, the reference ranges from serum calcium (ULN /LLN) from the local or central lab are being utilized. |
| Hypoglycemia | Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L | Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L | Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L | Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures* | Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded. |
| Hypokalemia | *Potassium <LLN - 3.0 mmol/L* | *Symptomatic with* Potassium <LLN - 3.0 mmol/L; intervention indicated | Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated* | Potassium <2.5 mmol/L; *life-threatening consequences* | "Symptomatic" ranges are applied for grade 2, grade 1 not assigned, i.e. worst case applied.<br>Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4. |
| Hypomagnesemia | Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L | Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L | Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L | Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences* | Clinical signs and symptoms are not taken into consideration for grading. |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Janssen implementation notes |
|---|---|---|---|---|---|
| Hyponatremia | Sodium <LLN - 130 mmol/L | *Sodium 125-129 mmol/L and asymptomatic* | *Sodium 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms*<br><br>Sodium <130-120 mmol/L | Sodium <120 mmol/L; *life-threatening consequences* | Clinical signs and symptoms are not taken into consideration for grading.<br>Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used. |
| **Renal and urinary disorders** | | | | | |
| Proteinuria | 1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs; urinary protein ≥ULN - <1000 mg/day | **Adult:**<br>2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; urinary protein 1000 - <3500 mg/day<br><br>**Pediatric:**<br>Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9; Urine P/C (Protein/Creatinine) 56.5 – 214.7 g/mol | **Adult:**<br>4+ proteinuria; urinary protein >=3.5 g/24 hrs; urinary protein >=3500 mg/day;<br><br>**Pediatric:**<br>Urine P/C (Protein/Creatinine) ratio >1.9; Urine P/C (Protein/Creatinine) >214.7 g/mol | - | In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine collection take precedence over dipstick.<br>Added ranges in SI unit for urinary protein (mg/day) and for urine P/C (g/mol).<br>Pediatric grading is applied to age range [0-18]. Adult grading is applied for ages [>18]. |

* Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.

## 6.11. Appendix 11 Imputation Rule

- Partial AE onset dates will be imputed as follows:

If the onset date of an adverse event is missing day only, it will be set to:

- First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study intervention start.
- The day of study intervention start, if the month/year of the onset of AE is the same as month/year of the study intervention start and month/year of the AE resolution date is different.
- The day of study intervention start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study intervention start date and month/year of the AE resolution date are same.

If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:

- January 1 of the year of onset, as long as this date is on or after the study intervention start date.
- Month and day of the study intervention start date, if this date is the same year that the AE occurred.
- Last day of the year if the year of the AE onset is prior to the year of the study intervention start date.

  Completely missing onset dates will not be imputed.
- Partial AE resolution dates not marked as ongoing will be imputed as follows:
  - If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
  - If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.

  Completely missing resolution dates will not be imputed.

- AE onset/resolution dates with missing times will be imputed as follows:
  - A missing time of onset of an adverse event will be set to the earlier of:
    - 00:01 as long as the onset date is after the study intervention start date
    - The time of the study intervention start if this is the same day the AE occurred.
- The missing time of resolution of an adverse event will be set to 23:59.

  If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

## 6.12. Appendix 12 CDAI

### 6.12.1. Partial CDAI Score Calculation Logic

- **Pre-Calculation Logic**

  **Step 1: Determine if a Partial CDAI total score can be calculated**.

  Sufficient CDAI Daily Diary data/components. CDAI score components are defined as:

  – CDAI Daily Diary (participant diary) components:

    1. Number of liquid or soft stools each day for seven days
    2. Abdominal pain each day for seven days
    3. General well-being each day for seven days
    4. Fever (Yes/No)
    5. Anti-diarrhea medication (Yes/No)

  **For CDAI Daily Diary components, if there is not enough data in the previous 7 days (a minimum of 4 days of eligible diary data), then Partial CDAI total score cannot be calculated.**

### 6.12.2. CDAI Score Calculation Logic

- **Pre-Calculation Logic**

  **Step 1: Determine if a CDAI total score can be calculated.**

  Sufficient CDAI Daily Diary data/components AND CDAI Site Form completion for the current visit is required to calculate a total CDAI Score. CDAI score components are defined as:

  – CDAI Daily Diary (participant diary) components:

    6. Number of liquid or soft stools each day for seven days
    7. Abdominal pain each day for seven days
    8. General well-being each day for seven days
    9. Fever (Yes/No)
    10. Anti-diarrhea medication (Yes/No)

  – CDAI Site Form (site worksheet) components:

    1. Manifestations (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum/aphthous stomatitis, anal fissure, fistula or abscess and other fistula)
    2. Abdominal mass evaluation
    3. Hematocrit
    4. Weight

**For CDAI Daily Diary components, if there is not enough data in the previous 7 days (a minimum of 4 days of eligible diary data), then CDAI total score cannot be calculated. For CDAI Site Form components, if the CDAI Site Form has not been completed (and synced) on the tablet for the current visit, then CDAI score cannot be calculated.**

**Step 2: Determine if there is missing data for the CDAI Evening Diary components**:

- For the current visit's CDAI Site Form, if the site user enters bowel preparation and video ileocolonoscopy dates (required if they answered, 'Yes' to "Has the participant had a video ileocolonoscopy since their last site visit?") (CDAI Site Form questions ebf0226f-b3a0-433a-82a7-aefd0e510c93_Question and 422e412e-1189-4b32-bcef-b7481d90dec9_Question), then any diary entries (if in the previous 7 days) between and including those 2 dates entered should be ineligible for the current calculation.
- A minimum of 4 days of diary data entry is required for components from the participant's CDAI Evening Diary in the 7 days prior to the current visit activation date.

### 6.12.3. CDAI Score Calculation

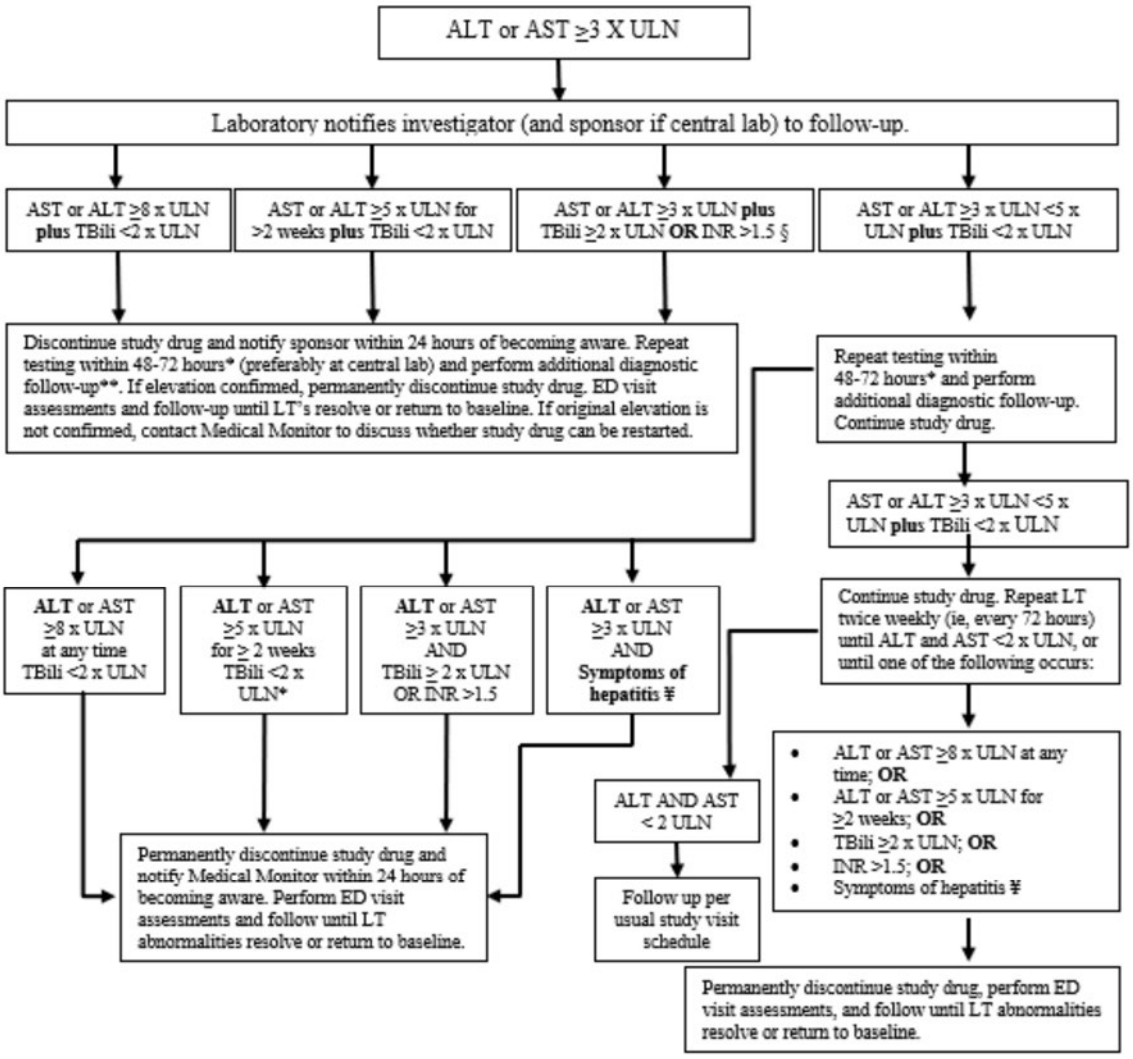
Has the participant had a video ileocolonoscopy since the last site visit? Yes/no
If yes,
Date of video ileocolonoscopy: _____
Date of the start of the bowel preparation: _____

| DISEASE ACTIVITY INDEX | SUM | XFACTOR | 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):<br>0 = none 2 = moderate<br>1 = mild 3 = severe | _____ | x 5 = | _____ |
| Sum general well-being ratings (total for previous 7 days):<br>0 = generally well 3 = very poor<br>1 = slightly under par 4 = terrible<br>2 = poor | _____ | x 7 = | _____ |
| Categories currently present and presumed to be related to Crohn's disease: 0 = no; 1 = yes | | | |
| □ = arthritis/arthralgia | _____ | x 20 = | _____ |
| □ = iritis/uveitis | _____ | x 20 = | _____ |
| □ = erythema nodosum/pyoderma gangrenosum/aphthous stomatitis | _____ | x 20 = | _____ |
| □ = anal fissure, fistula or abscess | _____ | x 20 = | _____ |
| □ = other fistula | _____ | x 20 = | _____ |
| □ = fever over 100° F (37.8° C) during the previous 7 days. | _____ | x 20 = | _____ |
| During the previous 7 days has subject received antidiarrheal or opiate medications for diarrhea at least once:<br>0 = no<br>1 = yes | _____ | x 30 = | _____ |
| Abdominal mass:<br>0 = none 2 = questionable 5 = definite | _____ | x 10 = | _____ |
| Hematocrit:<br>Males: (47-Hct) = SUM<br>Females: (42-Hct) = SUM | _____ (add or subtract by sign) | x 6 = | _____ |
| (Standard Weight - Actual Body Weight) / Standard Weight x 100 = | _____* (add or subtract by sign, round to 3 decimal places) | x 1 = | _____ |

* 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)

## 6.13. Appendix 13: Liver Safety: Suggested Actions and Follow-up Assessments




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

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

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

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

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

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

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

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

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

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

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

7. Based on potential baseline confounders of the disease target population consider (optionally): gamma-glutamyl transferase (to confirm the liver origin of elevated ALP levels), serum creatine phosphokinase (to confirm the liver origin of elevated AST levels], lactate dehydrogenase (to help exclude hemolysis), glutamate dehydrogenase (if muscle injury is suspected or if muscle disease is target population).
8. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including antinuclear antibody, anti-liver kidney microsomal antibody type 1, anti-liver-kidney microsomal antibodies, anti-smooth muscle antibodies (to screen for additional immune-related etiologies), erythrocyte sedimentation rate, and CRP (to screen for potential systemic inflammatory causes).
9. If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions below), then gamma-glutamyl transferase, anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/total iron binding capacity and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If patient is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.

**Patterns of DILI Based on Elevations of Liver Tests**

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

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

    A liver biopsy may be considered:

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

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