Janssen Research & Development

Statistical Analysis Plan

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

Protocol CNTO1959CRD3001; Phase 2/3

Phase 2 (GALAXI 1), Long-term Extension, including Week 152 DBL, Week 192 DBL and Final Analysis DBL Amendment

CNTO1959 (guselkumab)

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

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	8 June 2021	Not Applicable	Initial release
2	21 October 2022	Include Week 152 DBL analysis plan. Week 96 analyses are retained and remain unchanged in general. However, Week 96 table shells have been deleted as they belong in the DPS. The objective of the W152 DBL has been updated compared to the W96 DBL. Efficacy endpoints for the W152 DBL remain largely similar to those for the W96 DBL but with additional time points added, and some deletions and additions. Treatment Failure terminology has been replaced as Intercurrent Events. There are some changes to the Safety analyses in general for the W152 DBL compared to the W96 DBL. The RLPH substudy section has been revised for the W152 DBL compared to the W96 DBL including analysis set definitions and the addition of Safety analysis definitions.	
3	26 May 2023	Include Week 192 DBL analysis plan. The objective of the W192 DBL has been updated compared to the W152 DBL. Efficacy endpoints for the W192 DBL remain largely similar to those for the W152 DBL but with additional time points added, and some deletions. There are some changes to the Safety analyses in general for the W192 DBL compared to the W152 DBL. The scope of safety analyses for the RLPH substudy has been clarified.	
4		Include Final Analysis DBL analysis plan. Efficacy endpoints for the Final Analysis DBL remain largely similar to those for the W192 DBL but with additional time points added, and a few additions. There are some additions to the Safety analyses for the Final Analysis DBL compared to the W192 DBL.	

1. INTRODUCTION

The protocol CNTO1959CRD3001 is a Phase 2/3 clinical development program that is comprised of 3 independent studies. Study 1 (GALAXI 1) represents the Phase 2 portion of the protocol, while Study 2 (GALAXI 2) and Study 3 (GALAXI 3) represent the Phase 3 portion of the protocol.

At Week 48 of GALAXI 1, all participants who, in the opinion of the investigator, will continue to benefit from treatment, are eligible to enter the LTE to receive approximately 4 additional years of treatment, during which time the longer-term efficacy and safety of guselkumab will be evaluated. This Statistical Analysis Plan (SAP) contains definitions of analyses sets, derived variables and statistical methods for all planned analyses for the Long-Term Extension (LTE) portion of GALAXI 1 and specifically outlines the analyses planned at Week 96 and Week 152 of the LTE. The planned analyses for GALAXI 2 and GALAXI 3, as well as for GALAXI 1 through Week 48 are covered under separate SAPs.

1.1. Objectives

The protocol did not specify objectives relative to the long-term extension data. However, the Sponsor has identified the key long-term extension objectives as follows:

- To evaluate long term efficacy of clinical and endoscopic outcomes
- To evaluate long-term safety
- To evaluate the benefit of treatment adjustment for participants with inadequate response between Week 52 through Week 80
- To evaluate the ability of participants or their caregivers to perform guselkumab administration with either the 2.0 mL PFS-UltraSafe Plus (PFS-U) or 2.0 mL YpsoMate autoinjector (PFS-Y) in the standard of care setting (eg, at home or in the clinic), and to assess the reliability of each drug-device
- To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of guselkumab therapy, including changes in C-reactive protein (CRP) and fecal calprotectin
- To evaluate the impact of guselkumab on health-related quality of life (HRQOL) and health economics outcome measures
- To evaluate the efficacy of guselkumab on histologic improvement

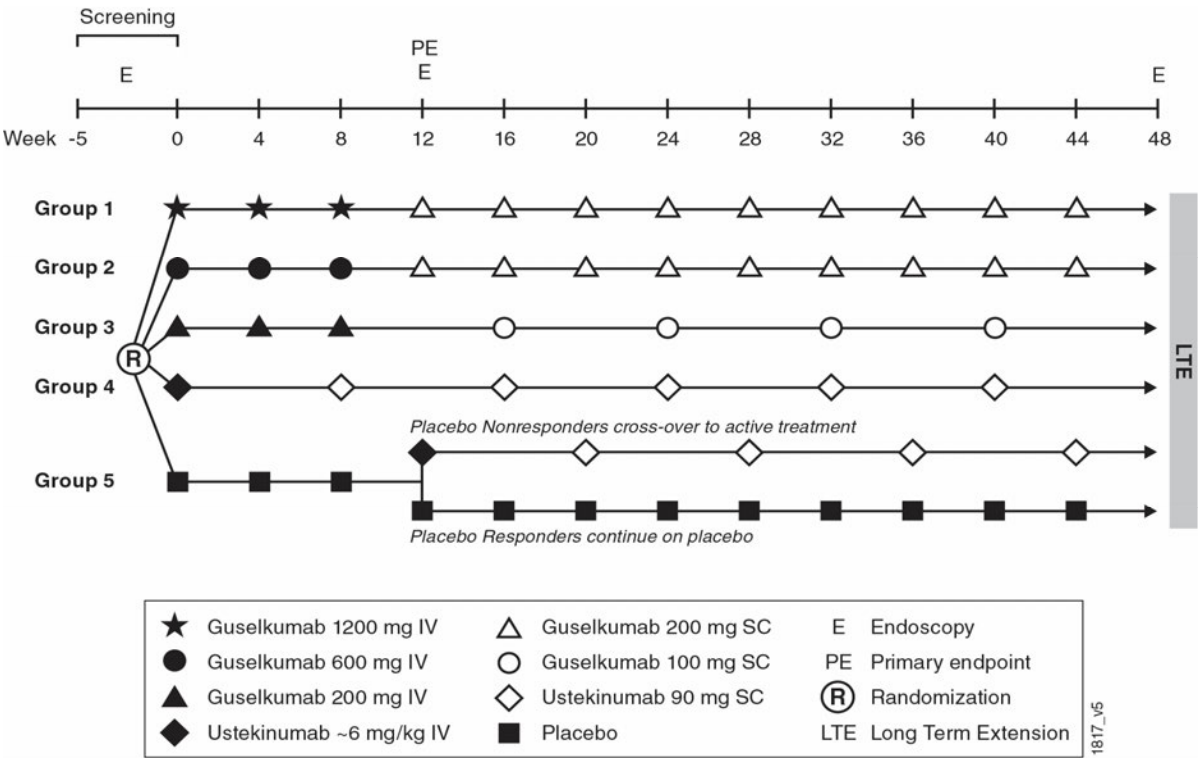
1.2. Study Design

The clinical development program for guselkumab in Crohn's disease will be conducted under a single protocol: a Phase 2/3, randomized, double-blind, placebo- and active-controlled (ustekinumab), parallel-group, multicenter protocol to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active Crohn's disease who have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy. The study design for GALAXI 1 is described below. In GALAXI 1, ustekinumab was designed as a reference arm. In GALAXI 2/3, ustekinumab is an active comparator.

Induction and Maintenance Phase

At Week 0, participants will be randomized in a 1:1:1:1:1 ratio to receive 1 of 3 dose regimens of guselkumab, ustekinumab, or placebo. Participants will be allocated to a treatment group using a permuted block randomization with baseline CDAI score (≤ 300 or > 300) and prior BIO-Failure status (Yes/No) as the stratification variables. A minimum of 25% and a maximum of 50% of the total enrolled population will be CON-Failure participants. In addition, a maximum of 10% of the total enrolled population will have baseline scores for SES-CD < 4 (ie, for participants with isolated ileal disease), or SES-CD < 7 (ie, for participants with colonic or ileocolonic disease). Allocation to treatment group will be performed using a central randomization center by means of an interactive web response system (IWRS). An overview of the 5 treatment groups and their corresponding dosing schemes from Week 0 through Week 48 of the Phase 2 study is provided below and illustrated in Figure 1.

Figure 1: Design schematic illustrating the dosing schemes for the 5 treatment groups from Week 0 to Week 48 in Phase 2 (ie, GALAXI 1)



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

Group 1: Guselkumab Regimen 1 (1200 mg IV q4w x 3 → 200 mg SC q4w)

Group 2: Guselkumab Regimen 2 (600 mg IV q4w x 3 → 200 mg SC q4w)

Group 3: Guselkumab Regimen 3 (200 mg IV q4w x 3 → 100 mg SC q8w)

Group 4: Active Control, Ustekinumab (~6 mg/kg IV → 90 mg SC q8w)

Group 5: Placebo → Placebo or Ustekinumab crossover

Participants will receive placebo IV q4w from Week 0 through Week 8 (ie, total of 3 IV doses). At Week 12, participants will continue treatment based on their clinical response status as follows:

- **Placebo responders:** Continue placebo treatment q4w from Week 12 through Week 44.
- **Placebo nonresponders:** Receive a single ustekinumab IV induction dose at Week 12 (weight-based IV doses approximating 6 mg/kg as outlined above). At Week 20, participants will receive ustekinumab SC maintenance (90 mg SC q8w) through Week 44.

  No dosing adjustments are planned for any of the treatment groups from Week 0 through Week 48, except for Group 5 (Placebo) at Week 12 based on clinical response status as described above.

Long-Term Extension Phase

At Week 48, all participants who, in the opinion of the investigator, will continue to benefit from treatment (ie, based on Week 48 clinical and endoscopic evaluations) are eligible to enter the LTE to receive approximately 4 additional years of treatment, during which time the longer-term efficacy and safety of guselkumab will be evaluated. The final efficacy and safety follow-up (FES) visit of the LTE will occur at approximately Week 248 or 252 (ie, approximately 16 weeks after their last study intervention administration at Week 232 [for q8w dosing] or 236 [for q4w dosing]).

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

During the LTE, all participants will continue to receive the same treatment regimen (ie, guselkumab, ustekinumab, or placebo) that they were receiving at the end of GALAXI 1. The first study intervention administration in the LTE will occur at Week 48 and the last study intervention administration will occur at Week 232 or 236. Treatment adjustment for inadequate response is permitted between Week 52 and Week 80 of the LTE (described below).

Study Unblinding

All participants will continue to receive active or placebo study intervention administration in the LTE in a blinded fashion until study unblinding to the investigative sites, which will occur after the Week 48 DBL and the Week 48 analyses have been completed for the Phase 2 study (for participants entering the LTE from GALAXI 1). After study unblinding, all participants who are on active treatment (ie, guselkumab or ustekinumab) will continue to receive their assigned active treatment for the remaining duration of the LTE through Week 232 or 236 unless eligible for dose adjustment between weeks 52 and 80. Participants who are on placebo will be discontinued from study intervention upon study unblinding and will have an FES visit at that time.

RLPH Substudy

A real-life patient-handling (RLPH) substudy will be implemented as an open-label substudy during the Phase 2 (GALAXI 1) LTE. The purpose of this substudy is to assess the ability of participants or their caregivers to perform guselkumab administration with either the 2.0 mL PFS-UltraSafe Plus (PFS-U) or 2.0 mL YpsoMate autoinjector (PFS-Y) in the standard of care setting (eg, at home or in the clinic), and to assess the reliability of each drug-device. When the Phase 2 study is unblinded, only those participants who are still in the Phase 2 LTE on the 200 mg q4w guselkumab dose will participate in this substudy. Additional details are provided in Section 5.5.7.

Treatment Adjustment for Inadequate Response

Participants from all treatment groups (ie, guselkumab, ustekinumab, and placebo) who meet inadequate response criteria between Week 52 (ie, the first visit at which treatment adjustment is permitted) and Week 80 (ie, the last visit at which treatment adjustment is permitted) will be eligible for a single treatment adjustment (ie, the first-time inadequate response criteria are met). Inadequate response is defined as not being in clinical response AND having a CDAI score of at least 220 points. Clinical response is defined as a reduction from baseline (ie, Week 0) in the CDAI score of ≥100 points or being in clinical remission (CDAI <150).

CDAI assessments will be conducted at q8w visits and may be conducted at q4w visits between Weeks 52 and 80 (inclusive) to support the evaluation of CDAI response status. Participants who meet inadequate response criteria, and who are not already receiving the highest guselkumab SC maintenance dose regimen, are eligible to receive treatment adjustment as described below.

Participants who are receiving placebo, ustekinumab, or the lower SC maintenance dose of guselkumab will be eligible to receive a single, blinded, treatment adjustment to the highest guselkumab SC maintenance dose as defined in the Phase 2 study (200 mg SC q4w). Participants who are already receiving the highest guselkumab SC maintenance dose will receive a single, blinded, sham treatment adjustment. Participants who have received treatment adjustments will remain on their new treatment regimen for the remainder of the LTE.

At Week 96, the benefit of treatment adjustment will be evaluated. Continued participation in the remaining duration of the LTE will be decided on investigator's clinical judgment. Discontinuation of study intervention should be considered in participants with persistent unsatisfactory response or clinically significant worsening Crohn's disease where continuation of the study intervention is not in the best interest of the participant.

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

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

Beginning at Week 48, at the discretion of the investigator and participant, and after appropriate and documented training, participants may self-administer study intervention at the investigative

site according to regional/local regulations and instruction. A caregiver may also be trained to administer study intervention.

After receiving training at Week 48, participants who are eligible for self- (or caregiver) study intervention administration will be supplied with study intervention for at-home administration and will have their first at-home administration at Week 52. Participants will record all at-home study intervention administrations on a diary card. Participants will also be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding. Finally, participants will continue to have study visits and assessments at the investigative sites approximately q8w through Week 240.

Participants who are unable or unwilling to have injections administered away from the site will be required to return to the site for administration of study intervention injection(s). Participants will continue to have study visits and assessments at the investigative site approximately q4w (if receiving q4w dosing per protocol) or q8w (if receiving q8w dosing per protocol) through Week 240.

1.3. Final Analysis

The Final Analysis is conducted when all participants who completed LTE participation have completed the Final Efficacy and Safety (FES) visit. The FES visit occurs around Week 248 or 252, which is approximately 16 weeks after the last study intervention administration at Week 232 for q8w dosing or Week 236 for q4w dosing. Final Analysis efficacy endpoints are evaluated at Week 240. Reporting of Safety data through to the FES visit for the Final Analysis is described in Section 5.1.1 Visit Windows. The Final Analysis will be referred to as the 'Final Analysis' within this document.

2. STATISTICAL HYPOTHESES

2.1. Week 96 DBL

The objective of the Week 96 DBL is to generate descriptive statistics relative to maintenance of clinical remission and endoscopic response. In addition, the benefit of dose adjustment will be evaluated using descriptive statistics.

2.2. Week 152 DBL

An objective of the Week 152 DBL is to generate descriptive statistics relative to evaluating long term efficacy of clinical and endoscopic outcomes. An additional objective is to assess the ability of participants or their caregivers to perform guselkumab administration with either the 2.0 mL PFS-UltraSafe Plus (PFS-U) or 2.0 mL YpsoMate autoinjector (PFS-Y) in the standard of care setting (eg, at home or in the clinic), and to assess the reliability of each drug-device. Lastly, long-term safety will be assessed.

2.3. Week 192 DBL

An objective of the Week 192 DBL is also to generate descriptive statistics relative to evaluating long term efficacy of clinical and endoscopic outcomes. Long-term safety will continue to be assessed.

2.4. Final Analysis DBL

An objective of the Final Analysis DBL is to generate descriptive statistics relative to evaluating long term efficacy of clinical and endoscopic outcomes for the duration of the LTE. Long-term safety will be assessed for the duration of the LTE.

3. SAMPLE SIZE DETERMINATION

The sample size determination was provided in the GALAXI 1 Week 48 SAP (EDMS-ERI-208136587, 2.0).

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Table 2: Analysis Sets

Analysis Sets	Description
LTE Efficacy Analysis Set	The LTE efficacy analysis set consists of randomized participants who entered the long-term extension phase of the study and received at least one dose of study intervention (including a partial dose) during the LTE phase.
Primary Efficacy Analysis Set	The primary efficacy analysis set consists of randomized participants who received at least one dose of study intervention (including a partial dose defined as either an incomplete infusion for an IV dose or the total syringe of a Subcutaneous dose was not administered), excluding those participants whose induction dosing was discontinued as a result of the Urgent Safety Measure. (n=309)
LTE Safety Analysis Set	The LTE safety analysis set consists of randomized participants who entered the long-term extension phase of the study and received at least one dose of study intervention (including a partial dose) during the LTE phase.
Full Safety Analysis Set	The Full safety analysis set consists of all participants who were randomized and received at least one dose of study intervention (including a partial dose). The safety data will be analyzed according to the treatment they actually received. (n=360)
LTE Pharmacokinetics Analysis Set	The guselkumab LTE PK analysis set is defined as randomized participants who entered the LTE phase of the study, have received at least one dose of guselkumab and have at least one valid blood sample drawn for PK analysis during the LTE. The ustekinumab LTE PK analysis set is defined as randomized participants who entered the LTE phase of the study, have received at least one dose of ustekinumab and have at least one valid blood sample drawn for PK analysis during the LTE.
Pharmacokinetics Analysis Set	The guselkumab PK analysis set is defined as randomized participants who have received at least one dose of guselkumab and have at least one valid blood sample drawn for PK analysis. The ustekinumab PK analysis set is defined as randomized participants who have received at least one dose of ustekinumab and have at least one valid blood sample drawn for PK analysis.

Table 2: Analysis Sets

Analysis Sets	Description
LTE Immunogenicity Analysis Set	The guselkumab LTE immunogenicity analysis set is defined as randomized participants who entered the LTE phase of the study, have received at least one dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab during the LTE. The ustekinumab LTE immunogenicity analysis set is defined as randomized participants who entered the LTE phase of the study, have received at least one dose of ustekinumab and have appropriate samples for detection of antibodies to ustekinumab during the LTE.
Immunogenicity Analysis Set	The guselkumab immunogenicity analysis set is defined as randomized participants who have received at least one dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab. The ustekinumab immunogenicity analysis set is defined as randomized participants who have received at least one dose of ustekinumab and have appropriate samples for detection of antibodies to ustekinumab.

Unless otherwise specified, all over-time (from Week 0) efficacy analyses will be based on the Primary Efficacy Analysis Set, and all over-time (from Week 0) safety analyses will be based on the Full Safety Analysis Set. All LTE-specific efficacy analyses will be based on the LTE Efficacy Analysis set, and all LTE-specific safety analyses will be based on the LTE Safety Analysis Set. All LTE-specific PK analyses will be based on the LTE PK analysis sets, and all LTE-specific immunogenicity analyses will be based on the LTE immunogenicity analysis sets.

5. STATISTICAL ANALYSES

5.1. General Considerations

Study Day and Relative Day: (from the GALAXI 1 Week 48 SAP EDMS-ERI-208136587, 2.0, section 2.4)

Study Day 1 refers to the start of the first study intervention administration date. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

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: (from the GALAXI 1 Week 48 SAP EDMS-ERI-208136587, 2.0, section 2.5)
Baseline is defined as the last observation prior to or at the date of the first study intervention, unless otherwise specified.

Imputation Rules for Missing AE Date/Time of Onset/Resolution: (from the GALAXI 1 Week 48 SAP EDMS-ERI-208136587, 2.0, section 2.6

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.

The LTE phase begins on the date of the first administration of Week 48 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.

5.1.1. Visit Windows

Unless otherwise specified, actual scheduled visits (nominal visit labels) will be used for over time summaries and listings with no visit windows applied.

Study Intervention Discontinuation (SID) visits (not endoscopy or histology assessment) will be mapped to scheduled visits according to windowing rules that will be prespecified in Data Presentation Specifications (DPS) Part 2 prior to the database lock.

When an endoscopy or histology assessment is performed at a USV or SID visit, then an endoscopy or histology assessment that occurs in the following time intervals will be slotted to a visit as follows:

Days 57-113, inclusive	Week 12
Days 309-365, inclusive	Week 48
Days 645-701, inclusive	Week 96
Days 981-1037, inclusive	Week 144
Days 1317-1373, inclusive	Week 192
Days 1653-1709, inclusive	Week 240

For Final Efficacy and Safety (FES) visits regardless of whether the subject completed or discontinued study intervention, the following will be applied. The FES visit will not be mapped to scheduled visits. Efficacy endpoints collected at the FES visit will not be analyzed. Safety data recorded up to the End of Study (to include the FES visit) will be included in analyses. For the Final Analysis, Safety lab parameter data collected at all FES visits will be included as a separate FES visit.

5.2. Participant Dispositions

Participant dispositions will be summarized using frequency distributions. No formal statistical analyses for treatment comparisons will be performed.

"(Week 152)" indicates that a similar summary or listing will be provided after the Week 152 DBL. "(Week 192)" indicates that a similar summary or listing will be provided after the Week 192 DBL. "(Final Analysis)" indicates that a similar summary or listing will be provided after the Final Analysis DBL.

The number of participants in the following disposition categories will be summarized:

- Participants in the LTE efficacy analysis set
- Participants in the LTE efficacy analysis set discontinuing study intervention prior to Week 96 (Week 152) (Week 192) (Final Analysis) and reasons for discontinuation, including those

due to COVID-19 related events, and major disruption (Week 152) (Week 192) (Final Analysis). Include a separate row for participants who completed at Week 144 under Protocol Amendment 3.

- Participants in the LTE efficacy analysis set who terminated study participation prior to Week 96 (Week 152) (Week 192) (Final Analysis) and reasons for termination, including those due to COVID-19 related events, and major disruption (Week 152) (Week 192) (Final Analysis). Include a separate row for participants who completed at Week 144 under Protocol Amendment 3.
- The number of participants summarized by last visit completion (Weeks 52-96 for W96 DBL) while the study was still blinded.
- Study Assessment Compliance from Week 48 through Week 96 (Week 152) (Final Analysis)

A listing of participants in the LTE efficacy analysis set will be provided for the following:

- Participants who discontinued study intervention between Week 48 to Week 96 (Week 152) (Final Analysis)
- Participants who terminated study participation from Week 48 to Week 96 (Week 152) (Final Analysis)
- Listing of Participants Who Discontinued Study Agent Due to COVID-19-related Reasons or Infection from Week 48 to Week 96 (Week 152) (Final Analysis)
- Listing of Participants Who Terminated Study Participation Prematurely Due to COVID-19-related Reasons or Infection from Week 48 to Week 96 (Week 152) (Final Analysis)
- Listing of Study Assessment Compliance from Week 48 through Week 96 (Week 152) (Week 192) (Final Analysis)

In addition, for the subset of participants in the LTE efficacy analysis set who had a dose adjustment, disposition information will be further summarized (Week 96 DBL).

5.3. Efficacy Endpoint(s) Analysis

5.3.1. Endpoints

5.3.1.1. Week 96 DBL

The efficacy endpoints specific to the Week 96 DBL are provided below.

There are seven different types of planned analyses, which are described in Table 3. The analysis type associated with each endpoint is coded as 1, 2, 3, 4, 5, 6, 7:

Table 3: Pre-specified Analyses for Long-term Efficacy

Analysis Type	Description

1. ITT Analyses of participants who entered the long-term extension, over first year of long-term extension, Dose Adjustment considered a TF
(ITT-LTE-DATF)
	• **This is the main analysis approach and will be used for all endpoints evaluated for the LTE**
	• Uses the Main Estimand described in Section 5.3.3.1
	• Evaluates clinical efficacy during the first year of the LTE For binary endpoints, participants with missing data are considered to be non-responders. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICEs, will not be imputed.
	• Dose adjustment during LTE is considered a TF and participants who dose adjust are considered not to be in remission at efficacy visits from the point of TF through Week 96
	• Other intercurrent events considered TFs include:
	  • A CD related surgery (with the exception of minor procedures)
	  • DC of study intervention due to LOE or AE of worsening CD

2. ITT Analyses of participants who entered the long-term extension, over first year of long-term extension, Dose Adjustment not considered a TF
(ITT-LTE)
	• This analysis type will be done only for the endpoints of change from baseline in CDAI, Clinical Remission, Clinical Response, Clinical Biomarker Response, PRO-2 Remission, and Endoscopic Response
	• For binary endpoints, participants with missing data are considered to be non-responders. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICEs, will not be imputed.
	• Uses LTE Supplemental Estimand 1 described in Section 5.3.3.2
	• Evaluates clinical efficacy during the first year of the LTE
	• Dose adjustment during LTE is not considered a TF and observed measurements after dose adjustment are used in the analyses (Treatment Strategy Approach)
	• Other intercurrent events considered TFs include:
	  • A CD related surgery (with the exception of minor procedures)
	  • DC of study intervention due to LOE or AE of worsening CD
	• NOTE: Only columns for the GUS dose groups will be provided in these tables; participants randomized to placebo or ustekinumab will be excluded from these analyses.

3. Observed case analysis of participants who entered the long-term extension, over first year of long-term extension, limited TF rules apply **(OA-LTE-TF)**	• This analysis type will be done only for the endpoints of change from baseline in CDAI, Clinical Remission, Clinical Response, Clinical Biomarker Response, PRO-2 Remission, and Endoscopic Response • Uses LTE Supplemental Estimand 2 described in Section 5.3.3.3 • Evaluates rates of remission observed during the first year of the LTE in participants who entered the LTE and remained on treatment at that specific timepoint • Participants who dose adjust are censored at the time of dose adjustment • The same TF rules as described in Analysis Type 2 will be applied. • After accounting for TFs, participants who did not have data at a visit are excluded from analysis for that visit.
4. Observed case analysis of participants who entered the long-term extension, over first year of long-term extension, no treatment failure rules apply **(OA-LTE)**	• This analysis type will be done only for the endpoints of change from baseline in CDAI, Clinical Remission, Clinical Response, Clinical Biomarker Response, PRO-2 Remission, and Endoscopic Response • Uses LTE Supplemental Estimand 3 described in Section 5.3.3.4 • Evaluates rates of remission observed during the first year of the LTE in participants who entered the LTE and remained on treatment at that specific timepoint • Participants who dose adjust are censored at the time of dose adjustment. • No TF rules will be applied. • Participants who do not have data at a visit are excluded from analysis for that visit.
5. ITT Analyses of participants who dose adjusted during the LTE **(ITT-DA)**	• Performed on those participants having a dose adjustment (or sham adjustment) and for a limited number of endpoints identified in Section 5.3.1 • Uses LTE Supplemental Estimand 4 described in Section 5.3.3.5 • For these analyses, dose adjustment is not considered a TF; all other TF rules as described in Analysis Type 2 will be applied. • Evaluates clinical efficacy after dose adjustment • For binary endpoints, participants with missing data are considered to be non-responders. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICEs, will not be imputed.

Table 3: Pre-specified Analyses for Long-term Efficacy

Analysis Type	Description
6. ITT analysis of randomized participants from Week 0* (Dose adjustment is a TF) **(ITT-OT-DATF)** * Primary Efficacy analysis set	• This analysis type will be done only for the endpoints of change from baseline in CDAI, Clinical Remission, Clinical Response, Clinical Biomarker Response, PRO-2 Remission, and Endoscopic Response • Uses OT Supplemental Estimand 1 described in Section 5.3.3.6 • Evaluates rates of remission through Week 96 among all participants originally randomized in GALAXI 1 (with the exception of the 51 participants impacted by the USM) • Conservative assessment of 96 week clinical efficacy, as participants who did not enter the LTE or discontinued were considered to not be in remission • Participants who met any treatment failure criterion before or after Week 48 were considered not to be in remission from that point onward with one exception: participants with changes in concomitant medications after week 48 were not considered treatment failures if the con med start date was after Week 48. • For binary endpoints, participants with missing data are considered to be non-responders. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICEs, will not be imputed.
7. ITT analysis of randomized participants from Week 0* (Dose adjustment not a TF) **(ITT-OT)** *Primary Efficacy analysis set	• This analysis type will be done only for the endpoints of change from baseline in CDAI, Clinical Remission, Clinical Response, Clinical Biomarker Response, PRO-2 Remission, and Endoscopic Response • Uses OT Supplemental Estimand 2 described in Section 5.3.3.7 • Evaluates rates of remission through Wk 96 among all participants originally randomized in GALAXI 1 (except USM participants) • Conservative assessment of 96 Week clinical efficacy, as participants who did not enter the LTE or discontinued prior to Week 48 were considered to not be in remission • Dose adjustment is not considered a TF • Participants who met any treatment failure criterion before or after Week 48 were considered not to be in remission from that point onward with one exception: participants with changes in concomitant medications after week 48 were not considered treatment failures if the con med start date was after Week 48. • For binary endpoints, participants with missing data are considered to be non-responders. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICEs, will not be imputed. • NOTE: Only columns for the GUS dose groups will be provided in these tables; participants randomized to placebo or ustekinumab will be excluded from these analyses.

Clinical Remission

1. Clinical remission at Weeks 48, 56, 64-96 q8w, defined as CDAI score < 150 [1, 2, 3, 4]
2. Summary of Clinical remission (CDAI score <150) from Week 4 through Week 96 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-96) [6, 7]
3. Durable clinical remission if 6/7 of visits 48, 56, 64, 72, 80, 88, 96, including Week 96, achieve clinical remission [1]
4. Clinical remission at both Weeks 48 and 96 [1]
5. Corticosteroid-free (90-days) clinical remission at Week 96 (defined as CDAI <150 at Week 96 and not receiving corticosteroids for at least 90 days prior to Week 96) [1]
6. Number of participants in clinical remission for those in LTE efficacy analysis set who were still blinded at the time of the assessment at Week 48, 56, 64, 72, 80, 88, 96. [1]

Endoscopic Response

7. Endoscopic response at Week 96 [1, 2, 3, 4]
8. Endoscopic response at both Week 48 and 96 [1]

9. Endoscopic response at Weeks 12, 48, 96 [6, 7]

Clinical Response

10. Clinical response at Weeks 48, 56, 64-96 q8w [1, 2, 3, 4]
11. Summary of Clinical response from Week 4 through Week 96 (every 4 through Week 48, and every 8 weeks from Weeks 56-96) [6, 7]
12. Clinical response at both Weeks 48 and 96 [1]

PRO-2 Remission

13. PRO-2 remission at Weeks 48, 56, 64-96 q8w [1, 2, 3, 4]
14. PRO-2 remission at all post-baseline visits through Week 96 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-96) [6, 7]
15. Durable PRO-2 remission at Week 96 (defined as 6/7 of visits 48, 56, 64, 72, 80, 88, 96, including Week 96, achieve PRO-2 remission) [1]
16. Corticosteroid-free (90-days) PRO-2 remission at Week 96 (defined as achieving PRO-2 remission at Week 96 and not receiving corticosteroids for at least 90 days prior to Week 96) [1]
17. Number of participants in PRO-2 remission for those in LTE efficacy analysis set who were still blinded at the time of the assessment at Week 48, 56, 64, 72, 80, 88, 96. [1]

CDAI, AP, SF

18. Change from baseline in CDAI score at Weeks 48, 56-96 q8w [1, 2, 3, 4]
19. Change from baseline in CDAI score from Week 4 through Week 96 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-96) [6, 7]
20. Change in AP score at Weeks 48, 56-96 q8w [1]
21. Abdominal pain score $\leq$1 at Weeks 48, 56-96 q8w among participants with daily average AP score >1 at baseline [1]
22. Change in the number of liquid or very soft stools from baseline at Weeks 48-96 q8w [1]
23. Number of liquid or very soft stools $\leq$3 at Weeks 52, 56, 64-96 q8w among participants with daily average number of liquid or very soft stools >3 at baseline [1]

Fistula

24. Fistula response at all post-baseline visits during the LTE, among participants with 1 or more fistulas at baseline [1]
25. Complete fistula response at all post-baseline visits during the LTE, among participants with 1 or more fistulas at baseline [1]

SES-CD

26. Change in SES-CD score from baseline at Week 96 [1]

Endoscopic Healing and Remission

27. Endoscopic healing at Week 96 [1]
28. Endoscopic remission at Week 96 [1]

Biomarkers

29. Change in CRP from baseline during the LTE [1]
30. Normalization of CRP concentrations during the LTE among participants with abnormal CRP at baseline [1]
31. Change in fecal calprotectin from baseline during the LTE [1]
32. Fecal calprotectin concentration ≤250 µg/g during the LTE, and fecal calprotectin ≤100 µg/g during the LTE, among participants with abnormal fecal calprotectin at baseline [1]
33. Clinical-biomarker response during the LTE [1, 2, 3, 4]
34. Clinical-biomarker response from Week 4 through Week 96 [6, 7]
35. Clinical remission and CRP <=3 or fecal calprotectin concentration ≤250 µg/g during the LTE [1]
36. Clinical remission and CRP <=3 and fecal calprotectin concentration ≤250 µg/g during the LTE [1]
37. Clinical remission and normalization of CRP concentration or fecal calprotectin concentration ≤250 µg/g during the LTE, among participants with abnormal CRP or fecal calprotectin >250 µg/g at baseline [1]
38. Clinical remission and normalization of CRP concentration and fecal calprotectin concentration ≤250 µg/g during the LTE, among participants with abnormal CRP or fecal calprotectin >250 µg/g at baseline [1]

Health-related Quality of Life

39. Change in IBDQ score and domain scores during the LTE [1]
40. IBDQ remission during the LTE [1]
41. IBDQ response during the LTE [1]
42. Change from baseline in the 7 domains and the pain NRS score of PROMIS-29 during the LTE [1]
43. Proportion of participants who achieve an improvement of ≥ 5 points in PROMIS-29 domain scores during the LTE [1]
44. Proportion of participants who achieve an improvement of ≥ 3 points in pain NRS score of PROMIS-29 during the LTE among participants with pain NRS score ≥ 3 at baseline [1]

Histology

45. Change in the total GHAS score at Week 96 [1]
46. Histologic Response (≥50% reduction in total GHAS score from baseline) at Week 96 [1]
47. Histo-Endoscopic Response (histologic response and endoscopic response) at Week 96 [1]

Corticosteroids

48. Summary of the average daily prednisone-equivalent (P.Eq) corticosteroid dose (excluding budesonide and beclomethasone dipropionate) during the LTE; Participants in the LTE efficacy analysis set who were receiving corticosteroids other than budesonide and beclomethasone dipropionate at baseline [1]
49. Summary of the change from baseline in the average daily prednisone equivalent (P.EQ) oral corticosteroids dose (mg/day; excluding budesonide and beclomethasone dipropionate) at each visit during the LTE; participants in the LTE efficacy analysis set who were receiving oral corticosteroids other than budesonide and beclomethasone dipropionate at baseline [1]
50. Plot of median average daily prednisone equivalent (P.Eq) corticosteroid dose (excluding budesonide and beclomethasone dipropionate) during the LTE [1]
51. Number of participants who were not receiving corticosteroids for at least 90 days prior to Week 96; participants in LTE Efficacy Analysis Set who were receiving concomitant corticosteroids at baseline [1]

Other endpoints

52. Clinical Remission AND Endoscopic response at Week 96 [1]
53. Change in SES-CD score from baseline at Week 96, endoscopic response at Week 96, endoscopic remission at Week 96 and endoscopic healing at Week 96, among participants with baseline SES-CD ≥4 (ie, for participants with isolated ileal disease) or SES-CD ≥6 (ie, for participants with colonic or ileocolonic disease) [1]
54. Clinical remission at Week 96 among participants in clinical response at Week 48 [1]
55. Clinical remission at Week 96 among participants in clinical remission at Week 48 [1]
56. Endoscopic Response at Week 96 among participants in clinical response at Week 48 [1]
57. Endoscopic Response at Week 96 among participants in clinical remission at Week 48 [1]
58. Endoscopic Response at Week 96 among participants in endoscopic response at Week 48 [1]

In addition, to determine the benefit of dose adjustment, the following endpoints will be explored in the subset of participants with dose adjustment between Weeks 52-80:

59. Number of participants in clinical remission 16 weeks after dose adjustment [5]
60. Number of participants in clinical remission at Week 96 by time of first dose adjustment visit [5]
61. Number of participants in clinical response 16 weeks after dose adjustment [5]
62. Number of participants in clinical response at Week 96 by time of first dose adjustment visit [5]
63. Number of participants in PRO-2 Remission 16 weeks after dose adjustment [5]
64. Number of participants in PRO-2 Remission at Week 96 by time of first dose adjustment visit [5]
65. Change from baseline in the CDAI score 16 weeks after dose adjustment [5]

66. Change from last pre-dose-adjustment CDAI score 16 weeks after dose adjustment [5]
67. Number of participants in endoscopic remission at Week 96 by time of first dose adjustment visit [5]
68. Number of participants in endoscopic response at Week 96 by time of first dose adjustment visit [5]

5.3.1.2. Week 152 DBL

The efficacy endpoints specific to the Week 152 DBL are provided below.

There are two different types of planned analyses, which are described in Table 4. The analysis type associated with each endpoint is coded as 1 and 2. For the W152 DBL, efficacy will be analyzed through to Week 144. Efficacy is analyzed through Week 144 as 13 participants completed the study at Week 144 under Protocol Amendment 3. Further, previous efficacy analyses have been at Week 48 and at Week 96, so the next ’48 week’ block would be at Week 144. It is considered that efficacy through to Week 144, with safety through to Week 152 is an acceptable approach.

Table 4: Pre-specified Analyses for Long-term Efficacy

Analysis Type	Description

1. ITT Analyses of participants who entered the long-term extension, over the first two years of long-term extension, Dose Adjustment is considered as an ICE. **(ITT-LTE-DAICE)** * LTE Efficacy analysis set	• **This is the main analysis approach and will be used for all endpoints evaluated for the LTE**
	• Uses the Main Estimand described in Section 5.3.5.1
	• Evaluates clinical efficacy during the first two years of the LTE. For binary endpoints, participants with missing data are considered to be non-responders. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed.
	• Dose adjustment during LTE is considered an ICE and participants who dose adjust are considered not to have achieved the endpoint at efficacy visits from the point of the ICE through Week 144
	• Other intercurrent events include:
	  • A CD related surgery (with the exception of minor procedures)
	  • DC of study intervention due to LOE or AE of worsening CD

2. ITT analysis of randomized participants from Week 0* (Dose adjustment is considered as an ICE) **(ITT-OT-DAICE)** * Primary Efficacy analysis set	• This analysis type will be done only for the endpoints of change from baseline in CDAI, Clinical Remission, Clinical Response, Clinical Biomarker Response, PRO-2 Remission, and Endoscopic Response • Uses OT Supplemental Estimand 1 described in Section 5.3.5.2 • Evaluates the endpoints listed above through Week 144 among all participants originally randomized in GALAXI 1 (with the exception of the 51 participants impacted by the USM) • Conservative assessment of Week 144 clinical efficacy, as participants who did not enter the LTE or discontinued were considered to not be in remission • Participants with any ICE as defined in Section 5.3.5.2 before or after Week 48 were considered not to be in remission from that point onward with one exception: changes in concomitant medications after week 48 were not considered as an ICE if the con med start date was after Week 48. • For binary endpoints, participants randomized to an active treatment group, or randomized to placebo and who crossed over to ustekinumab at Week 12 with missing data after accounting for ICE strategies are considered to be non-responders, while participants randomized to placebo and who did not crossover to ustekinumab at Week 12, and with missing data after accounting for ICE strategies will not be imputed and will be excluded from the analysis at that time point. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed. • Dose adjustment is considered an ICE and participants who dose adjust are considered not to have achieved the endpoint at efficacy visits from the point of the ICE through Week 144.

5. ITT Analyses of participants who dose adjusted during the LTE **(ITT-DA)**	• Performed on those participants having a dose adjustment (or sham adjustment) and for a limited number of binary endpoints identified in Section 5.3.1.2
	• Uses LTE Supplementary Estimand 4 described in Section 5.3.5.3
	• For these analyses, dose adjustment is not considered as an ICE and observed measurements after dose adjustment are used in the analyses (Treatment Strategy Approach)
	• Intercurrent events include:
	  • A CD related surgery (with the exception of minor procedures)
	  • DC of study intervention due to LOE or AE of worsening CD
	• Evaluates clinical efficacy after dose adjustment by visit at Week 96 and Week 144
	• For binary endpoints, participants with missing data are considered to be non-responders.

Clinical Remission

1. Clinical remission at Weeks 48, 56, 64-144 q8w [1]
2. Clinical remission from Week 4 through Week 144 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-144) [2]

3. Durable clinical remission in the LTE [1]
4. Clinical remission at all of Weeks 48, 96 and 144 [1]

Endoscopic Response

5. Endoscopic response at Weeks 48, 96 and 144 [1]
6. Endoscopic response at all of Week 48, 96 and 144 [1]
7. Endoscopic response at Weeks 12, 48, 96 and 144 [2]

Clinical Response

8. Clinical response at Weeks 48, 56, 64-144 q8w [1]
9. Clinical response from Week 4 through Week 144 (every 4 through Week 48, and every 8 weeks from Weeks 56-96) [2]
10. Clinical response at all of Weeks 48, 96 and 144 [1]

PRO-2 Remission

11. PRO-2 remission at Weeks 48, 56, 64-144 q8w [1]
12. PRO-2 remission at all post-baseline visits through Week 144 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-144) [2]
13. Durable PRO-2 remission in the LTE [1]

CDAI, AP, SF

14. Change from baseline in CDAI score at Weeks 48, 56-144 q8w [1]
15. Change from baseline in CDAI score from Week 4 through Week 144 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-144) [2]
16. Change from baseline in AP score at Weeks 48, 56-144 q8w [1]
17. Abdominal pain score ≤1 at Weeks 48, 56-144 q8w among participants with daily average AP score >1 at baseline [1]
18. Change in the number of liquid or very soft stools from baseline at Weeks 48-144 q8w [1]
19. Number of liquid or very soft stools ≤3 at Weeks 48, 56, 64-144 q8w among participants with daily average number of liquid or very soft stools >3 at baseline [1]

Note: Fistula endpoints deleted

SES-CD

20. Change in SES-CD score from baseline at Week 144 [1]

Endoscopic Healing and Remission

21. Endoscopic healing at Week 144 [1]
22. Endoscopic remission at Weeks 48, 96 and 144 [1]
23. Endoscopic remission at Weeks 12, 48, 96 and 144 [2]

Biomarkers

24. Normalization of CRP concentrations (≤3 mg/L) among participants with abnormal CRP at baseline [1, 2]
25. Fecal calprotectin concentration ≤250 µg/g, fecal calprotectin ≤100 µg/g, and fecal calprotectin ≤50 µg/g among participants with abnormal fecal calprotectin at baseline [1, 2]
26. Clinical biomarker remission during the LTE [1]

Health-related Quality of Life

27. IBDQ remission during the LTE [1]

Histology

28. Change in the total GHAS at Week 144 [1]
29. Histologic Response at Week 144 [1]
30. Histo-Endoscopic Response (histologic response and endoscopic response) at Week 144 [1]

Corticosteroids

31. Summary of the change from baseline in the average daily prednisone equivalent (P.EQ) oral corticosteroids dose (mg/day; excluding budesonide and beclomethasone dipropionate) at each visit during the LTE; participants in the LTE efficacy analysis set [1]
32. Percent initiation/increase corticosteroids for treatment of Crohn's disease during the LTE; participants in LTE Efficacy Analysis Set [1]
33. Number of participants who achieved steroid free clinical remission at week 144; participants in LTE Efficacy Analysis Set who achieved steroid free clinical remission at week 48 [1]
34. Number of participants who achieved steroid free endoscopic response at week 144; participants in LTE Efficacy Analysis Set who achieved steroid free endoscopic response at week 48 [1]

Other endpoints

35. Clinical remission AND Endoscopic response at Week 48, 96 and 144[1]
36. Clinical remission AND Endoscopic remission (deep remission) at Week 48, 96 and 144[1]
37. Change in SES-CD score from baseline at Week 144, endoscopic response at Week 144, endoscopic remission at Week 144 and endoscopic healing at Week 144, among participants with baseline SES-CD ≥4 (ie, for participants with isolated ileal disease) or SES-CD ≥6 (ie, for participants with colonic or ileocolonic disease) [1]
38. Clinical remission at Week 144 among participants in clinical response at Week 48 [1]
39. Clinical remission at Week 144 among participants in clinical remission at Week 48 [1]
40. Endoscopic Response at Week 144 among participants in clinical response at Week 48 [1]
41. Endoscopic Response at Week 144 among participants in clinical remission at Week 48 [1]
42. Endoscopic Response at Week 144 among participants in endoscopic response at Week 48 [1]

43. Endoscopic Remission at Week 144 among participants in endoscopic response at Week 48 [1]
44. Clinical remission by visit at Week 96 and Week 144 [5]
45. Endoscopic Response by visit at Week 96 and Week 144 [5]
46. Endoscopic Remission by visit at Week 96 and Week 144 [5]

In addition, Endpoints 59-68 from the Week 96 DBL Section 5.3.1.1 for the subset of participants with dose adjustment between Weeks 52-80 will be re-run for the W152 DBL

5.3.1.3. Week 192 DBL

The efficacy endpoints specific to the Week 192 DBL are provided below.

There are two different types of planned analyses, which are described in Table 5. The analysis type associated with each endpoint are coded as 1 and 2 respectively. For the W192 DBL, efficacy will be analyzed through to Week 192. Observed case analysis for selected endpoints may be performed and may be specified in the DPS.

Table 5: Pre-specified Analyses for Long-term Efficacy

Analysis Type	Description

1. ITT Analyses of participants who entered the long-term extension, over the first three years of long-term extension, Dose Adjustment is considered as an ICE. **(ITT-LTE-DAICE)** * LTE Efficacy analysis set	• **This is the main analysis approach and will be used for all endpoints evaluated for the LTE. These are indicated below with a [1].**
	• Uses the Main Estimand described in Section 5.3.5.1
	• Evaluates clinical efficacy during the first three years of the LTE. For binary endpoints, participants with missing data are considered to be non-responders. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed.
	• Dose adjustment during LTE is considered an ICE and participants who dose adjust are considered not to have achieved the endpoint at efficacy visits from the point of the ICE through Week 192
	• Other intercurrent events include:
	  • A CD related surgery (with the exception of minor procedures)
	  • Discontinuation of study intervention due to LOE or AE of worsening CD

2. ITT analysis of randomized participants from Week 0* (Dose adjustment is considered as an ICE) **(ITT-OT-DAICE)** * Primary Efficacy analysis set	• This analysis type will be done only for selected endpoints indicated below with a [2]. • Uses OT Supplemental Estimand 1 described in Section 5.3.5.2 • Evaluates the selected endpoints through Week 192 among all participants originally randomized in GALAXI 1 (with the exception of the 51 participants impacted by the USM) • Conservative assessment of Week 192 clinical efficacy, as participants who did not enter the LTE or discontinued were considered to not be in remission • Participants with any ICE as defined in Section 5.3.5.2 before or after Week 48 were considered not to be in remission from that point onward with one exception: changes in concomitant medications after week 48 were not considered as an ICE if the con med start date was after Week 48. • For binary endpoints, participants randomized to an active treatment group, or randomized to placebo and who crossed over to ustekinumab at Week 12 with missing data after accounting for ICE strategies are considered to be non-responders, while participants randomized to placebo and who did not crossover to ustekinumab at Week 12, and with missing data after accounting for ICE strategies will not be imputed and will be excluded from the analysis at that time point. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed. • Dose adjustment is considered an ICE and participants who dose adjust are considered not to have achieved the endpoint at efficacy visits from the point of the ICE through Week 192.

Clinical Remission

1. Clinical remission at Weeks 48, 56, 64-192 q8w [1]
2. Clinical remission from Week 4 through Week 192 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-192) [2]
3. Durable clinical remission in the LTE (W192 DBL definition) [1]

Endoscopic Response

4. Endoscopic response at Weeks 48, 96, 144 and 192 [1]
5. Endoscopic response at Weeks 12, 48, 96, 144 and 192 [2]

PRO-2 Remission

6. PRO-2 remission at Weeks 48, 56, 64-192 q8w [1]
7. PRO-2 remission at all post-baseline visits through Week 192 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-192) [2]

Endoscopic Remission

8. Endoscopic remission (Region Specific) at Weeks 48, 96, 144 and 192 [1]
9. Endoscopic remission (Region Specific) at Weeks 12, 48, 96, 144 and 192 [2]
10. Endoscopic remission (Global) at Weeks 48, 96, 144 and 192 (Not for the Global Defined subset) [1]
11. Endoscopic remission (Global) at Weeks 12, 48, 96, 144 and 192 (Not for the Global Defined subset) [2]

Biomarkers

12. Normalization of CRP concentrations (≤3 mg/L) among participants with abnormal CRP at baseline [1, 2]
13. Fecal calprotectin concentration ≤250 µg/g, and fecal calprotectin ≤100 µg/g, among participants with abnormal fecal calprotectin at baseline [1, 2]
14. Clinical biomarker remission during the LTE [1]

Histology

15. Histologic Response at Week 192 (GHAS derived) [1]
16. Histologic Response at Week 192 (Geboes derived) [1]
17. Histo-Endoscopic Response (GHAS derived histologic response and endoscopic response) at Week 192 [1]
18. Histo-Endoscopic Response (Geboes derived histologic response and endoscopic response) at Week 192 [1]

Corticosteroids

19. Number of participants who achieved steroid free (90-Days) clinical remission at week 192; participants in LTE Efficacy Analysis Set [1]

Other endpoints

20. Clinical remission AND Endoscopic remission (Region Specific) (deep remission) at Weeks 48, 96, 144 and 192 [1, 2]
21. Clinical remission AND Endoscopic remission (Global) (deep remission) at Weeks 48, 96, 144 and 192 [1, 2]
22. Durable clinical remission (W192 DBL definition) among participants in clinical remission at Week 192 [1]
23. Clinical remission AND Endoscopic response at Weeks 48, 96, 144 and 192 [1]
24. Clinical remission AND Endoscopic response at Weeks 12, 48, 96, 144 and 192 [2]

The endpoints below will be evaluated on the subset of participants with baseline SES-CD ≥4 (ie, for participants with isolated ileal disease) or SES-CD ≥6 (ie, for participants with colonic or ileocolonic disease). This subset is referred to as the Global defined subset.

25. Endoscopic remission (Region Specific) at Week 192 [1, 2]
26. Clinical remission AND Endoscopic remission (Global) (deep remission) at Weeks 48, 96, 144 and 192 [1]
27. Clinical remission AND Endoscopic remission (Global) (deep remission) at Weeks 12, 48, 96, 144 and 192 [2]
28. Endoscopic remission (Global) at Weeks 48, 96, 144 and 192 [1]
29. Endoscopic remission (Global) at Weeks 12, 48, 96, 144 and 192 [2]

5.3.1.4. Final Analysis DBL

The efficacy endpoints specific to the Final Analysis DBL are provided below.

There are three different types of planned analyses, which are described in Table 6. The analysis type associated with each endpoint are coded as 1, 2 and 3 respectively. Twelve subjects completed the study at Week 144 under Protocol Amendment 3. These 12 subjects are included in the analysis for efficacy endpoints at Week 144 but excluded from the analysis (and hence the denominator) for efficacy endpoints at time points after Week 144. These 12 subjects were also not scheduled to have an endoscopy performed at Week 144 and are excluded from endoscopy related analyses (and hence the denominator) at Week 144.

Table 6: Pre-specified Analyses for Long-term Efficacy

Analysis Type	Description

1. ITT Analyses of participants who entered the long-term extension, through Week 240, Dose Adjustment is considered as an ICE.
(ITT-LTE-DAICE)
LTE Efficacy analysis set
	• **This is the main analysis approach and will be used for all endpoints evaluated for the LTE. These are indicated below with a [1].**
	• Uses the Main Estimand described in Section 5.3.9.1.
	• Evaluates clinical efficacy through Week 240. For binary endpoints, participants with missing data after accounting for ICE strategies are considered to be non-responders. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed.
	• Dose adjustment during LTE is considered an ICE and participants who dose adjust are considered not to have achieved the endpoint at efficacy visits from the point of the ICE through Week 240.
	• Other intercurrent events include:
	  • A CD related surgery (with the exception of minor procedures)
	  • Discontinuation of study intervention due to lack of efficacy or AE of worsening CD

2. ITT analysis of randomized participants from Week 0* (Dose adjustment is considered as an ICE) **(ITT-OT-DAICE)** Primary Efficacy analysis set	• This analysis type will be done only for selected endpoints indicated below with a [2]. • Uses OT Supplemental Estimand 1 described in Section 5.3.9.3. • Evaluates the endpoints listed above through Week 240 among all participants originally randomized in GALAXI 1 (with the exception of the 51 participants impacted by the USM) • Conservative assessment of clinical efficacy, as participants who did not enter the LTE or discontinued were considered not to have achieved the endpoint. • Participants with any ICE as defined in Section 5.3.9.3 before or after Week 48 were considered not to be in remission from that point onward with one exception: changes in concomitant medications after week 48 were not considered as an ICE if the con med start date was after Week 48. • For binary endpoints, participants randomized to an active treatment group, or randomized to placebo and who crossed over to ustekinumab at Week 12 with missing data after accounting for ICE strategies are considered to be non-responders, while participants randomized to placebo and who did not crossover to ustekinumab at Week 12, and with missing data after accounting for ICE strategies will not be imputed and will be excluded from the analysis at that time point. However, for continuous endpoints, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed. • Dose adjustment is considered an ICE and participants who dose adjust are considered not to have achieved the endpoint at efficacy visits from the point of the ICE through Week 240.
3. Observed case analysis of participants who entered the long-term extension, through Week 240, no treatment failure rules apply **(OA-LTE)**	• This analysis type will be done only for the endpoints of Clinical Remission, PRO-2 Remission, Endoscopic Remission (Region Specific), Endoscopic Remission (Global) and Endoscopic Response. • Uses LTE Supplemental Estimand 3 described in Section 5.3.9.2. • Evaluates rates observed up to Week 240 of the LTE in participants who entered the LTE and remained on treatment at that specific timepoint • Participants who dose adjust are censored at the time of dose adjustment. • No TF rules will be applied. • Participants who do not have data at a visit are excluded from analysis for that visit.

Clinical Remission

1. Clinical remission at Weeks 48, 56, 64-240 q8w [1, 3]
2. Clinical remission from Week 4 through Week 240 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-240) [2]
3. Durable clinical remission in the LTE (Final Analysis DBL definition) [1]

Endoscopic Response

4. Endoscopic response at Weeks 48, 96, 144, 192 and 240 [1, 3]

5. Endoscopic response at Weeks 12, 48, 96, 144, 192 and 240 [2]

PRO-2 Remission

6. PRO-2 remission at Weeks 48, 56, 64-240 q8w [1, 3]
7. PRO-2 remission at all post-baseline visits through Week 240 (every 4 weeks through Week 48, and every 8 weeks from Weeks 56-240) [2]

Endoscopic Remission

8. Endoscopic remission (Region Specific) at Weeks 48, 96, 144, 192 and 240 [1, 3]
9. Endoscopic remission (Region Specific) at Weeks 12, 48, 96, 144, 192 and 240 [2]
10. Endoscopic remission (Global) at Weeks 48, 96, 144, 192 and 240 [1, 3]
11. Endoscopic remission (Global) at Weeks 12, 48, 96, 144, 192 and 240 [2]

Biomarkers

12. Normalization of CRP concentrations (≤3 mg/L) among participants with abnormal CRP at baseline [1, 2]
13. Fecal calprotectin concentration ≤250 µg/g, and fecal calprotectin ≤100 µg/g, among participants with abnormal fecal calprotectin at baseline [1, 2]
14. Clinical biomarker remission [1, 2]

Histology

15. Histologic Response at Weeks 12, 48, 96, 144, 192 and 240 (GHAS derived) amongst participants with histologic disease activity at baseline (Week 0) [1]
16. Histologic Response at Weeks 12, 48, 96, 144, 192 and 240 (Geboes derived) amongst participants with histologic disease activity at baseline (Week 0) [1]
17. Histologic Response at Weeks 12, 48, 96, 144, 192 and 240 (RHI derived) amongst participants with histologic disease activity at baseline (Week 0) [1]
18. Histo-Endoscopic Response (GHAS derived histologic response and endoscopic response) at Weeks 12, 48, 96, 144, 192 and 240 [1]
19. Histo-Endoscopic Response (Geboes derived histologic response and endoscopic response) at Weeks 12, 48, 96, 144, 192 and 240 [1]
20. Histo-Endoscopic Response (RHI derived histologic response and endoscopic response) at Weeks 12, 48, 96, 144, 192 and 240 [1]

Corticosteroids

21. Summary of the average daily prednisone-equivalent (P.Eq) corticosteroid dose (excluding budesonide and beclomethasone dipropionate) during the LTE; Participants in the LTE efficacy analysis set who were receiving corticosteroids other than budesonide and beclomethasone dipropionate at baseline [1]
22. Percent initiation/increase corticosteroids for treatment of Crohn's disease during the LTE [1]

23. Number of participants who stayed off corticosteroids in the LTE amongst those who were on corticosteroids at baseline [1]
24. Number of participants who achieved steroid free (90-Days) clinical remission over time through to the time point of the analysis [1]
25. Number of participants who achieved steroid free (90-Days) clinical remission at the time point of the analysis amongst those who were in clinical remission at the time point of analysis [1]

Fistula

26. Fistula response at all post-baseline visits during the LTE, among participants with 1 or more fistulas at baseline [1]
27. Complete fistula response at all post-baseline visits during the LTE, among participants with 1 or more fistulas at baseline [1]

Health-related Quality of Life

28. IBDQ remission at all scheduled visits with available data during the LTE [1]
29. Change from baseline in the 7 domains,the pain NRS score and physical and mental summary scores of PROMIS-29 at all scheduled visits with available data during the LTE [1]
30. Proportion of participants who achieve an improvement of ≥ 5 points, and also ≥ 7 points in PROMIS-29 domain scores and physical and mental summary scores at all scheduled visits with available data during the LTE [1]
31. Proportion of participants who achieve an improvement of ≥ 3 points in pain NRS score of PROMIS-29 at all scheduled visits with available data during the LTE among participants with pain NRS score ≥ 3 at baseline [1]

Other endpoints

32. Clinical remission AND Endoscopic remission (Region Specific) (deep remission) at Weeks 48, 96, 144, 192 and 240 [1, 2]
33. Clinical remission AND Endoscopic remission (Global) (deep remission) at Weeks 48, 96, 144, 192 and 240 [1, 2]
34. Durable clinical remission (Final Analysis DBL (W252) definition) among participants in clinical remission at Week 240 [1]
35. Clinical remission AND Endoscopic response at Weeks 48, 96, 144, 192 and 240 [1]
36. Clinical remission AND Endoscopic response at Weeks 12, 48, 96, 144, 192 and 240 [2]

The endpoints below will be evaluated on the subset of participants with baseline SES-CD ≥4 (ie, for participants with isolated ileal disease) or SES-CD ≥6 (ie, for participants with colonic or ileocolonic disease). This subset is referred to as the Global defined subset.

37. Endoscopic remission (Region Specific) at Weeks 48, 96, 144, 192 and 240 [1]
38. Endoscopic remission (Region Specific) at Weeks 12, 48, 96, 144, 192 and 240 [2]

39. Clinical remission AND Endoscopic remission (Global) (deep remission) at Weeks 48, 96, 144, 192 and 240 [1]
40. Clinical remission AND Endoscopic remission (Global) (deep remission) at Weeks 12, 48, 96, 144, 192 and 240 [2]
41. Endoscopic remission (Global) at Weeks 48, 96, 144, 192 and 240 [1]
42. Endoscopic remission (Global) at Weeks 12, 48, 96, 144, 192 and 240 [2]

5.3.2. Definition of Endpoint(s)

CDAI: The CDAI is a validated multi-item measure of severity of illness derived as a weighted sum of 8 different Crohn's disease-related variables[1]. These 8 variables are:

- extra-intestinal manifestations
- abdominal mass
- weight
- hematocrit
- use of antidiarrheal drug(s) and/or opiate
- total number of liquid or very soft stools
- abdominal pain/cramps
- general well-being.

The last 3 variables are scored over 7 days by the participant on a diary card. For the total number of liquid or very soft stools, abdominal pain/cramps, and general well-being, if only 5 days or 6 days of data are available for the calculation, the weights of 7/5 and 7/6, respectively, will be used for the calculation; if the values are recorded for less than 5 days, the component will not be calculated. The CDAI score calculation algorithm is presented in Attachment 10 of the protocol.

At each timepoint, the CDAI score will only be calculated if ≥ 4 of the 8 components are available. If the CDAI score cannot be calculated (ie, <4 components available), the CDAI score will be considered missing. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last non-missing component.

Clinical remission is defined as a CDAI score < 150

W152 DBL Durable clinical remission in the LTE is achieved if 11/13 of visits at Weeks 48, 56, 64, 72, 80, 88, 96, 104, 112, 120, 128, 136, 144 including Week 144 achieve clinical remission

W192 DBL Durable clinical remission in the LTE is achieved if 17/19 of visits at Weeks 48, 56, 64, 72, 80, 88, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192 including Week 192 achieve clinical remission

Final Analysis DBL Durable clinical remission in the LTE is achieved if ≥80% of all visits between Week 48 and Week 240 (Weeks 48, 56, 64, 72, 80, 88, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, 216, 224, 232, 240) (i.e. at least 20/25 of these visits), including Week 240 achieve clinical remission.

Clinical response is defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150

PRO-2 remission is defined as the unweighted CDAI component of daily average abdominal pain (AP) score at or below 1 AND the unweighted CDAI component of daily average stool frequency (SF) score at or below 3, ie, AP ≤ 1 and SF ≤ 3 and no worsening of AP or SF from baseline

W152 DBL Durable PRO-2 remission in the LTE is achieved if 11/13 of visits at Weeks 48, 56, 64, 72, 80, 88, 96, 104, 112, 120, 128, 136, 144 including Week 144 achieve PRO-2 remission

Clinical-biomarker response is defined as clinical response and ≥50% reduction from baseline in CRP or fecal calprotectin

Initiating or increasing the dose of a corticosteroid in the LTE is defined as a duration of use > 28 days if the reason for initiating or increasing the dose was NOT due to worsening Crohn's disease, or any duration of use if the reason for initiating or increasing the dose was due to worsening Crohn's disease.

Endoscopic response is defined as at least 50% improvement from baseline in SES-CD score or SES-CD score ≤2

Daily average abdominal pain score is defined as: the sum of abdominal pain/cramps ratings in previous 7 days in a dairy card ÷ total days assessment performed. Daily average abdominal pain score at a scheduled visit will not be calculated if the total days of assessment is less than 5.

Daily average stool frequency score is defined as: total number of liquid or very soft stools in previous 7 days in a dairy card ÷ total days assessment performed. Daily average stool frequency score at a scheduled visit will not be calculated if the total days of assessment is less than 5.

The **Simple Endoscopic Score for Crohn's Disease (SES-CD)** is a scoring system developed to provide a more granular evaluation of endoscopic disease severity in participants with Crohn's disease. It is constructed based on the evaluation of 4 endoscopic components across 5 predefined ileocolonic segments. The 4 endoscopic components within each segment are: the presence/size of ulcers, the proportion of mucosal surface covered by ulcers, the proportion of mucosal surface affected by any other lesions, and the presence/ type of narrowing (also commonly referred to as strictures/ stenosis clinically). Each endoscopic component is scored from 0 to 3 for each segment, and a total score is calculated as a sum of all the component scores across all the segments, as outlined in Table 7. The total SES-CD score ranges from 0 to 56.

Table 7: Sample Score Sheet and Scoring Definitions for the Simple Endoscopic Score for Crohn's Disease (SES-CD)

	Ileum	Right Colon	Transverse Colon	Left Colon	Rectum	Total
1. Presence and size of ulcers (0-3)						15 max
2. Extent of ulcerated surface (0-3)						15 max
3. Extent of affected surface (0-3)						15 max
4. Presence and type of narrowings (0-3)						11 max*
Total 1 + 2 + 3 + 4 =						SES-CD (56 max)

	Score = 0	Score = 1	Score = 2	Score = 3
Size of ulcers	None	Aphthous ulcers (ø 0.1 – 0.5 cm)	Large ulcers (ø 0.5 – 2.0 cm)	Very large ulcers (ø > 2.0 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

* The maximum sub-score for narrowings (ie, stricturing) is 11 points. The presence of a narrowing that cannot be passed can be only observed once.
ø =Diameter.

Calculation of the SES-CD score:

The total SES-CD score at a visit will be calculated based on all segments scored at the visit. If the total SES-CD score cannot be calculated (i.e., no segment is scored) at a visit, the total SES-CD score will be considered missing.

Endoscopic remission (Region Specific) is defined as an SES-CD score ≤ 2.

W192 DBL and Final Analysis DBL: Endoscopic remission (Global) is defined as an SES-CD score ≤ 4 with at least a 2-point reduction from baseline and no subscore greater than 1 in any individual subcomponent.

Clinical biomarker remission is defined as clinical remission and CRP ≤3 mg/L or fecal calprotectin concentration ≤250 µg/g.

The **Inflammatory Bowel Disease Questionnaire** (Irvine et al, 1994) is a 32-item questionnaire specifically designed for participants with IBD. The range of the IBDQ score is 32 to 224. Higher scores indicate better quality of life. The IBDQ has 4 dimension scores (bowel, systemic, social, and emotional). Each of the individual IBDQ dimensions will be calculated when ≤ 1 item is missing in the dimension. The missing item will be estimated using the average value across the nonmissing items. If any one of the dimensions within the IBDQ cannot be calculated, then the total IBDQ score cannot be calculated.

IBDQ remission is defined as an IBDQ score ≥ 170.

The **PROMIS-29** is a validated general health profile instrument that is not disease-specific. It is a collection of short forms containing 4 items for each of 7 domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities). PROMIS-29 also includes an overall average pain intensity 0-10 numeric rating scale (NRS). They assess all domains over the past seven days except for Physical Function which has no timeframe specified. 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). For PROMIS domains of Depression, Anxiety, Physical Function, Pain Interference, and Fatigue, a score of 50 is the average for the United States general population with a standard deviation of 10, because testing was performed on a large sample of the general population. However, the other two domains (Ability to Participate in Social Roles and Activities and Sleep Disturbance) were not centered in a national sample. For these two domains, a score of 50 represents the average of the calibration sample which was generally more enriched for chronic illness, and a score of 50 likely represents somewhat sicker people than the general population. For symptom-oriented domains of PROMIS-29 (anxiety, depression, fatigue, pain interference, and sleep disturbance), higher scores represent worse symptoms and a T-score of 60 is one SD worse than average. For the function oriented domains (physical functioning and social role), higher scores represent better functioning and a T-score of 60 is one SD better than average. Additionally, the physical component summary score (PCS) and mental component summary score (MCS) will each be derived from all 7 domain scores of PROMIS-29 (reference) as measures for general health related quality (HRQOL). Higher PCS and MCS scores indicate better HRQOL

Histologic assessment will be performed using biopsy samples collected during endoscopy. Biopsy samples will be collected at screening, Week 12, Week 48, Week 96, Week 144, Week 192 and Week 240 from each of 3 predefined anatomic locations: the terminal ileum, splenic flexure, and rectum. Biopsies will be collected from representative areas that are consistent with the inflammation status visually observed during endoscopy. Histologic assessment will be conducted by a central reader who is blinded to treatment groups, sites and visits.

The original Global Histology Activity Score (GHAS) was evaluated up to and including Week 144. At Week 192 and Week 240 the modified GHAS was evaluated. Histologic assessments using Geboes scores and RHI scores will be evaluated at Weeks 12, 48, 96, 144, 192 and 240.

The **Global Histology Activity Score** was first described in 1998, and has been subsequently utilized in a number of studies resulting in peer-reviewed publications.[2,3,4,5,6,7] The GHAS components and related scores are listed in Table 8. All biopsies for each region will be scored in a blinded manner using the GHAS, with minor adaptations for the circumstances of this study.

Modified GHAS (evaluated at Week 192 and Week 240)

- At each time point, all biopsies (up to 2 biopsies per region) obtained from each of the predefined anatomic regions will be scored separately for each of the 8 histological features; feature 8 has been modified from the original GHAS:

1. epithelial damage (scored 0-2)
2. architectural changes (scored 0-2)
3. infiltration of mononuclear cells into the lamina propria (scored 0-2)
4. polymorphonuclear cells in the lamina propria (scored 0-2)
5. polymorphonuclear cells in the epithelium (scored 0-3)
6. the presence of erosions/ulcers (1 for presence and 0 for absence)
7. presence of granulomas (1 for presence and 0 for absence)
8. percentage of the tissue affected on the slide image(s) (0 for none, 1 for >0 and <33%, 2 for 33-66%, and 3 for >66%); blinded readers will assess the percentage of tissue involved, considering both biopsies for a given segment (note that in the original GHAS, this component was measured as "number of biopsies affected")

- For items 1-7, the single highest scoring feature from each of the biopsy will be used as the score for that feature.
- The sum of the 8 scores within a region (terminal ileum, splenic flexure, rectum) will be used as the Total score for that region (range 0-16). Furthermore,
  - The worst available scores for each feature across the 3 regions will be summed to obtain a Subject Score

If both biopsies within a region (ileum, splenic flexure, rectum) are missing or unevaluable, the GHAS score will be missing for that region.

Histologic response and histo-endoscopic response are evaluated. These are on a subject level only.

Original GHAS (evaluated up to and including Week 144)

- At each time point, all biopsies (up to 2 biopsies per region) obtained from each of the predefined anatomic regions will be scored separately for each of the 6 histological features: epithelial damage, architectural changes, infiltration of mononuclear cells into the lamina propria, polymorphonuclear cells in the lamina propria (all scored 0-2); polymorphonuclear cells in the epithelium (scored 0-3); the presence of erosions/ulcers (1 for presence and 0 for absence)
- The component of presence of granulomas in the original GHAS will be excluded due to the rarity and potentially sporadic nature of granulomas, particularly in individual biopsy specimens (prevalence ~2%)
- The component of number of biopsies affected in the original GHAS will also be excluded because only up to 2 biopsies will be taken from each anatomic region in this study, while the component score was constructed based on the assumption that 6 biopsies per region are available
- The single highest scoring biopsy from each of the anatomic regions will be used as the final score for that region.

At each visit, the overall total histologic score will be derived based on the sum of the 3 regional scores. The total GHAS can be calculated when all 3 regional scores are available. A regional score

for a biopsy will be missing if any of the 6 histological features is missing. For missing regional scores at post-baseline visit(s), the last available regional scores will be carried forward.

Table 8: Scoring System for Histologic Abnormalities in Crohn's Disease Mucosal Biopsy Specimens

Histologic findings	Score
Epithelial damage	0, Normal
	1, Focal pathology
	2, Extensive pathology
Architectural changes	0, Normal
	1, Moderately disturbed (<50%)
	2, Severely disturbed (>50%)
Infiltration of mononuclear cells in the lamina propria	0, Normal
	1, Moderate increase
	2, Severe increase
Polymorphonuclear cells in the lamina propria	0, Normal
	1, Moderate increase
	2, Severe increase
Polymorphonuclear cells in epithelium	1, In surface epithelium
	2, Cryptitis
	3, Crypt abscess
Presence of erosion and/or ulcers	0, No
	1, Yes
Presence of granuloma	0, No
	1, Yes
No. of biopsy specimens affected	0, None (0 of 6)
	1, ≤33% (1 or 2 of 6)
	2, 33%–66% (3 or 4 of 6)
	3, >66% (5 or 6 of 6)
Total	

NOTE. Each topic should be scored independently. Moderate increase, up to twice the number of cells that can normally be expected; severe increase, more than twice the normal of cells. Reprinted with permission from D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastro-

Histologic response (original GHAS) evaluated up to and including Week 144 is defined as GHAS of 0 or ≥50% reduction in total GHAS from baseline.

Histologic response (modified GHAS) evaluated at Week 192 and Week 240 is defined as ≥ 50% reduction in subject-level GHAS score from baseline, or absence of mucosal neutrophils (epithelium and lamina propria), epithelial damage, erosions and ulceration [Q1 = 0, Q4 = 0, Q5 = 0 and Q6 = 0]. For this analysis, baseline will be re-calculated according to the modified GHAS procedure to evaluate the GHAS histologic response at Week 192 and at Week 240. Additionally, at both the time point of analysis and baseline, feature 8 will be excluded.

Histo-endoscopic response (GHAS) is defined as a combination of histologic response and endoscopic response (≥50% improvement from baseline in SES-CD score or SES-CD score ≤2).

Histologic disease activity at baseline (GHAS) is defined as a score > 0 for infiltration of polymorphonuclear cells in the lamina propria, polymorphonuclear cells in epithelium, or presence of erosions and/or ulcers [Q1 > 0 or Q4 >0 or Q5 > 0 or Q6 > 0] at baseline.

Geboes Grading System

Histological disease activity will be scored in a blinded manner by an experienced pathologist using the Geboes Scoring system (GS). The GS is a 7-item scale (with 4 levels of severity for each item) that categorizes inflammation as grade 0 (architectural change only), grade 1 (chronic inflammation), grade 2 (2a, lamina propria eosinophils and 2b, lamina propria neutrophils), grade 3 (neutrophils in the epithelium), grade 4 (crypt destruction), or grade 5 (erosion or ulceration), as illustrated in Table 9.

Table 9: Grading Criteria for the Histological Evaluation of Disease Activity in CD (Geboes Grading System)

Grade 0	Structural (architectural change)
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	Chronic inflammatory infiltrate
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	Lamina propria neutrophils and eosinophils
2A Eosinophils	
2A. 0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B. 0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	Neutrophils in epithelium
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4	Crypt destruction
4.0	None
4.1	Probable—local excess of neutrophils in part of crypt
4.2	Probable—marked attenuation
4.3	Unequivocal crypt destruction
Grade 5	Erosion or ulceration
5.0	No erosion, ulceration, or granulation tissue
5.1	Recovering epithelium+adjacent inflammation
5.2	Probable erosion—focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

- At each time point, all biopsies (up to 2 biopsies per region) obtained from each of the predefined anatomic regions will be scored separately for each of the 7 items:
- The single highest scoring item from each of the biopsy will be used as the score for that item.
- The Subject score is equal to the highest grade with a score > 0 across the ileum, splenic flexure and rectum.

If both biopsies within a region are missing or unevaluable, the GS will be missing for that region.

Histologic response and histo-endoscopic response are evaluated. These are on a subject level only.

Histologic response (Geboes) is defined as ≤ 3.1 indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue).

Histo-Endoscopic response (Geboes) is defined as Histologic response and endoscopic response (≥50% improvement from baseline in SES-CD score or SES-CD score ≤2).

Histologic disease activity at baseline (Geboes) is defined as >2B.0 [Grade 2B ≠ 0 OR Grade 3 ≠ 0 OR Grade 4 ≠ 0 OR Grade 5 ≠ 0] at baseline.

Robarts Histologic Index (RHI) Grading System

Histological disease activity will be scored by a blinded experienced pathologist using the Robarts Histopathology Index (RHI). The RHI is a 4-item index (with 4 levels for each item) that evaluates chronic inflammation, lamina propria neutrophils, neutrophils in the epithelium, and erosion or ulceration as illustrated in Table 10. Total score ranges from 0 to 33, where higher scores denote more severe inflammation.

Table 10: Robarts Histologic Index

Component
1. Chronic inflammatory infiltrate
0=No increase
1=Mild but unequivocal increase
2=Moderate increase
3=Marked increase
2. Lamina propria neutrophils
0=None
1=Mild but unequivocal increase
2=Moderate increase
3=Marked increase
3. Neutrophils in epithelium
0=None
1=<5% crypts involved
2=<50% crypts involved
3=>50% crypts involved
4. Erosion or ulceration
0=No erosion, ulceration or granulation tissue
1=Recovering epithelium+adjacent inflammation
1=Probable erosion—focally stripped
2=Unequivocal erosion
3=Ulcer or granulation tissue

RHI = 1 x chronic inflammatory infiltrate level (4 levels)
+ 2 x lamina propria neutrophils (4 levels)
+ 3 x neutrophils in epithelium (4 levels)
+ 5 x erosion or ulceration (4 levels)

- At each time point, all biopsies (up to 2 biopsies per region – splenic flexure, rectum, ileum) obtained from each of the predefined anatomic regions will be scored separately for each of the 4 items:

- The single highest scoring item from each of the biopsy will be used as the score for that item. If both biopsies within a region are missing or unevaluable, the RHI will be missing for that region. RHI is calculated using the Geboes scoring system.
- The weighted sum of the 4 scores within a region will be used as the score for that region (range 0-33). Specifically,

- Within the ileum, "Grades" 1 (chronic inflammatory infiltrate), 2B (lamina propria neutrophils), 3 (Neutrophils in epithelium) and 5 (erosion or ulceration) must be non-missing in order for the RHI Ileal score to be obtained. If any of these items are missing, the Ileal RHI will be missing.
- The RHI Colonic score is equal to the highest grade with a score > 0 across the splenic flexure and rectum. To calculate the RHI colonic score, each of the 4 Grades (1, 2B, 3, 5) must be non-missing for at least one of the segments (splenic flexure or rectum). The RHI colonic score is equal to the weighted sum of the highest scores across the 2 segments.
- The RHI Subject score is equal to the highest grade with a score > 0 across the ileum, rectum, and splenic flexure. To calculate the RHI subject-level score, each of the 4 Grades (1, 2B, 3, 5) must be non-missing for at least one of the regions (splenic flexure, rectum, ileum). The RHI subject score is equal to the weighted sum of the highest scores across the 3 segments.

Histologic response and histo-endoscopic response will be evaluated on a subject level only.

Histologic response (RHI) is defined as ≥ 50% reduction in RHI score from baseline or [a score ≤ 3 with sub-scores of lamina propria neutrophils and neutrophils in epithelium must be equal to 0, with no ulcers or erosions.]

Histo-Endoscopic response (RHI) is defined as Histologic response and endoscopic response (≥50% improvement from baseline in SES-CD score or SES-CD score ≤2).

Histologic disease activity at baseline (RHI) is defined as a score > 0 for any of Items 2-4 of RHI (lamina propria neutrophils, neutrophils in epithelium, or erosions or ulcerations) at baseline.

5.3.3. Estimands for Week 96 DBL

5.3.3.1. Main Estimand for analyses specific to LTE

The Main LTE Estimand will be used for Analysis Type 1 as defined in Table 3.

The estimand is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received during the LTE preceded by the induction and maintenance doses:

Experimental:

- Guselkumab 200 mg SC q4w (after receiving 1200 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 200 mg SC q4w (after receiving 600 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 100 mg IV q8w (after receiving 200 mg IV q4w during induction and 100 mg SC q8w during maintenance)

Reference:

- Ustekinumab 90 mg SC q8w (after receiving ~6 mg/kg IV at Week 0)

For the purpose of completeness, summaries will be provided for the randomized Placebo group (further categorized by whether they remained on Placebo or switched to Ustekinumab at Week 12), but these treatment groups are not the focus of the efficacy analyses.

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study.

Intercurrent Events and Corresponding Strategies:

The main estimand will be considered for both continuous and binary endpoints in which ICE 5 (ie, dose adjustment) is handled using the composite strategy:

1. A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)

2. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease

3. Discontinuation of study intervention due to reasons other than COVID-19 restrictions/issues, lack of efficacy or AE of worsening Crohn's disease; this includes discontinuation of study intervention due to COVID-19 Infection

4. Discontinuation of study intervention due to COVID-19 restrictions/issues and placebo discontinuations due to study unblinding

5. Dose adjustment from Weeks 52-80 for participants receiving placebo, ustekinumab, or guselkumab 100 mg, OR inadequate response for participants receiving guselkumab 200 mg (these participants receive a "sham" adjustment)

- ICEs 1, 2 and 5 will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable.
- ICE 3 will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.

- ICE 4 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

Participants may have more than one ICE (ie, categories 1, 5 and 2, 3 or 4). If ICE 1 or 5 occurs prior to ICE 2, 3 or 4, the composite strategy will be used at the point of ICE 1 or 5 going forward. If ICE 3 or 4 occurs prior to ICE 1 or 5, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1 or 5 (whichever is first), at which point the composite strategy will be used going forward.

CONTINUOUS ENDPOINTS

Variable (Endpoint): change from baseline to Week 96 (change = Week 96 - baseline).

- For the LTE-only analyses, participants who have intercurrent events in categories 1, 2, or 5 between Week 48-96 will have a zero change from baseline assigned from the point of the ICE, regardless of the observed data.

Population-level summary: means within each guselkumab group, within guselkumab 200 mg SC combined, and the randomized ustekinumab group.

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical Remission at Week 96); Percentage of participants who achieved clinical remission at Week 96 within each guselkumab group, combined guselkumab 200 mg SC group, and the randomized ustekinumab group**.**

- For the LTE-only analyses, participants who have an intercurrent events in categories 1, 2 or 5 between Week 48-96 will be considered non-responders from the point of the ICE, regardless of the observed data.

The variables and population -level summaries for the other binary endpoints (eg, clinical response at Week 96, PRO-remission at Week 96) are similarly described.

5.3.3.2. LTE Supplementary Estimand 1

LTE Supplementary Estimand 1 will be used for Analysis Types 2 as defined in Table 3.

LTE Supplementary Estimand 1 is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received during the LTE preceded by the induction and maintenance doses:

Experimental:

- Guselkumab 200 mg SC q4w (after receiving 1200 mg IV q4w during induction and 200 mg SC q4w during maintenance)

- Guselkumab 200 mg SC q4w (after receiving 600 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 100 mg IV q8w (after receiving 200 mg IV q4w during induction and 100 mg SC q8w during maintenance)

Only the guselkumab dose groups will be summarized for analyses related to this estimand. Participants randomized to placebo or ustekinumab will be excluded from these analyses.

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study.

Intercurrent Events and Corresponding Strategies:

The same 5 ICEs provided for the Main Estimand apply to LTE Supplementary Estimand 1.

- ICEs 1 and 2 will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable.
- ICE 3 will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).
- ICE 5 will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.

Participants may have more than one ICE (ie, categories 2, 3, or 4 and (ICE 1 and/or 5)). If ICE 1 occurs prior to ICE 2, 3, 4 or 5, the composite strategy will be used at the point of ICE 1 going forward. If ICE 3 or 4 occurs prior to ICE 1, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1, at which point the composite strategy, will be used going forward. If ICE 5 occurs prior to any other ICE, the treatment policy strategy will be used until the time of the next ICE, at which point the composite strategy (ICE 1, 2) or hypothetical strategy (ICE 4) will be used going forward.

The composite strategy assesses the treatment effects not only based on the variable measurements, but also based on intercurrent events. This estimand acknowledges that having an intercurrent event in category 1 or 2 is an unfavorable outcome. For participants experiencing ICEs 3 or 5, observed values of the variable will be used, if available. For ICE 4, the estimand will consider data after this ICE as missing at random.

CONTINUOUS ENDPOINTS

Variable (Endpoint): change from baseline to Week 96 (change = Week 96-baseline).

- For the LTE-only analyses, participants who have an intercurrent events in categories 1 or 2 between Week 48-96 will have a zero change from baseline assigned from the point of the ICE, regardless of the observed data.

Population-level summary: means within each guselkumab group and within guselkumab 200 mg SC combined.

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical Remission at Week 96); Percentage of participants who achieved clinical remission at Week 96 within each guselkumab group and the combined guselkumab 200 mg SC group**.**

- For the LTE-only analyses, participants who have an intercurrent events in categories 1 and 2 between Week 48-96 will be considered non-responders from the point of the ICE, regardless of the observed data.

The variables and population -level summaries for the other binary endpoints (eg, clinical response at Week 96, PRO-remission at Week 96) are similarly described.

5.3.3.3. LTE Supplementary Estimand 2

LTE Supplementary Estimand 2 will be used for Analysis Type 3 as defined in Table 3.

LTE Supplementary Estimand 2 is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received during the LTE preceded by the induction and maintenance doses:

Experimental:

- Guselkumab 200 mg SC q4w (after receiving 1200 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 200 mg SC q4w (after receiving 600 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 100 mg IV q8w (after receiving 200 mg IV q4w during induction and 100 mg SC q8w during maintenance)

Reference:

- Ustekinumab 90 mg SC q8w (after receiving ~6 mg/kg IV at Week 0)

For the purpose of completeness, summaries will be provided for the randomized Placebo group (further categorized by whether they remained on Placebo or switched to Ustekinumab at Week 12), but these treatment groups are not the focus of the efficacy analyses.

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study.

Intercurrent Events and Corresponding Strategies:

The same 5 ICEs provided for the Main Estimand apply to LTE Supplementary Estimand 2.

- ICEs 1 and 2 will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable.
- ICEs 3 will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 and 5 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

Participants may have more than one ICE (ie, categories 2, 3, or 4 and (ICE 1 and/or 5)). If ICE 1 occurs prior to ICE 2, 3, 4 or 5, the composite strategy will be used at the point of ICE 1 going forward. If ICE 3 or 4 occurs prior to ICE 1, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1, at which point the composite strategy, will be used going forward. If ICE 5 occurs prior to any other ICE, the hypothetical strategy will be used.

The composite strategy assesses the treatment effects not only based on the variable measurements, but also based on intercurrent events. This estimand acknowledges that having an intercurrent event in category 1 or 2 is an unfavorable outcome. For participants experiencing ICEs 3, observed values of the variable will be used, if available. For ICEs 4 and 5, the estimand will consider data after this ICE as missing at random.

CONTINUOUS ENDPOINTS

Variable (Endpoint): change from baseline to Week 96 (change = Week 96-baseline).

- For the LTE-only analyses, participants who have an intercurrent events in categories 1 or 2 between Week 48-96 will have a zero change from baseline assigned from the point of the ICE, regardless of the observed data.

Population-level summary: means within each guselkumab group and within the guselkumab 200 mg SC combined group.

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical Remission at Week 96); Percentage of participants who achieved clinical remission at Week 96 within each guselkumab group and the combined guselkumab 200 mg SC group**.**

- For the LTE-only analyses, participants who have an intercurrent events in categories 1 and 2 between Week 48-96 will be considered non-responders from the point of the ICE, regardless of the observed data.

The variables and population -level summaries for the other binary endpoints (eg, clinical response at Week 96, PRO-remission at Week 96) are similarly described.

5.3.3.4. LTE Supplementary Estimand 3

LTE Supplementary Estimand 3 will be used for Analysis Type 4 as defined in Table 3.

LTE Supplementary Estimand 3 is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received during the LTE preceded by the induction and maintenance doses:

Experimental:

- Guselkumab 200 mg SC q4w (after receiving 1200 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 200 mg SC q4w (after receiving 600 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 100 mg IV q8w (after receiving 200 mg IV q4w during induction and 100 mg SC q8w during maintenance)

Reference:

- Ustekinumab 90 mg SC q8w (after receiving ~6 mg/kg IV at Week 0)

For the purpose of completeness, summaries will be provided for the randomized Placebo group (further categorized by whether they remained on Placebo or switched to Ustekinumab at Week 12), but these treatment groups are not the focus of the efficacy analyses.

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study.

Intercurrent Events and Corresponding Strategies:

The same 5 ICEs provided for the Main Estimand apply to LTE Supplementary Estimand 3.

ICEs 1, 2 and 3 will be handled using the Treatment Policy strategy, and ICEs 4 and 5 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used.

CONTINUOUS ENDPOINTS

Variable (Endpoint): change from baseline to Week 96 (change = Week 96-baseline).

Population-level summary: means within each guselkumab group and the guselkumab 200 mg SC combined group.

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical Remission at Week 96); Percentage of participants who achieved clinical remission at Week 96 within each guselkumab group and the combined guselkumab 200 mg SC group**.**

The variables and population -level summaries for the other binary endpoints (eg, clinical response at Week 96, PRO-remission at Week 96) are similarly described.

5.3.3.5. LTE Supplementary Estimand 4

LTE Supplementary Estimand 4 will be used for Analysis Type 5 as defined in Table 3.

LTE Supplementary Estimand 4 is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received after and immediately before dose adjustment:

Experimental:

- Guselkumab 200 mg SC q4w after receiving Guselkumab 100 mg SC q8w during LTE
- Guselkumab 200 mg SC q4w after receiving Guselkumab 200 mg SC q4w during LTE
- Guselkumab 200 mg SC q4w after receiving Ustekinumab 90 SC q8w during LTE
- Guselkumab 200 mg SC q4w after receiving Placebo SC during LTE

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study; participants who dose-adjusted from Weeks 52-80 of the LTE.

Intercurrent Events and Corresponding Strategies:

The ICEs 1-4 provided for the Main Estimand apply to LTE Supplementary Estimand 4. These ICEs would occur after the dose adjustment.

- ICEs 1 and 2 will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable.
- ICEs 3 will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.

- ICE 4 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

CONTINUOUS ENDPOINTS

Variable (Endpoint): change from baseline to Week 96 (change = Week 96-baseline).

- For the LTE-only analyses, participants who have an intercurrent events in categories 1 or 2 between Week 48-96 will have a zero change from baseline assigned from the point of the ICE, regardless of the observed data.

Population-level summary: means within each treatment group.

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical Remission at Week 96); Percentage of participants who achieved clinical remission at Week 96 within each guselkumab group and the combined guselkumab 200 mg SC group**.**

- For the LTE-only analyses, participants who have an intercurrent events in categories 1 and 2 between Week 48-96 will be considered non-responders from the point of the ICE, regardless of the observed data.

The variables and population -level summaries for the other binary endpoints (eg, clinical response at Week 96, PRO-remission at Week 96) are similarly described.

5.3.3.6. Supplementary Estimand 1 for the Overtime Analyses

OT Supplementary Estimand 1 will be used for Analysis Type 6 as defined in Table 3.

Population: participants with moderately to severely active Crohn's disease. For the overtime analyses (ie, from Week 0 through Week 96), OT Supplementary Estimand 1 will be considered for both continuous and binary endpoints in which the following ICEs will be considered:

1. A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.);

2. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease;

3. Discontinuation of study intervention due to reasons other than COVID-19 restrictions/issues, lack of efficacy or AE of worsening Crohn's disease; this includes discontinuation of study intervention due to COVID-19 infection;

4. Discontinuation of study intervention due to COVID-19 restrictions/issues;

5. Dose adjustment from Weeks 52-80 for participants receiving placebo, ustekinumab, or guselkumab 100 mg, OR inadequate response for participants receiving guselkumab 200 mg (these participants receive a "sham" adjustment)

6. A prohibited change in CD medications prior to Week 48 (for details, see Appendix 11)

If a participant did not enter the LTE, their discontinuation of study intervention is noted as one of the ICEs above.

- ICEs 1 (from weeks 0-96), 2 (from weeks 0-96), 5, and 6 (prior to Week 48) will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable.
- ICE 3 (from Weeks 0-96) will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 (from Weeks 0-96) will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

If ICE 6 occurs prior to Week 48, the composite approach will be used through Week 96. After Week 48, a prohibited change in CD medications will not be considered an ICE.

The intercurrent events for SES-CD related endpoints overtime are the same as those listed above with the exception of ICE 6. ICE 6 for estimands related to SES-CD is described in Appendix 11.

Participants may have more than one ICE. If ICE 1 or 5 occurs prior to ICE 2, 3 or 4, the composite strategy will be used at the point of ICE 1 or 5 going forward. If ICE 3 or 4 occurs prior to ICE 1 or 5, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1 or 5, at which point the composite strategy will be used going forward. If ICE 6 occurs prior to Week 48, the composite strategy will be used at the point of ICE 6 through Week 96. The strategy for handling ICE 6 will override the strategies for handling ICE 3 or 4 only if ICE 6 occurs prior to Week 48.

The Treatment component of the OT Supplementary Estimand 1 is the same as those for the Main Estimand.

Variable (Continuous Endpoint): change from baseline to Week 96 (change = Week 96-baseline). Participants who have an intercurrent event described by categories 1, 2, or 5 will have a zero change from baseline assigned, regardless of the observed data. Participants who have an ICE described by category 6 prior to Week 48 will have a zero change from baseline assigned, regardless of the observed data, through Week 96.

Variable (Binary Endpoint): Achievement of endpoint (eg, clinical remission) at Week 96. Participants who have an intercurrent event described by categories 1, 2 or 5 will be considered non-responders, regardless of the observed data. Participants who have an ICE described by category 6 prior to Week 48 will be considered non-responders, regardless of the observed data, through Week 96.

5.3.3.7. Supplementary Estimand 2 for the Overtime Analyses

OT Supplementary Estimand 2 will be used for Analysis Type 7 as defined in Table 3.

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

For the overtime analyses (ie, from Week 0 through Week 96), OT Supplementary Estimand 2 will be considered for both continuous and binary endpoints in which the 6 ICEs described in Section 5.3.3.6 will be considered.

- ICEs 1 (from weeks 0-96), 2 (from weeks 0-96), and 6 (prior to Week 48) will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable.
- ICEs 3 and 5 (from Weeks 0-96) will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 (from Weeks 0-96) will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

Intercurrent events (ICEs) in categories 1 and 2 will be handled by the composite strategy from the point of the ICE forward. This means that if the ICE occurred at any time from Weeks 0 – 96, the baseline score (for continuous endpoints) or non-responder imputation (for binary endpoints) will be used from the point of the ICE through Week 96. ICE categories 3 and 5 will be handled by the treatment policy strategy at any time during the 96-week study period. ICE category 4 occurring at any time during the 96-week study period will be handled using the hypothetical strategy. Finally, if ICE 6 occurs prior to Week 48, the composite approach will be used through Week 96. After Week 48, a prohibited change in CD medications will not be considered an ICE.

The intercurrent events for SES-CD related endpoints overtime are the same as those listed above with the exception of ICE 6. ICE 6 for estimands related to SES-CD is described in Appendix 11. If a participant did not enter the LTE, their discontinuation of study intervention is noted as one of the ICEs above.

Participants may have more than one ICE. If ICE 1 occurs prior to ICE 2, 3 or 4, the composite strategy will be used at the point of ICE 1 going forward. If ICE 3, 4 or 5 occurs prior to ICE 1, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1, at which point the composite strategy will be used going forward. If ICE 6 occurs prior to Week 48, the composite strategy will be used at the point of ICE 6 through Week 96. The strategy for handling ICE 6 will override the strategies for handling ICE 3, 4 or 5 only if ICE 6 occurs prior to Week 48.

The Treatment component of the OT Supplementary Estimand 1 is the same as those for the LTE Supplementary Estimand 1.

Variable (Continuous Endpoint): change from baseline to Week 96 (change = Week 96-baseline). Participants who have an intercurrent event described by categories 1 or 2 will have a zero change from baseline assigned, regardless of the observed data. Participants who have an ICE described by category 6 prior to Week 48 will have a zero change from baseline assigned, regardless of the observed data, through Week 96.

Variable (Binary Endpoint): Achievement of endpoint (eg, clinical remission) at Week 96. Participants who have an intercurrent event described by categories 1 or 2 will be considered non-responders, regardless of the observed data. Participants who have an ICE described by

category 6 prior to Week 48 will be considered non-responders, regardless of the observed data, through Week 96.

5.3.4. Analysis Methods for Week 96 DBL

LTE-Only Analyses

The analyses of the LTE efficacy endpoints will be based on the LTE Efficacy Analysis Set. Descriptive statistics (i.e., N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts, percentages and 95% CIs for point estimates will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data.

For the main analyses, the treatments groups to be summarized will be each guselkumab treatment group, the guselkumab 200 mg SC q4w combined group, the guselkumab combined treatment group, and the ustekinumab group. The placebo group will be summarized for completeness but is not the focus of this analysis. No formal comparisons will be made, but descriptive statistics will be explored to estimate the long-term effects of guselkumab.

For binary endpoints using Analysis Types 1, 2, and 5, participants with missing data are considered to be non-responders. However, for continuous endpoints using Analysis Types 1, 2 and 5, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICEs, will not be imputed.

An observed case approach will be used for Analysis Types 3 and 4, and missing data, after accounting for the intercurrent events, will be excluded from the analyses. This approach will apply only to 6 key endpoints identified in Section 5.3.1.

Overtime Analyses

The analyses of the overtime endpoints will be based on the Primary Efficacy Analysis Set. Descriptive statistics (i.e., N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts, percentages and 95% CIs for point estimates will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data.

For ITT Analysis Types 6 and 7, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICEs, will not be imputed for continuous endpoints. However, for binary endpoints, participants with missing data are considered to be non-responders.

5.3.5. Estimands for Week 152 DBL

5.3.5.1. Main Estimand for analyses specific to LTE

The Main LTE Estimand will be used for Analysis Type 1 as defined in Table 4.

The estimand is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received during the LTE preceded by the induction and maintenance doses:

Experimental:

- Guselkumab 200 mg SC q4w (after receiving 1200 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 200 mg SC q4w (after receiving 600 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 100 mg IV q8w (after receiving 200 mg IV q4w during induction and 100 mg SC q8w during maintenance)

Reference:

- Ustekinumab 90 mg SC q8w (after receiving ~6 mg/kg IV at Week 0)

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study.

Intercurrent Events and Corresponding Strategies:

The following are the intercurrent events considered in the main estimand in which ICE 5 (ie, dose adjustment) is handled using the composite strategy:

1. A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)
2. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease
3. Discontinuation of study intervention due to reasons other than COVID-19 restrictions/issues, lack of efficacy or AE of worsening Crohn's disease; this includes discontinuation of study intervention due to COVID-19 Infection
4. Discontinuation of study intervention due to COVID-19 restrictions/issues and placebo discontinuations due to study unblinding
5. Dose adjustment from Weeks 52-80 for participants receiving placebo, ustekinumab, or guselkumab 100 mg, OR "sham" adjustment from Weeks 52-80 for participants receiving guselkumab 200 mg

- ICEs 1, 2 and 5 will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable as follows. For continuous endpoints, participants who have ICEs in categories 1, 2, or 5 between Week 48-144 will have a zero change from baseline assigned from the point of the ICE, regardless of the observed data. For binary endpoints, participants who have ICEs in categories 1, 2 or 5 between Week 48-144 will be considered non-responders from the point of the ICE, regardless of the observed data.

- ICE 3 will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

Participants may have more than one ICE (ie, categories 1, 5 and 2, 3 or 4). If ICE 1 or 5 occurs prior to ICE 2, 3 or 4, the composite strategy will be used at the point of ICE 1 or 5 going forward. If ICE 3 or 4 occurs prior to ICE 1 or 5, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1 or 5 (whichever is first), at which point the composite strategy will be used going forward.

CONTINUOUS ENDPOINTS

Variable (Endpoint): change from baseline to Week 144 (change = Week 144 - baseline).

Population-level summary: means within each guselkumab group, and the randomized ustekinumab group.

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical Remission at Week 144); Percentage of participants who achieved clinical remission at Week 144 within each guselkumab group, and the randomized ustekinumab group**.**

The variables and population -level summaries for the other binary endpoints (eg, clinical response at Week 144, PRO-remission at Week 144) are similarly described.

5.3.5.2. Supplementary Estimand 1 for the Overtime Analyses

OT Supplementary Estimand 1 will be used for Analysis Type 2 as defined in Table 4.

Population: participants with moderately to severely active Crohn's disease. For the overtime analyses (ie, from Week 0 through Week 144), OT Supplementary Estimand 1 will be considered for both continuous and binary endpoints in which the following ICEs will be considered:

1. A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.);

2. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease;

3. Discontinuation of study intervention due to reasons other than COVID-19 restrictions/issues, lack of efficacy or AE of worsening Crohn's disease; this includes discontinuation of study intervention due to COVID-19 infection;

4. Discontinuation of study intervention due to COVID-19 restrictions/issues and placebo discontinuations due to study unblinding;

5. Dose adjustment from Weeks 52-80 for participants receiving placebo, ustekinumab, or guselkumab 100 mg, OR "sham" adjustment from Weeks 52-80 for participants receiving guselkumab 200 mg
6. A prohibited change in CD medications prior to Week 48 (for details, see Appendix 11)

If a participant did not enter the LTE, their discontinuation of study intervention is noted as one of the ICEs above.

- ICEs 1 (from weeks 0-144), 2 (from weeks 0-144), 5, and 6 (prior to Week 48) will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable as follows. For continuous endpoints, participants who have an ICE described by categories 1 (from weeks 0-144), 2 (from weeks 0-144), 5 or 6 (prior to Week 48) will have a zero change from baseline assigned from the point of the ICE onwards through Week 144, regardless of the observed data. For binary endpoints, participants who have an ICE described by categories 1 (from weeks 0-144), 2 (from weeks 0-144), 5 or 6 (prior to Week 48) will be considered non-responders from the point of the ICE onwards through Week 144, regardless of the observed data.
- ICE 3 (from Weeks 0-144) will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 (from Weeks 0-144) will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

If ICE 6 occurs prior to Week 48, the composite approach will be used through Week 144. A prohibited change in CD medications that occurs after Week 48 will not be considered an ICE.

The intercurrent events for SES-CD related endpoints overtime are the same as those listed above with the exception of ICE 6. ICE 6 for estimands related to SES-CD is described in Appendix 11.

Participants may have more than one ICE. If ICE 1 or 5 occurs prior to ICE 2, 3 or 4, the composite strategy will be used at the point of ICE 1 or 5 going forward. If ICE 3 or 4 occurs prior to ICE 1 or 5, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1 or 5, at which point the composite strategy will be used going forward. For ICE 6 the composite strategy will be used at the point of ICE 6 through Week 144. The strategy for handling ICE 6 will override the strategies for handling ICE 3 or 4.

The Treatment component of the OT Supplementary Estimand 1 is the same as those for the Main Estimand.

Variable (Continuous Endpoint): change from baseline to Week 144 (change = Week 144-baseline).

Variable (Binary Endpoint): Achievement of endpoint (e.g. clinical remission) at Week 144.

5.3.5.3. LTE Supplementary Estimand 4

LTE Supplementary Estimand 4 will be used for Analysis Type 5 as defined in Table 4.

LTE Supplementary Estimand 4 is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received after and immediately before dose adjustment:

Experimental:

- Guselkumab 200 mg SC q4w after receiving Guselkumab 100 mg SC q8w during LTE
- Guselkumab 200 mg SC q4w after receiving Guselkumab 200 mg SC q4w during LTE
- Guselkumab 200 mg SC q4w after receiving Ustekinumab 90 SC q8w during LTE
- Guselkumab 200 mg SC q4w after receiving Placebo SC during LTE

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study; participants who dose-adjusted from Weeks 52-80 of the LTE.

Intercurrent Events and Corresponding Strategies:

The ICEs 1-4 provided for the Main Estimand apply to LTE Supplementary Estimand 4. These ICEs would occur after the dose adjustment.

- ICEs 1 and 2 will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable as follows. For binary endpoints, participants who have ICEs in categories 1 or 2 will be considered non-responders from the point of the ICE, regardless of the observed data.
- ICE 3 will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical remission by visit at Week 96 and Week 144); Percentage of participants who achieved clinical remission at Week 144 within each guselkumab group and the combined guselkumab 200 mg SC group**.**

The variables and population -level summaries for the other binary endpoints (Endoscopic Response by visit at Week 96 and Week 144, Endoscopic Remission by visit at Week 96 and Week 144) are similarly described.

5.3.6. Analysis Methods for Week 152 DBL

LTE-Only Analyses

The analyses of the LTE efficacy endpoints will be based on the LTE Efficacy Analysis Set. Descriptive statistics (i.e., N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts, percentages and 95% CIs for point estimates will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data.

The treatments groups to be summarized will be participants who were receiving 100 mg SC q8w at the start of the long-term extension (100 mg SC q8w), participants who were receiving 200 mg SC at the start of the long-term extension (200 mg SC q4w), guselkumab combined (100 mg SC q8w and 200 mg SC q4w), randomized ustekinumab which consists of participants randomized to ustekinumab at Week 0, and the combined ustekinumab group which consists of participants randomized to ustekinumab and participants who switched to ustekinumab at Week 12 after receiving placebo. For the LTE Efficacy Analysis set, the placebo group will be excluded from tables and graphical displays. No formal comparisons will be made, but descriptive statistics will be explored to estimate the long-term effects of guselkumab.

For binary endpoints using Analysis Types 1 and 5, participants with missing data are considered to be non-responders. However, for continuous endpoints using Analysis Type 1 missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed.

Overtime Analyses from Week 0

The analyses of the overtime endpoints will be based on the Primary Efficacy Analysis Set. Descriptive statistics (i.e., N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts, percentages and 95% CIs for point estimates will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data.

The treatments groups to be summarized will be each guselkumab treatment group (200 mg IV q4w → 100 mg SC q8w; 600 mg IV q4w → 200 mg SC q4w; 1200 mg IV q4w → 200 mg SC q4w), combined guselkumab 200 mg SC q4w, combined guselkumab, ustekinumab 6 mg/kg IV → 90 mg SC q8w, placebo (participants receiving placebo on entry to the LTE), and placebo → ustekinumab (participants randomized to placebo who switched over to ustekinumab at Week 12). For the Primary Efficacy Analysis set, the placebo group will be shown in tables but not in graphical displays. No formal comparisons will be made, but descriptive statistics will be explored to estimate the long-term effects of guselkumab.

For binary endpoints, using Analysis Type 2 participants randomized to an active treatment group, or randomized to placebo and who crossed over to ustekinumab at Week 12 with missing data after accounting for ICE strategies are considered to be non-responders, while participants randomized to placebo and who did not crossover to ustekinumab at Week 12, and with missing data after accounting for ICE strategies will not be imputed and will be excluded from the analysis at that time point. However, for continuous endpoints using Analysis Type 2 missing data due to missed

visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed.

5.3.7. Estimands for Week 192 DBL

5.3.7.1. Main Estimand for analyses specific to LTE

The Main LTE Estimand will be used for Analysis Type 1 as defined in Table 5.

The estimand is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received during the LTE preceded by the induction and maintenance doses:

Experimental:

- Guselkumab 200 mg SC q4w (after receiving 1200 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 200 mg SC q4w (after receiving 600 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 100 mg IV q8w (after receiving 200 mg IV q4w during induction and 100 mg SC q8w during maintenance)

Reference:

- Ustekinumab 90 mg SC q8w (after receiving ~6 mg/kg IV at Week 0)

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study.

Intercurrent Events and Corresponding Strategies:

The following are the intercurrent events considered in the main estimand in which ICE 5 (ie, dose adjustment) is handled using the composite strategy:

1. A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)
2. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease
3. Discontinuation of study intervention due to reasons other than COVID-19 restrictions/issues, lack of efficacy or AE of worsening Crohn's disease; this includes discontinuation of study intervention due to COVID-19 Infection
4. Discontinuation of study intervention due to COVID-19 restrictions/issues and placebo discontinuations due to study unblinding

5. Dose adjustment from Weeks 52-80 for participants receiving placebo, ustekinumab, or guselkumab 100 mg, OR "sham" adjustment from Weeks 52-80 for participants receiving guselkumab 200 mg

- ICEs 1, 2 and 5 will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable as follows. For continuous endpoints, participants who have ICEs in categories 1, 2, or 5 between Week 48-192 will have a zero change from baseline assigned from the point of the ICE, regardless of the observed data. For binary endpoints, participants who have ICEs in categories 1, 2 or 5 between Week 48-192 will be considered non-responders from the point of the ICE, regardless of the observed data.
- ICE 3 will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

Participants may have more than one ICE (ie, categories 1, 5 and 2, 3 or 4). If ICE 1 or 5 occurs prior to ICE 2, 3 or 4, the composite strategy will be used at the point of ICE 1 or 5 going forward. If ICE 3 or 4 occurs prior to ICE 1 or 5, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1 or 5 (whichever is first), at which point the composite strategy will be used going forward.

CONTINUOUS ENDPOINTS

Variable (Endpoint): change from baseline to Week 192 (change = Week 192 - baseline).

Population-level summary: means within each guselkumab group, and the randomized ustekinumab group.

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical Remission at Week 192); Percentage of participants who achieved clinical remission at Week 192 within each guselkumab group, and the randomized ustekinumab group**.**

The variables and population -level summaries for the other binary endpoints (eg, clinical response at Week 192, PRO-remission at Week 192) are similarly described.

5.3.7.2. Supplementary Estimand 1 for the Overtime Analyses

OT Supplementary Estimand 1 will be used for Analysis Type 2 as defined in Table 5.

Population: participants with moderately to severely active Crohn's disease. For the overtime analyses (ie, from Week 0 through Week 192), OT Supplementary Estimand 1 will be considered for both continuous and binary endpoints in which the following ICEs will be considered:

1. A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.);

2. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease;

3. Discontinuation of study intervention due to reasons other than COVID-19 restrictions/issues, lack of efficacy or AE of worsening Crohn's disease; this includes discontinuation of study intervention due to COVID-19 infection;

4. Discontinuation of study intervention due to COVID-19 restrictions/issues and placebo discontinuations due to study unblinding;

5. Dose adjustment from Weeks 52-80 for participants receiving placebo, ustekinumab, or guselkumab 100 mg, OR "sham" adjustment from Weeks 52-80 for participants receiving guselkumab 200 mg

6. A prohibited change in CD medications prior to Week 48 (for details, see Appendix 11)

If a participant did not enter the LTE, their discontinuation of study intervention is noted as one of the ICEs above.

- ICEs 1 (from weeks 0-192), 2 (from weeks 0-192), 5, and 6 (prior to Week 48) will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable as follows. For continuous endpoints, participants who have an ICE described by categories 1 (from weeks 0-192), 2 (from weeks 0-192), 5 or 6 (prior to Week 48) will have a zero change from baseline assigned from the point of the ICE onwards through Week 192, regardless of the observed data. For binary endpoints, participants who have an ICE described by categories 1 (from weeks 0-192), 2 (from weeks 0-192), 5 or 6 (prior to Week 48) will be considered non-responders from the point of the ICE onwards through Week 192, regardless of the observed data.
- ICE 3 (from Weeks 0-192) will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 (from Weeks 0-192) will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used (as if the event did not occur).

If ICE 6 occurs prior to Week 48, the composite approach will be used through Week 192. A prohibited change in CD medications that occurs after Week 48 will not be considered an ICE.

The intercurrent events for SES-CD related endpoints overtime are the same as those listed above with the exception of ICE 6. ICE 6 for estimands related to SES-CD is described in Appendix 11.

Participants may have more than one ICE. If ICE 1 or 5 occurs prior to ICE 2, 3 or 4, the composite strategy will be used at the point of ICE 1 or 5 going forward. If ICE 3 or 4 occurs prior to ICE 1 or 5, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1 or 5, at which point the composite strategy will be used going forward. For ICE 6 the composite strategy will be used at the point of ICE 6 through Week 192. The strategy for handling ICE 6 will override the strategies for handling ICE 3 or 4.

The Treatment component of the OT Supplementary Estimand 1 is the same as those for the Main Estimand.

Variable (Continuous Endpoint): change from baseline to Week 192 (change = Week 192-baseline).

Variable (Binary Endpoint): Achievement of endpoint (e.g. clinical remission) at Week 192.

5.3.8. Analysis Methods for Week 192 DBL

LTE-Only Analyses

The analyses of the LTE efficacy endpoints will be based on the LTE Efficacy Analysis Set. Descriptive statistics (i.e., N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts, percentages and 95% CIs for point estimates will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data.

The treatments groups to be summarized will be participants who were receiving 100 mg SC q8w at the start of the long-term extension (100 mg SC q8w), participants who were receiving 200 mg SC at the start of the long-term extension (200 mg SC q4w), guselkumab combined (100 mg SC q8w and 200 mg SC q4w), randomized ustekinumab which consists of participants randomized to ustekinumab at Week 0, and the combined ustekinumab group which consists of participants randomized to ustekinumab and participants who switched to ustekinumab at Week 12 after receiving placebo. For the LTE Efficacy Analysis set, the placebo group will be excluded from tables and graphical displays. No formal comparisons will be made, but descriptive statistics will be explored to estimate the long-term effects of guselkumab.

For binary endpoints using Analysis Type 1, participants with missing data are considered to be non-responders. However, for continuous endpoints using Analysis Type 1 missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed.

Overtime Analyses from Week 0

The analyses of the overtime endpoints will be based on the Primary Efficacy Analysis Set. Descriptive statistics (i.e., N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts, percentages and 95% CIs for point estimates will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data.

The treatments groups to be summarized will be each guselkumab treatment group (200 mg IV q4w → 100 mg SC q8w; 600 mg IV q4w → 200 mg SC q4w; 1200 mg IV q4w → 200 mg SC q4w), combined guselkumab 200 mg SC q4w, combined guselkumab, ustekinumab 6 mg/kg IV → 90 mg SC q8w, placebo (participants receiving placebo on entry to the LTE), and placebo → ustekinumab (participants randomized to placebo who switched over to ustekinumab at Week 12).

For the Primary Efficacy Analysis set, the placebo group will be shown in tables but not in graphical displays. No formal comparisons will be made, but descriptive statistics will be explored to estimate the long-term effects of guselkumab.

For binary endpoints, using Analysis Type 2 participants randomized to an active treatment group, or randomized to placebo and who crossed over to ustekinumab at Week 12 with missing data after accounting for ICE strategies are considered to be non-responders, while participants randomized to placebo and who did not crossover to ustekinumab at Week 12, and with missing data after accounting for ICE strategies will not be imputed and will be excluded from the analysis at that time point. However, for continuous endpoints using Analysis Type 2 missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed.

5.3.9. Estimands for Final Analysis DBL

5.3.9.1. Main Estimand for analyses specific to LTE

The Main LTE Estimand will be used for Analysis Type 1 as defined in Table 6.

The estimand is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received during the LTE preceded by the induction and maintenance doses:

Experimental:

- Guselkumab 200 mg SC q4w (after receiving 1200 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 200 mg SC q4w (after receiving 600 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 100 mg SC q8w (after receiving 200 mg IV q4w during induction and 100 mg SC q8w during maintenance)

Reference:

- Ustekinumab 90 mg SC q8w (after receiving ~6 mg/kg IV at Week 0 and 90 mg SC q8w during maintenance)

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study.

Intercurrent Events and Corresponding Strategies:

The following are the intercurrent events considered in the main estimand:

1. A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)
2. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease
3. Discontinuation of study intervention due to reasons other than COVID-19 restrictions/issues, lack of efficacy or AE of worsening Crohn's disease; this includes discontinuation of study intervention due to COVID-19 Infection
4. Discontinuation of study intervention due to COVID-19 restrictions/issues and placebo discontinuations due to study unblinding
5. Dose adjustment from Weeks 52-80 for participants receiving placebo, ustekinumab, or guselkumab 100 mg, OR "sham" adjustment from Weeks 52-80 for participants receiving guselkumab 200 mg

- ICEs 1, 2 and 5 will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable as follows. For continuous endpoints, participants who have ICEs in categories 1, 2, or 5 between Week 48-240 will have a zero change from baseline assigned from the point of the ICE, regardless of the observed data. For binary endpoints, participants who have ICEs in categories 1, 2 or 5 between Week 48-240 will be considered non-responders from the point of the ICE, regardless of the observed data.
- ICE 3 will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used.

Participants may have more than one ICE (ie, categories 1, 5 and 2, 3 or 4). If ICE 1 or 5 occurs prior to ICE 2, 3 or 4, the composite strategy will be used at the point of ICE 1 or 5 going forward. If ICE 3 or 4 occurs prior to ICE 1 or 5, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1 or 5 (whichever is first), at which point the composite strategy will be used going forward. If an ICE 2 occurs prior to ICE 1 or 5, then the composite strategy will be used at the point of ICE 2 going forward.

CONTINUOUS ENDPOINTS

Variable (Endpoint): change from baseline to Week 240 (change = Week 240 - baseline).

Population-level summary: means within each guselkumab group, and the randomized ustekinumab group.

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical Remission at Week 240); Percentage of participants who achieved clinical remission at Week 240 within each guselkumab group, and the randomized ustekinumab group**.**

The variables and population -level summaries for the other binary endpoints (eg, clinical response at Week 240, PRO-remission at Week 240) are similarly described.

5.3.9.2. LTE Supplementary Estimand 3

LTE Supplementary Estimand 3 will be used for Analysis Type 3 as defined in Table 6.

LTE Supplementary Estimand 3 is defined by the following 5 attributes:

Treatment:

The treatment groups are defined by the treatment received during the LTE preceded by the induction and maintenance doses:

Experimental:

- Guselkumab 200 mg SC q4w (after receiving 1200 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 200 mg SC q4w (after receiving 600 mg IV q4w during induction and 200 mg SC q4w during maintenance)
- Guselkumab 100 mg SC q8w (after receiving 200 mg IV q4w during induction and 100 mg SC q8w during maintenance)

Reference:

- Ustekinumab 90 mg SC q8w (after receiving ~6 mg/kg IV at Week 0 and 90 mg SC q8w during maintenance)

For the purpose of completeness, summaries will be provided for the randomized Placebo group (further categorized by whether they remained on Placebo or switched to Ustekinumab at Week 12), but these treatment groups are not the focus of the efficacy analyses.

Population: participants with moderately to severely active Crohn's disease who, in the opinion of the investigator, would continue to benefit from treatment and thereby entered into the LTE phase of the study.

Intercurrent Events and Corresponding Strategies:

The same 5 ICEs provided for the Main Estimand apply to LTE Supplementary Estimand 3.

ICEs 1, 2 and 3 will be handled using the Treatment Policy strategy, and ICEs 4 and 5 will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used.

BINARY ENDPOINTS

Variables and Population-level Summary: Achievement of endpoint (eg, Clinical Remission at Week 240); Percentage of participants who achieved clinical remission at Week 240 within each guselkumab group and the combined guselkumab 200 mg SC group**.**

The variables and population -level summaries for the other binary endpoints (eg, PRO-2 remission at Week 240) are similarly described.

5.3.9.3. Supplementary Estimand 1 for the Overtime Analyses

OT Supplementary Estimand 1 will be used for Analysis Type 2 as defined in Table 6.

Population: participants with moderately to severely active Crohn's disease. For the overtime analyses (ie, from Week 0 through Week 240), OT Supplementary Estimand 1 will be considered for both continuous and binary endpoints in which the following ICEs will be considered:

1. A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.);
2. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease;
3. Discontinuation of study intervention due to reasons other than COVID-19 restrictions/issues, lack of efficacy or AE of worsening Crohn's disease; this includes discontinuation of study intervention due to COVID-19 infection;
4. Discontinuation of study intervention due to COVID-19 restrictions/issues and placebo discontinuations due to study unblinding;
5. Dose adjustment from Weeks 52-80 for participants receiving placebo, ustekinumab, or guselkumab 100 mg, OR "sham" adjustment from Weeks 52-80 for participants receiving guselkumab 200 mg
6. A prohibited change in CD medications prior to Week 48 (for details, see Appendix 11)

If a participant did not enter the LTE, their discontinuation of study intervention is noted as one of the ICEs above.

- ICEs 1 (from weeks 0-240), 2 (from weeks 0-240), 5, and 6 (prior to Week 48) will be handled by the composite strategy, where the occurrence of the ICE will be incorporated into the variable as follows. For continuous endpoints, participants who have an ICE described by categories 1 (from weeks 0-240), 2 (from weeks 0-240), 5 or 6 (prior to Week 48) will have a zero change from baseline assigned from the point of the ICE onwards through Week 240, regardless of the observed data. For binary endpoints, participants who have an ICE described by categories 1 (from weeks 0-240), 2 (from weeks 0-240), 5 or 6 (prior to Week 48) will be considered non-responders from the point of the ICE onwards through Week 240, regardless of the observed data.
- ICE 3 (from Weeks 0-240) will be handled using the treatment policy strategy. Whether the ICE has occurred or not is irrelevant; the data will be analyzed regardless, if available.
- ICE 4 (from Weeks 0-240) will be handled using the hypothetical strategy, where the data collected after the ICE occurred will not be used.

A prohibited change in CD medications that occurs after Week 48 will not be considered an ICE.

The intercurrent events for SES-CD related endpoints overtime are the same as those listed above with the exception of ICE 6. ICE 6 for estimands related to SES-CD is described in Appendix 11.

Participants may have more than one ICE. If ICE 1 or 5 occurs prior to ICE 2, 3 or 4, the composite strategy will be used at the point of ICE 1 or 5 going forward. If ICE 3 or 4 occurs prior to ICE 1 or 5, the treatment policy or hypothetical strategy will be used, respectively, until the time of ICE 1 or 5, at which point the composite strategy will be used going forward. If an ICE 2 occurs prior to ICE 1 or 5, then the composite strategy will be used at the point of ICE 2 going forward. For ICE 6 the composite strategy will be used at the point of ICE 6 through Week 240. The strategy for handling ICE 6 will override the strategies for handling ICE 3 or 4.

The Treatment component of the OT Supplementary Estimand 1 is the same as those for the Main Estimand.

Variable (Continuous Endpoint): change from baseline to Week 240 (change = Week 240-baseline).

Variable (Binary Endpoint): Achievement of endpoint (e.g. clinical remission) at Week 240.

5.3.10. Analysis Methods for Final Analysis DBL

LTE-Only Analyses

The analyses of the LTE efficacy endpoints will be based on the LTE Efficacy Analysis Set. Descriptive statistics (i.e., N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts, percentages and 95% CIs for point estimates will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data.

The treatment groups to be summarized will be participants who were receiving 100 mg SC q8w at the start of the long-term extension (100 mg SC q8w), participants who were receiving 200 mg SC at the start of the long-term extension (200 mg SC q4w), guselkumab combined (100 mg SC q8w and 200 mg SC q4w), randomized ustekinumab which consists of participants randomized to ustekinumab at Week 0, and the combined ustekinumab group which consists of participants randomized to ustekinumab and participants who switched to ustekinumab at Week 12 after receiving placebo. For the LTE Efficacy Analysis set, the placebo group will be excluded from tables and graphical displays. No formal comparisons will be made, but descriptive statistics will be explored to estimate the long-term effects of guselkumab.

For binary endpoints using Analysis Type 1, participants with missing data after accounting for ICE strategies are considered to be non-responders. However, for continuous endpoints using Analysis Type 1, missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed.

An observed case approach will be used for Analysis Type 3, and missing data, after accounting for the intercurrent events, will be excluded from the analyses. This approach will apply only to the key endpoints identified in Section 5.3.1.4.

Overtime Analyses from Week 0

The analyses of the overtime endpoints will be based on the Primary Efficacy Analysis Set. Descriptive statistics (i.e., N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts, percentages and 95% CIs for point estimates will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data.

The treatments groups to be summarized will be each guselkumab treatment group (200 mg IV q4w → 100 mg SC q8w; 600 mg IV q4w → 200 mg SC q4w; 1200 mg IV q4w → 200 mg SC q4w), combined guselkumab 200 mg SC q4w, combined guselkumab, ustekinumab 6 mg/kg IV → 90 mg SC q8w, placebo (participants receiving placebo on entry to the LTE), and placebo → ustekinumab (participants randomized to placebo who switched over to ustekinumab at Week 12). For the Primary Efficacy Analysis set, the placebo group will be shown in tables but not in graphical displays. No formal comparisons will be made, but descriptive statistics will be explored to estimate the long-term effects of guselkumab.

For binary endpoints, using Analysis Type 2 participants randomized to an active treatment group, or randomized to placebo and who crossed over to ustekinumab at Week 12 with missing data after accounting for ICE strategies are considered to be non-responders, while participants randomized to placebo and who did not crossover to ustekinumab at Week 12, and with missing data after accounting for ICE strategies will not be imputed and will be excluded from the analysis at that time point. However, for continuous endpoints using Analysis Type 2 missing data due to missed visits or missed data collection, as well as missing data after accounting for ICE strategies, will not be imputed.

5.3.11. Subgroup Analyses

Subgroup analyses will be performed when the number of participants in each subgroup permits.

5.3.11.1. Week 96 DBL

Summary data for **Clinical Remission at Week 96, Clinical Response at Week 96, Endoscopic Response at Week 96, PRO-2 Remission at Week 96, and Endoscopic Remission at Week 96** endpoints will be presented for the subgroups defined in Section 5.5.6. The main estimand and ITT analysis approach (ITT-LTE-DATF) will be used for all subgroup analyses.

Summary data for Clinical Remission, Clinical Response, Endoscopic Response and PRO-2 Remission endpoints over time through Week 96 will be presented for the subgroups defined in Section 5.5.6. Analysis Types 6 and 7 will be used for these analyses.

5.3.11.2. Week 152 DBL

Summary data for **Clinical Remission at Week 144, Clinical Response at Week 144, Endoscopic Response at Week 144, PRO-2 Remission at Week 144, and Endoscopic Remission at Week 144** endpoints will be presented for the subgroups defined in Section 5.5.6. The main estimand and ITT analysis approach (ITT-LTE-DAICE) will be used for all subgroup analyses.

Summary data for Clinical Remission, Clinical Response, Endoscopic Response and PRO-2 Remission endpoints over time through Week 144 will be presented for the subgroups defined in Section 5.5.6. Analysis Type 2 will be used for these analyses.

5.3.11.3. Week 192 DBL

Summary data for **Clinical Remission from Week 48 to Week 192, Endoscopic Response from Week 48 to Week 192, Endoscopic Remission (Region Specific) from Week 48 to Week 192, and Endoscopic Remission (Global) from Week 48 to Week 192 (NOT for the Global Defined subset)** endpoints will be presented for the subgroups defined in Section 5.5.6. The main estimand (Analysis Type 1, LTE Efficacy Analysis Set) will be used for these subgroup analyses.

Summary data for **Clinical Remission, PRO-2 Remission, Endoscopic Response, and Endoscopic Remission (Region Specific), Endoscopic Remission (Global) (NOT for the Global Defined subset) endpoints over time through Week 192** will be presented for the subgroups defined in Section 5.5.6. The Supplementary Estimand 1 (Analysis Type 2, Primary Efficacy Analysis Set) will be used for these analyses.

5.3.11.4. Final Analysis DBL

Summary data for **Clinical Remission from Week 48 to Week 240, Endoscopic Response from Week 48 to Week 240, Endoscopic Remission (Region Specific) from Week 48 to Week 240, and Endoscopic Remission (Global) from Week 48 to Week 240** endpoints will be presented for the subgroups defined in Section 5.5.6. The main estimand (Analysis Type 1, LTE Efficacy Analysis Set) will be used for these subgroup analyses.

Summary data for **Clinical Remission, PRO-2 Remission, Endoscopic Response, and Endoscopic Remission (Region Specific), Endoscopic Remission (Global) endpoints over time through Week 240** will be presented for the subgroups defined in Section 5.5.6. The Supplementary Estimand 1 (Analysis Type 2, Primary Efficacy Analysis Set) will be used for these analyses.

5.4. Safety Analyses

Safety data, including but not limited to, AEs and changes in laboratory assessments, will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

For all continuous safety variables, descriptive statistics will include N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. No formal statistical comparisons are planned.

Week 96 DBL

An overall summary of AEs from Baseline through Week 96 or until the time of dose adjustment will be provided using the Full Analysis Set.

Safety data limited to the LTE period (ie, from Week 48 through Week 96) will be summarized in two ways. The first will include data through Week 96 if there is no dose adjustment, or:

- up to the time of dose adjustment; or
- for those participants already receiving guselkumab 200 mg SC at the start of LTE, the time of meeting inadequate response criteria for dose adjustment (LTE Safety Analysis Set).

The second will include the data that was collected after the dose adjustment (LTE Safety Analysis Set with Data before and After Dose adjustment).

5.4.1. Extent of Exposure

The number and percentage of participants who receive study intervention will be summarized by treatment group for the LTE Safety analysis set. The following summaries will be presented:

- Distribution of Participants from Week 48 through Week 96 (Week 152) by Study Agent. Study Agent Lot will be summarized including data through dose adjustment.
- Summary of Cumulative SC Dose of Guselkumab and Ustekinumab From Week 48 Through Week 96 (Week 152) (Week 192) (Week 240) or Up to the time of Dose Adjustment
- Summary of Cumulative SC Dose of Guselkumab From the Time of Dose Adjustment Through Week 96 (Week 152); Randomized Participants Who Were Dose-Adjusted in the Long-Term Extension.

The average duration of study participation follow-up in weeks, defined by study discontinuation date, will be summarized by treatment group as part of the adverse event tables.

5.4.2. Adverse Events

5.4.2.1. Week 96 DBL

Adverse event data limited to the LTE period (ie, from Week 48 through Week 96) will be summarized in two ways. The first will include data up to the time of meeting dose adjustment or through Week 96 if there is no dose adjustment (LTE Safety Analysis Set). The second will include the adverse event that occurred after the dose adjustment (LTE Safety Analysis Set). In addition, an overall summary of AEs from Baseline through Week 96 will be provided using the Full Safety analysis set.

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using MedDRA. Treatment-emergent AEs (TEAEs) are AEs with onset during the intervention phase or

that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs which are treatment-emergent will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. Since safety should be assessed relative to exposure and follow-up, all AE summary tables will summarize the average weeks of follow-up and average exposure (number of administrations) for each treatment group.

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

- Frequency and type of AEs*
- Frequency and type of SAEs*
- Frequency and type of reasonably related AEs as assessed by the investigator
- Frequency and type of AEs leading to discontinuation of study intervention*
- Frequency and type of infections*, including serious infections* and infections requiring oral or parenteral antimicrobial treatment.
- Frequency and type of injection-site reactions.

* Adverse events will also be summarized as events per 100 participant years of follow-up, which would account for the potential for differences in follow-up times

These summary tables will provide the count and percentage of participants with 1 or more of the specified TEAEs by treatment group, system-organ class and preferred term. In addition to the summary tables, listings of participants with SAEs, TEAEs leading to discontinuation of study intervention, and COVID-19 related TEAEs will be provided. Any deaths, possible anaphylactic or serum-sickness like reactions, or malignancies, will either be presented in a listing or described in the clinical study report.

5.4.2.2. Week 152 DBL

An overall summary of treatment-emergent AEs (TEAEs) from Week 0 through Week 152 or until the time of dose adjustment will be provided using the Full Safety Analysis Set. The overall summary of TEAEs will also be provided for the LTE Safety Analysis Set from Week 0 through Week 152 or until the time of dose adjustment, from Week 48 through Week 152 regardless of dose adjustment, from Week 48 through Week 96 regardless of dose adjustment, and from Week 96 through Week 152 regardless of dose adjustment.

Other summaries of TEAEs will be provided for the Full Safety Analysis Set from Week 0 through Week 152 or until the time of dose adjustment, for the LTE Safety Analysis Set from Week 0 through Week 152 or until the time of dose adjustment, and from Week 48 through Week 152 regardless of dose adjustment.

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using MedDRA. TEAEs are AEs with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs which are

treatment-emergent will be included in the analysis. For AE analyses looking at a specific time period, events are not included if onset date or worsening since baseline occurs prior to the administration date of the beginning of that time period. For example, an AE that is onset prior to the Week 48 administration is not included in the Week 48 to Week 152 AE time reporting period. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. Since safety should be assessed relative to exposure and follow-up, all AE summary tables will summarize the average weeks of follow-up and average exposure (number of administrations) for each treatment group.

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

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

* Adverse events will also be summarized as events per 100 participant years of follow-up, which would account for the potential for differences in follow-up times

These summary tables will provide the count and percentage of participants with 1 or more of the specified TEAEs by treatment group, system-organ class and preferred term. In addition to the summary tables, listings of participants with SAEs, TEAEs leading to discontinuation of study intervention, and COVID19 related TEAEs will be provided. Any deaths or adverse events of special interest (cases of active tuberculosis or malignancies) as described in Appendix 8 will either be presented in a listing or described in the clinical study report. Further, AEs of clinical interest will be presented, including but not limited to the following: Venous thromboembolism (VTEs), Opportunistic Infections (narrow SMQ), MACE, drug-related hepatic disorders, anaphylactic reactions or serum sickness reactions, Infections, Serious infections, Injection site reactions (ISR) and Suicidal ideation and behavior (SIB).

Definitions

- A reasonably related AE is defined as any event with a relationship to study intervention of ‘Very likely’, ‘Probable’, or ‘Possible’ on the AE eCRF page or if the relationship to study agent is missing.
- An infection is defined as an AE coded to the infection and infestation SOC.
- A study intervention injection-site reaction is any reaction at an SC study intervention injection site that was recorded as an injection-site reaction by the investigator on the eCRF.

5.4.2.3. Week 192 DBL

For the W192 DBL, primary Safety analyses will report incidence rates of treatment-emergent AEs (TEAEs) per one hundred participant years of follow-up. Table column layouts are provided in the DPS. These will be provided for the following TEAEs:

- All TEAEs
- SAEs
- AEs leading to discontinuation of study intervention
- AEs of clinical interest, including but not limited to the following: Venous thromboembolism (VTEs); Opportunistic Infections; MACE; hepatic disorders; anaphylactic reactions or serum sickness reactions.
- AEs of special interest: Active tuberculosis; Malignancy excluding NonMelanoma Skin Cancer (exclude basal cell and squamous cell carcinoma); NonMelanoma Skin Cancer (include only basal cell carcinoma and squamous cell carcinoma).

These will be provided for the following periods and analysis sets:

- **Week 48 to Week 192 including Dose Adjustment for the LTE Safety Analysis Set**
- **Week 0 to Week 192 including Dose Adjustment for the Full Safety Analysis Set**

Tabulations of frequency and type of AEs will also be produced for the following: TEAEs; SAEs; TEAEs leading to discontinuation of study intervention; Injection Site Reactions (ISR) to active study agent and placebo. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. These tables will provide the count and percentage of participants with 1 or more of the specified TEAEs by treatment group, MedDRA system-organ class and preferred term. Summary tables for TEAEs, AEs of clinical interest, and AEs of special interest will also be provided. **These analyses will be performed for Week 48 to Week 192 including Dose Adjustment for the LTE Safety Analysis Set; and for Week 0 to Week 192 including Dose Adjustment for the Full Safety Analysis Set.**

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using MedDRA. TEAEs are AEs with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs which are treatment-emergent will be included in the analysis. For AE analyses looking at a specific time period, events are not included if onset date or worsening since baseline occurs prior to the administration date of the beginning of that time period. For example, an AE that is onset prior to the Week 48 administration is not included in the Week 48 to Week 152 AE time reporting period.

Since safety should be assessed relative to exposure and follow-up, all AE tables will summarize the average weeks of follow-up and average exposure (number of administrations) for each treatment group.

In addition to the summary tables, listings to include participants with SAEs, TEAEs leading to discontinuation of study intervention, and AEs of clinical interest will be provided. Any deaths or

adverse events of special interest (cases of active tuberculosis or malignancies) as described in Appendix 8 will also be presented in a listing. **All AE listings will be provided for the Full Safety Analysis Set from Week 0 through to Week 192 (including Dose Adjustment).**

Definitions

- A reasonably related AE is defined as any event with a relationship to study intervention of 'Very likely', 'Probable', or 'Possible' on the AE eCRF page or if the relationship to study agent is missing.
- An infection is defined as an AE coded to the infection and infestation SOC.
- A study intervention injection-site reaction is any reaction at an SC study intervention injection site that was recorded as an injection-site reaction by the investigator on the eCRF.

5.4.2.4. Final Analysis DBL

For the Final Analysis DBL primary Safety analyses will report incidence rates with 95% CI of treatment-emergent AEs (TEAEs) per one hundred participant years of follow-up. 'Including Dose Adjustment' below will be clarified in a footnote as: 'Participants in the LTE were eligible for a one-time dose adjustment to guselkumab 200 mg q4w at any time between Weeks 52-80 based on CDAI score. Events were counted up to the time of dose adjustment (change in treatment, change in dose, or sham adjustment) in all columns except those listed as 'including dose adjustment'.' Table column layouts are provided in the DPS. These will be provided for the following TEAEs:

- All TEAEs
- Infections
- Serious Infections
- SAEs
- AEs leading to discontinuation of study intervention
- AEs of clinical interest, including but not limited to the following: Venous thromboembolism (VTEs); Opportunistic Infections; MACE; clinically important hepatic disorders; anaphylactic reactions or serum sickness reactions.
- AEs of special interest: Active tuberculosis; Malignancy excluding NonMelanoma Skin Cancer (exclude basal cell and squamous cell carcinoma); NonMelanoma Skin Cancer (include only basal cell carcinoma and squamous cell carcinoma).

These will be provided for the following periods and analysis sets:

- **Week 48 to End of Study including Dose Adjustment for the LTE Safety Analysis Set**
- **Week 0 to End of Study including Dose Adjustment for the Full Safety Analysis Set**

Additionally, incidence rates with 95% CI will be provided for treatment emergent infections and serious infections by 48 week time intervals for the following intervals and analysis sets:

- **Week 48 to Week 96, >Week 96 to Week 144, >Week 144 to Week 192, >Week 192 including Dose Adjustment for the LTE Safety Analysis Set**
- **Week 0 to Week 48, >Week 48 to Week 96, >Week 96 to Week 144, >Week 144 to Week 192, >Week 192 including Dose Adjustment for the Full Safety Analysis Set**

Tabulations of frequency and type of AEs will also be produced for the following: TEAEs; SAEs; TEAEs leading to discontinuation of study intervention; Injection Site Reactions (ISR) to active study agent and placebo (including the number of injections and the number of injections with an ISR). For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. These tables will provide the count and percentage of participants with 1 or more of the specified TEAEs by treatment group, MedDRA system-organ class and preferred term. Summary tables for TEAEs (including severe AEs and reasonably related AEs), AEs of clinical interest, and AEs of special interest will also be provided. **These analyses will be performed for Week 48 to End of Study including Dose Adjustment for the LTE Safety Analysis Set; and for Week 0 to End of Study including Dose Adjustment for the Full Safety Analysis Set.**

Tabulations reporting incidence rates with 95% CI per one hundred participant years of follow-up by treatment group, MedDRA system-organ class and preferred term will also be provided for the following TEAEs:

- TEAEs with Higher Level Group Term of viral infections
- TEAEs with Higher Level Group Term of Fungal infections
- TEAEs with Higher Level Group Term of Bacterial infections
- TEAEs of COVID-19 infections
- URI infections (unrestricted list)
- URI infections (Nasopharyngitis, Upper respiratory tract infection, Respiratory tract infection, Pharyngitis, Respiratory tract infection viral)
- URI infections (Nasopharyngitis, Upper respiratory tract infection, Respiratory tract infection, Pharyngitis, Respiratory tract infection viral) with infection checked YES
- URI infections (Nasopharyngitis, Upper respiratory tract infection, Respiratory tract infection, Pharyngitis, Respiratory tract infection viral) with infection checked NO
- Infections with COVID-19 and URI infections (Nasopharyngitis, Upper respiratory tract infection, Respiratory tract infection, Pharyngitis, Respiratory tract infection viral) not included

These will be provided for the following period and analysis set:

- **Week 48 to End of Study including Dose Adjustment for the LTE Safety Analysis Set**

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using MedDRA. TEAEs are AEs with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs which are treatment-emergent will be included in the analysis. For AE analyses looking at a specific time period, events are not included if onset date or worsening since baseline occurs prior to the administration date of the beginning of that time period. For example, an AE that is onset prior to the Week 48 administration is not included in the Week 48 to Week 152 AE time reporting period. An AE with a severity change during the time reporting period will be entered as a new AE and therefore included in the time reporting period.

Since safety should be assessed relative to exposure and follow-up, all AE tables will summarize the average weeks of follow-up and average exposure (number of administrations) for each treatment group.

In addition to the summary tables, listings to include participants with SAEs, TEAEs leading to discontinuation of study intervention, and AEs of clinical interest will be provided. Any deaths or adverse events of special interest (cases of active tuberculosis or malignancies) as described in Appendix 8 will also be presented in a listing. **All AE listings will be provided for the Full Safety Analysis Set from Week 0 through to End of Study (including Dose Adjustment).**

Definitions

- A reasonably related AE is defined as any event with a relationship to study intervention of 'Very likely', 'Probable', or 'Possible' on the AE eCRF page or if the relationship to study agent is missing.
- An infection is defined as an AE coded to the infection and infestation SOC.
- A study intervention injection-site reaction is any reaction at an SC study intervention injection site that was recorded as an injection-site reaction by the investigator on the eCRF.
- Clinically important hepatic disorders are defined as SAEs of hepatic disorder and TEAEs of hepatic disorder leading to discontinuation of study intervention.

5.4.3. Additional Safety Assessments

5.4.3.1. Clinical Laboratory Tests for Week 96 DBL

Blood samples for serum chemistry and hematology will be collected. The following tests will be performed by the central laboratory unless otherwise specified or approved by the medical monitor.

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

Clinical laboratory test values are to be graded based on CTCAE version 5.0 (Appendix 10). The laboratory tests not included in Appendix 10 will not be presented in the corresponding tables or listings.

The following summaries of clinical laboratory tests will be provided for participants in the LTE **Safety Analysis Set**:

1. Summary of maximum National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grade for postbaseline laboratory values through Week 96.
2. Shift tables for maximum NCI-CTCAE toxicity grade from baseline through Week 96 will be summarized for the following lab parameters: hematology: hemoglobin, platelets, total WBC, absolute lymphocytes, and absolute neutrophils; chemistry: ALT, AST, and Alkaline phosphatase.
3. Summary of maximum postbaseline measurement through Week 96 for ALT, AST, alkaline phosphatase and total bilirubin relative to ULN.

Laboratory data limited to the LTE period (ie, from Week 48 through Week 96) will be summarized in two ways. The first will include data up to the time of meeting dose adjustment or through Week 96 if there is no dose adjustment. The second will include the laboratory data that occurred after the dose adjustment.

The baseline value for a participant is the value closest to but prior to the first dose of study intervention. In addition, change from baseline is defined to be the assessment at the postbaseline visit minus the assessment at baseline. There will be no imputation for missing laboratory values.

Listings of participants with any abnormal post-baseline laboratory values of NCI-CTCAE grade ≥2 will also be provided.

5.4.3.2. Clinical Laboratory Tests for Week 152 DBL

Blood samples for serum chemistry and hematology will be collected. The last scheduled time point for laboratory assessments is W144 for the W152 DBL. The following tests will be performed by the central laboratory unless otherwise specified or approved by the medical monitor.

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

Clinical laboratory test values are to be graded based on CTCAE version 5.0 (Appendix 10) except for liver function tests (ALT, AST, total bilirubin and alkaline phosphatase) for which ULN thresholds are defined (Appendix 10). The laboratory tests not included in Appendix 10 will not be presented in the corresponding tables or listings. The baseline value for a participant is the value closest to but prior to the first dose of study intervention. In addition, change from baseline is

defined to be the assessment at the postbaseline visit minus the assessment at baseline. There will be no imputation for missing laboratory values.

The following summaries of clinical laboratory tests will be provided for:

- the Full Safety Analysis Set from Week 0 through Week 152 or until the time of dose adjustment;
- for the LTE Safety Analysis Set from Week 0 through Week 152 or until the time of dose adjustment;
- for the LTE Safety Analysis Set from Week 48 through Week 152 regardless of dose adjustment.
- Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry including liver function tests)
- Line graph for liver tests
- Summary of maximum NCI-CTCAE toxicity grade for post-baseline laboratory values (not for liver function tests)
- Shift tables for maximum NCI-CTCAE toxicity grade from baseline will be summarized for the following lab parameters: hematology: hemoglobin, platelets, total WBC, absolute lymphocytes, and absolute neutrophils
- Summary of maximum post-baseline ULN threshold for elevated liver function tests (ALT, AST, alkaline phosphatase and total bilirubin)
- Shift tables using the ULN threshold from baseline will be summarized for liver function tests: ALT, AST, Alkaline phosphatase, and total bilirubin.

Listings based on the Full Safety Analysis Set from Week 0 through Week 152 will be provided for participants with any of the following:

- Abnormal post-baseline lab values of NCI-CTCAE grade ≥ 2 except liver tests
- Post-baseline elevated liver tests of ALT or AST ≥ 5x ULN, or total bilirubin ≥2x ULN, or alkaline phosphatase ≥ 2x ULN
- Postbaseline elevated liver test with combined ALT/AST ≥ 3x ULN and total bilirubin ≥ 2x ULN

5.4.3.3. Clinical Laboratory Tests for Week 192 DBL

Blood samples for serum chemistry and hematology will be collected. The following tests will be performed by the central laboratory unless otherwise specified or approved by the medical monitor.

- **Hematology assessments** will include but are not limited to the following: hemoglobin, hematocrit, platelet count, total and differential WBC count.
- **Liver function tests** (ALT, AST, total bilirubin, and alkaline phosphatase) **(Note: Blood chemistry assessments other than LFTs are deleted.)**

Clinical laboratory test values are to be graded based on CTCAE version 5.0 (Appendix 10) except for liver function tests (ALT, AST, total bilirubin and alkaline phosphatase) for which ULN thresholds are defined (Appendix 10). The laboratory tests not included in Appendix 10 will not be presented in the corresponding tables or listings. The baseline value for a participant is the value closest to but prior to the first dose of study intervention. In addition, change from baseline is defined to be the assessment at the postbaseline visit minus the assessment at baseline. There will be no imputation for missing laboratory values.

The following summaries of clinical laboratory tests will be provided for the **LTE Safety Analysis Set for Week 48 to Week 192 including Dose Adjustment**:

- Laboratory parameters and change from baseline in laboratory parameters (hematology only)
- Summary of maximum NCI-CTCAE toxicity grade for post-baseline laboratory values (not for liver function tests)
- Shift tables for maximum NCI-CTCAE toxicity grade from baseline will be summarized for the following lab parameters: hematology: hemoglobin, platelets, total WBC, absolute lymphocytes, and absolute neutrophils
- Summary of maximum post-baseline ULN threshold for elevated liver function tests (ALT, AST, alkaline phosphatase and total bilirubin)
- Summary of participants with ALT ≥ 5x ULN OR AST ≥ 5x ULN
- Summary of participants with ALT ≥ 3x ULN OR AST ≥ 3x ULN AND total bilirubin ≥ 2x ULN

Listings based on the **Full Safety Analysis Set from Week 0 through to Week 192 (including Dose Adjustment)** will include:

- Postbaseline elevated liver test with combined ALT/AST ≥ 3x ULN and total bilirubin ≥ 2x ULN
- Highest Post-baseline Elevated Liver Function Tests (ALT or AST ≥ 5 x ULN)
- Highest Post-baseline Elevated Liver Function Tests (Alkaline Phosphatase ≥ 2)
- Combined Criteria (Total Bilirubin ≥ 2 x ULN and either AST or ALT ≥ 3 x ULN) or With Highest Post-baseline Elevated Liver Function Tests (ALT or AST ≥ 5 x ULN or Alkaline Phosphatase ≥ 2)

5.4.3.4. Clinical Laboratory Tests for Final Analysis DBL

Blood samples for serum chemistry and hematology will be collected. The following tests will be performed by the central laboratory unless otherwise specified or approved by the medical monitor.

- **Hematology assessments** will include but are not limited to the following: hemoglobin, hematocrit, platelet count, total and differential WBC count.

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

Clinical laboratory test values are to be graded based on CTCAE version 5.0 (Appendix 10) except for liver function tests (ALT, AST, total bilirubin and alkaline phosphatase) for which ULN thresholds are defined (Appendix 10). The laboratory tests not included in Appendix 10 will not be presented in the corresponding tables or listings. The baseline value for a participant is the value closest to but prior to the first dose of study intervention. In addition, change from baseline is defined to be the assessment at the postbaseline visit minus the assessment at baseline. There will be no imputation for missing laboratory values.

The following summaries of clinical laboratory tests will be provided for the **LTE Safety Analysis Set for Week 48 to End of Study including Dose Adjustment**:

- Laboratory parameters and change from baseline in laboratory parameters
- Summary of maximum NCI-CTCAE toxicity grade for post-baseline laboratory values (not for liver function tests)
- Shift tables for maximum NCI-CTCAE toxicity grade from baseline will be summarized for laboratory assessments (not for liver function tests)
- Summary of maximum post-baseline ULN threshold for elevated liver function tests (ALT, AST, alkaline phosphatase and total bilirubin)
- Summary of participants with ALT ≥ 5x ULN OR AST ≥ 5x ULN
- Summary of participants with total bilirubin ≥2 x ULN or INR > 1.5 within 5 days after ALT or AST ≥3 x ULN, and alkaline phosphatase <2 x ULN (Hy's law)
- Summary of Participants with ALT or AST ≥ 5x ULN; OR total bilirubin ≥2 x ULN or INR > 1.5 within 5 days after ALT or AST ≥3 x ULN, and alkaline phosphatase <2 x ULN; OR Alkaline Phosphatase ≥ 2 x ULN

The following summary of clinical laboratory tests will be provided for the **Full Safety Analysis Set for Week 0 to End of Study including Dose Adjustment**:

- Summary of Participants with ALT or AST ≥ 5x ULN; OR total bilirubin ≥2 x ULN or INR > 1.5 within 5 days after ALT or AST ≥3 x ULN, and alkaline phosphatase <2 x ULN; OR Alkaline Phosphatase ≥ 2 x ULN

Listings based on the **Full Safety Analysis Set from Week 0 through the End of Study (including Dose Adjustment)** will include:

- Elevated liver tests with total bilirubin ≥2 x ULN or INR > 1.5 within 5 days after ALT or AST ≥3 x ULN, and alkaline phosphatase <2 x ULN (Hy's law)
- Highest Post-baseline Elevated Liver Function Tests (ALT or AST ≥ 5 x ULN)
- Highest Post-baseline Elevated Liver Function Tests (Alkaline Phosphatase ≥ 2 x ULN)

- Combined Criteria: Total Bilirubin ≥ 2 x ULN or INR > 1.5 within 5 days after ALT or AST ≥ 3 x ULN), and alkaline phosphatase <2 x ULN; OR With Highest Post-baseline Elevated Liver Function Tests ALT or AST ≥ 5 x ULN; OR Alkaline Phosphatase ≥ 2 x ULN

5.4.3.5. Other Safety Parameters

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[8,9] 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 will be analyzed by the most severe/maximum post baseline C-SSRS outcome or AE of suicidal ideation and behavior. This will be analyzed from Week 48 on the LTE Safety Analysis Set.

Participants in the Full Safety Analysis set with positive (i.e., score > 0) postbaseline ideation and behavior will be presented in a data listing.

5.5. Other Analyses

5.5.1. Pharmacokinetics

Participants will be analyzed according to their actual treatment received for PK and immunogenicity analyses.

Blood samples for determining the serum guselkumab and ustekinumab concentrations will be drawn from all participants according to the Schedule of Activities in the Protocol. Unless otherwise mentioned, serum guselkumab and ustekinumab concentration summaries will be provided based on the LTE Pharmacokinetics Analysis Set. Descriptive statistics of the serum guselkumab and ustekinumab concentrations will be calculated by treatment group at each sampling time point, including n, arithmetic mean, SD, median, interquartile range, range (minimum and maximum).

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

Participants' data will be excluded from the PK analyses if their data do not allow for accurate assessment of the PK. In particular, all serum concentration summaries will exclude, from the time of occurrence, data collected for participants who 1) discontinue study intervention, 2) skip an infusion or injection, 3) receive an incomplete infusion or injection, 4) receive an incorrect infusion or injection, 5) receive an additional infusion or injection, and/or 6) receive commercial guselkumab or ustekinumab.

Additional samples excluded from the analysis are described as follows:

- pre-injection samples at Week 48, 56, 64, 72, 80, 88, and 96 that were outside of the visit window +/- 7 days (W96 DBL); additionally Week 112, 128 and 144 that were outside of the visit window +/- 10 days (W152 DBL); and Week 160, 176, 192 that were outside of the visit window +/- 10 days (W192 DBL); and Week 200, 208, 216, 224, 232, 240 that were outside of the visit window +/- 10 days (Final Analysis DBL).

To determine visit windows, the visit date is calculated as (W0 dosing date + Visit Week*7). Windowing is then applied as +/-7 days relative to this date for visits up to and including W96, and as +/-10 days relative to this date for visits after W96. The windowing is applied to all samples regardless of whether the participant received guselkumab or ustekinumab.

PK vs Efficacy

To explore the relationship between guselkumab serum concentrations and efficacy endpoints, the following analyses will be explored graphically:

The relationship between guselkumab serum concentrations (quartiles) and CRP and fecal calprotectin, and also the proportion of participants with clinical remission, normalized CRP, normalized fecal calprotectin, and endoscopic response at Week 96 (W96 DBL) / Week 144 (W152 DBL) / Week 192 (W192 DBL) / W240 (Final Analysis DBL) will be explored.

Additionally, the relationship between ustekinumab serum concentrations and efficacy endpoints will be explored graphically, specifically:

- ustekinumab serum concentrations and Week 96 (W96 DBL) / Week 144 (W152 DBL) / Week 192 (W192 DBL) / W240 (Final Analysis DBL) clinical remission
- ustekinumab serum concentrations and Week 96 (W96 DBL) / Week 144 (W152 DBL) / Week 192 (W192 DBL) / W240 (Final Analysis DBL) endoscopic response

5.5.2. Immunogenicity

Serum samples will be screened for antibodies binding to guselkumab or ustekinumab and the titer of confirmed positive samples will be reported. For these analyses, the full immunogenicity analysis set will be used.

The incidence and titers of antibodies to guselkumab will be summarized through induction and maintenance dosing, as well as Weeks 48, 64, 80 and 96 (W96 DBL) / Weeks 48, 64, 80, 96, 112, 128, 144 (W152 DBL) / Weeks 160, 176, 192 (W192 DBL) / Weeks 208, 224, 240 (Final Analysis DBL), for all participants who receive a dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab (ie, participants with at least 1 sample obtained after their first dose of guselkumab). Similarly, for all participants receiving ustekinumab and having appropriate samples for detection of antibodies to ustekinumab, the incidence and titers of antibodies to ustekinumab will be summarized. The maximum titers of antibodies to guselkumab or ustekinumab will be provided for participants who are positive for antibodies to guselkumab or ustekinumab.

Separate listings of participants who are positive for antibodies to guselkumab or ustekinumab will be provided. The listing will contain treatment group, visit, serum guselkumab/ustekinumab concentration at the visit, baseline immunomodulators use (Yes or No), CDAI score at the visit, injection-site reactions/AEs temporarily associated with an infusion, and antibody status (titer and neutralizing antibodies status) for all visits.

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. Likewise, for participants who are positive for antibodies to ustekinumab and have samples evaluable for NAbs to ustekinumab, the incidence of NAbs to ustekinumab will be summarized.

5.5.3. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between serum guselkumab concentrations and efficacy measures may be analyzed graphically. If appropriate, a suitable model may be developed to describe the exposure-response relationship. Details of such analysis will be presented in a separate technical report.

5.5.4. Biomarkers

Changes in serum protein analytes and whole blood ribonucleic acid (RNA) obtained over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and response to treatment will be explored. The biomarker analyses will characterize the effects of guselkumab to identify biomarkers relevant to treatment, and to determine if these biomarkers can predict response to guselkumab. Inflammatory pharmacodynamics markers (CRP and fecal calprotectin) will be evaluated. Results of serum, whole blood analyses, stool, and ileocolonic biopsy analyses 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.

5.5.5. Health Economics

The analyses of the Health Economics endpoints listed below will be based on both the LTE (not for W192 DBL or Final Analysis DBL) and Primary Efficacy Analysis Sets.

Endpoints for Week 96 DBL:

1. Change from baseline in each of 4 impairments from WPAI-CD at Weeks 64, 80, and 96.
2. Change from baseline in each of 4 impairment percentages from WPAI-CD at Weeks 64, 80, and 96.
3. Proportion of participants having any ER/hospitalizations (including surgeries) through Week 96

4. Time to first ER/hospitalization (including surgeries) through Week 96.
5. Proportion of participants with a CD-related surgery through Week 96.
6. Time to first CD-related surgery through Week 96.
7. Proportion of participants with a CD-related procedure through Weeks 96.

Endpoints for Week 152 DBL:

1. Proportion of participants having any ER/hospitalizations (including surgeries) through Week 152
2. Time to first ER/hospitalization (including surgeries) through Week 152.
3. Proportion of participants with a CD-related surgery through Week 152.
4. Time to first CD-related surgery through Week 152.
5. Proportion of participants with a CD-related procedure through Weeks 152.

Endpoints for Week 192 DBL:

1. Proportion of participants having any ER/hospitalizations (including surgeries) through Week 192
2. Time to first ER/hospitalization (including surgeries) through Week 192.
3. Proportion of participants with a CD-related surgery through Week 192.
4. Time to first CD-related surgery through Week 192.
5. Proportion of participants with a CD-related procedure through Week 192.

Endpoints for Final Analysis DBL:

1. Change from baseline in each of 4 impairments from WPAI-CD at Weeks 64 to 240 (every 16 weeks).
2. Change from baseline in each of 4 impairment percentages from WPAI-CD at Weeks 64 to 240 (every 16 weeks).
3. Proportion of participants having any ER/hospitalizations (including surgeries) through Week 240.
4. Time to first ER/hospitalization (including surgeries) through Week 240.
5. Proportion of participants with a CD-related surgery through Week 240.
6. Time to first CD-related surgery through Week 240.
7. Proportion of participants with a CD-related procedure through Week 240.

Analysis Methods

All endpoints will be summarized by treatment groups using descriptive statistics, such as mean, median, standard deviation, interquartile range, minimum and maximum for continuous variables, and counts and percentages for categorical variables.

For Time to Event endpoints, no treatment failure rules will apply for either the LTE-specific (not for W192 DBL or Final Analysis DBL) or over time analyses.

Kaplan-Meier (KM) curves will be generated by treatment (combined guselkumab group, ustekinumab group) for Time to Event endpoints. KM estimates for the combined guselkumab group vs. ustekinumab will be provided. The time to event is defined as the time from randomization, or from start of LTE (not for W192 DBL or Final Analysis DBL) to the date of the first event that occurred through Week 152 (W152 DBL) / Week 192 (W192 DBL) / Week 240 (Final Analysis DBL). Participants who had not had an event by Week 152 (W152 DBL) / Week 192 (W192 DBL) / Week 240 (Final Analysis DBL) or study termination will be censored at that timepoint. For tabulations of the number and proportion of participants with an event, censoring will not be applied at dose adjustment for any treatment arm. For KM curves, censoring will be applied at dose adjustment for all treatment arms.

No imputation will be performed for missing health economics values; the missing values will remain as missing.

5.5.6. Definition of Subgroups

The following subgroups will be evaluated for the endpoints identified in Sections 5.3.11.1 (W96DBL); 5.3.11.2 (W152 DBL); 5.3.11.3 (W192 DBL):

BIO-failure status

- BIO-Failure (Bio-failure status = yes)
- CON-Failure (Bio-failure status = no)

The following subgroups will be evaluated for the endpoints identified in 5.3.11.4 (Final Analysis DBL):

- BIO-Failure (Bio-failure status = yes)
- CON-Failure (Bio-failure status = no)
- BIO-Naïve

These subgroups are defined as:

BIO-Failure: participants who had previously demonstrated an inadequate response to, or had failed to tolerate, ≥1 biologic therapies at a dose approved for the treatment of CD.

CON-Failure: participants who had previously demonstrated an inadequate response to, or had failed to tolerate, at least 1 conventional therapy (ie, immunomodulators or oral corticosteroids) for CD and had not demonstrated failure to a biologic.

BIO-Naïve: participants in the CON-Failure population who had never been exposed to biologic therapy.

5.5.7. RLPH Substudy

Upon completion of the Phase 2 Week 48 database lock (DBL) and subsequent data analyses, participants in the Phase 2 LTE will be unblinded and those receiving the 200 mg subcutaneous (SC) dose by the current administration method (ie, PFS-U 1 mL × 2 SC injections) will participate in the Real Life Patient Handling (RLPH) substudy, and will be assigned by site (nonrandomized) to receive their 200 mg SC dose using one of the two 2.0 mL drug devices (either PFS-U or PFS-Y). Based on the current projected enrollment status, approximately 80 to 90 participants are expected to receive the 200 mg SC dose per protocol design and have at least 3 or 4 dosing visits remaining in their Phase 2 LTE participation at the time at which the RLPH substudy is initiated. Therefore, approximately 40 to 45 participants or caregivers are projected to perform at least 3 or 4 guselkumab administrations with either the 2.0 mL PFS-U or the 2.0 mL PFS-Y (ie, ~40 to 45 unique users/device) for the remainder of their participation in the Phase 2 LTE under the RLPH substudy. The resultant data from the RLPH substudy population will support the assessment of self- or caregiver administration and the reliability of use for each drug-device in the IBD population.

5.5.7.1. Objectives

The objectives of the RLPH substudy are:

- Primary objective: To assess the ability of users to perform safe and successful injections.
- Secondary objective: To determine the incidence of device-related AEs related to the use of the 2.0 mL PFS-U or 2.0 mL PFS-Y device
- Other objective: To evaluate the PK, immunogenicity, and user-perceived pain associated with injections.

5.5.7.1.1. Populations (Analysis Sets) for Analysis

Table 11: Analysis Sets

Analysis Sets	Description
RLPH Primary Analysis Set	The RLPH primary analysis set consists of randomized participants who entered the long-term extension phase of the study, received guselkumab 200 mg subcutaneous (SC) dose of study intervention (including a partial dose) during the LTE phase, and received at least one injection with a 2ml device through self-administration (self-administration is defined as study medication administered by the study participant or their caregiver).
RLPH All 2ml Device Use Analysis set	The RLPH All 2ml device use analysis set consists of randomized participants who entered the long-term extension phase of the study,

Table 11: Analysis Sets

Analysis Sets	Description
	received guselkumab 200 mg subcutaneous (SC) dose of study intervention (including a partial dose) during the LTE phase, and received at least one injection with a 2ml device through self-administration or by a Health Care Professional.
RLPH Safety Analysis Set	The RLPH Safety analysis set consists of randomized participants who entered the long-term extension phase of the study, received guselkumab 200 mg subcutaneous (SC) dose of study intervention (including a partial dose) during the LTE phase, and received at least one injection with a 2ml device through self-administration (self-administration is defined as study medication administered by the study participant or their caregiver).
RLPH Pharmacokinetics Analysis Set	The guselkumab RLPH PK analysis set is defined as randomized participants who entered the LTE phase of the study, have received at least one dose of guselkumab 200 mg subcutaneous (SC) dose, have received at least one injection with a 2ml device through self-administration or by a Health Care Professional, and have at least one valid blood sample drawn for PK analysis during the LTE.
RLPH Immunogenicity Analysis Set	The guselkumab RLPH immunogenicity analysis set is defined as randomized participants who entered the LTE phase of the study, have received at least one dose of guselkumab 200 mg subcutaneous (SC) dose, have received at least one injection with a 2ml device through self-administration or by a Health Care Professional, and have appropriate samples for detection of antibodies to guselkumab during the LTE.

Unless otherwise specified, all the analyses related to the primary endpoint will be based on the RLPH Primary Analysis Set. Safety analyses will be based on the RLPH Safety Analysis Set, or on the RLPH All 2ml Device Use Analysis Set as an ad-hoc analysis (see Section 5.5.7.1.4 below). All RLPH-specific PK analyses will be based on the RLPH PK analysis sets, and all RLPH-specific immunogenicity analyses will be based on the RLPH immunogenicity analysis sets.

5.5.7.1.2. Endpoints

The following will be assessed and analyzed in the RLPH substudy:

Primary Endpoint:

- Percentage of participants/caregivers who perform successful injections

Other Endpoints:

- Assessment of injection-site pain using the pain NRS
- Assessment of ease of use with the device and device-handling events from the device questionnaire
- Safety (to include but not limited to AEs, device-related AEs, injection-site reactions, hypersensitivity reactions)

- Pre vs Post PK/Immunogenicity

5.5.7.1.3. Definition of Endpoint(s)

Successful Injections: Reported in the Injection Assessment Questionnaire (Confirmation of Successful Injection) completed by each participant/caregiver

5.5.7.1.4. Analysis

Descriptive statistics (N, mean, standard deviation (SD), median, interquartile (IQ) range, minimum and maximum) will be provided for continuous variables. Frequency distributions will be provided for categorical variables. No formal statistical analyses for device comparisons will be performed.

Listing and Graphical data displays may also be used to present the data.

5.5.7.1.5. Safety

W152 DBL:

Tabulations of TEAEs, SAEs, Device Related AEs and TEAEs leading to discontinuation of study intervention by MedDRA SoC and preferred term will be provided. Incidence rates per 100 subject years for the number of TEAEs and also for the number of SAEs will be provided. A tabulation of the number of participants will one or more ISRs to guselkumab will be provided. A listing of participants with one or more anaphylactic or serum sickness-like reactions after dosing with the 2ml device will be provided.

A tabulation summarizing device complaints will be provided. Tabulations for injection site pain by injection, for the average over all injections, and over all injections will be provided.

For the W152 DBL, the following periods will be considered for safety analyses:

Main analysis: AEs from 1st self-administration through the injection assessment questionnaire.

ADHOC Analysis #1: AEs in participants receiving 2mL device from 1st dose of self-administration up to week 152 self-administration.

ADHOC Analysis #2 – AEs in participants receiving 2 mL device from 1st dose of administration up to Week 152 dose administration.

Reporting of the RLPH substudy was completed in the Week 152 CSR.

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
BSFS	Bristol Stool Form Scale
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CRF	case report form
CRP	C-reactive protein
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBL	Database lock
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
eCRF	electronic case report form
EQ-5D-5L	5-level EuroQol five dimensions
FAS	full analysis set
FES	Final Efficacy and Safety
FDA	Food and Drug Administration
GHAS	Global Histology Activity Score
GS	Geboes Scoring system
IA	Interim Analysis
IAP	Interim Analysis Plan
IBD	Inflammatory Bowel Disease
ICE	Intercurrent Event
ICH	International Conference on Harmonization
IQ	interquartile
IBDQ	Inflammatory Bowel Disease Questionnaire
ITT	Intention to treat
IWRS	interactive web response system
KM	Kaplan-Meier
LOCF	last observation carried forward
LTE	Long Term Extension
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-effect repeated measures
NAb	neutralizing antibodies
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRI	Non-responder Imputation
NRS	Numerical rating scale
OT	Overtime
PD	pharmacodynamic
PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity
PI	principal investigator
PK	pharmacokinetic(s)
PROMIS	Patient-Reported Outcomes Measurement Information System
PP	per protocol
RLPH	Real-life patient-handling
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease

SID	Study Intervention Discontinuation
TEAE	treatment-emergent adverse event
TF	Treatment Failure
ULN	upper limit of normal
USM	urgent safety measure

6.2. Appendix 2 Changes to Protocol-Planned Analyses

There are no changes from the protocol with respect to the LTE analyses.

6.3. Appendix 3 Demographics and Baseline Characteristics

Table 12 presents a list of the demographic and baseline Crohn's disease characteristics variables that will be summarized according to the treatment groups for the LTE efficacy analysis set. For the W96, W152 DBLs, demographic and baseline Crohn's disease characteristics will also be summarized within the BIO-failure and CON-failure subgroups for the LTE efficacy analysis set. For the Final Analysis DBL, demographic and baseline Crohn's disease characteristics will also be summarized within the BIO-failure, CON-failure and Bio-Naïve subgroups for the LTE efficacy analysis set. Baseline is defined as Week 0.

Table 12: Demographic and Baseline Characteristics Variables

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
BMI (kg/m^2)	
Crohn's disease duration (years)	
CDAI score	
Daily average abdominal pain (AP) score	
Daily average stool frequency (SF) score	
SES-CD score	
IBDQ	
CRP	
Fecal Calprotectin	
Categorical Variables	
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not Reported, Multiple)	Frequency distribution with the number and percentage of participants in each category.
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported)	
Region (Asia, Eastern Europe, North America, Rest of World)	
Crohn's disease complications	
Involved GI areas	
Endoscopic disease severity per SES-CD score [Mild (3-6), Moderate (7-16), Severe (>16)]	
Stool frequency > 3	
Abdominal pain > 1	
Stool frequency > 3 and Abdominal pain >1	
Fecal calprotectin > 250 µg/g	
CRP >3 mg/L	
Fecal calprotectin > 250 µg/g and CRP >3 mg/L	

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

6.4. Appendix 4 Protocol Deviations

Week 96 DBL

(1) Participants with a major protocol deviation from the start of the LTE through Week 96 will be summarized by the following categories based on the LTE Efficacy Analysis Set:
- Received wrong treatment or incorrect dose
- Received a disallowed concomitant treatment
- Developed withdrawal criteria but not withdrawn
- Other
  - COVID-19 related deviations

(2) A listing of participants in the LTE efficacy analysis set who have major protocol deviations from the start of the LTE through Week 96 will be provided.

(3) 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).

(4) A listing of participants with study intervention administration irregularities will be provided.

(5) A listing of participants with major protocol deviations related to COVID-19 by center

(6) A listing of participants with minor protocol deviations related to COVID-19 by center

Week 152 DBL

(1) Participants with a major protocol deviation from the start of the LTE through Week 152 will be summarized by the following categories based on the LTE Efficacy Analysis Set:
- Received wrong treatment or incorrect dose
- Received a disallowed concomitant treatment
- Developed withdrawal criteria but not withdrawn
- Other
  - COVID-19 related deviations
  - Major disruption deviations

(2) A listing of participants in the LTE efficacy analysis set who have major protocol deviations from the start of the LTE through Week 152 will be provided.

(3) 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).

(4) A listing of participants with study intervention administration irregularities will be provided.

(5) A listing of participants with major protocol deviations related to COVID-19 by center

(6) A listing of participants with minor protocol deviations related to COVID-19 by center

Final Analysis DBL

(1) Participants with a major protocol deviation from the start of the LTE through the end of the study will be summarized by the following categories based on the LTE Efficacy Analysis Set:

- Received wrong treatment or incorrect dose
- Received a disallowed concomitant treatment
- Developed withdrawal criteria but not withdrawn
- Other
  - COVID-19 related deviations
  - Major disruption deviations

(2) A listing of participants in the LTE efficacy analysis set who have major protocol deviations from the start of the LTE through the end of the study will be provided.

(3) 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).

6.5. Appendix 5 Prior and Concomitant Medications

The following summaries will be provided by treatment group for the LTE efficacy analysis set:

- CD medication history (participants who took medications for CD [including ustekinumab] and their length of exposure prior to the study)
- History of response to biologic treatment (infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars for these agents) (not for W192 DBL)
- History of response to or intolerance of Corticosteroids and Immunomodulators (6-MP/AZA/MTX)

In addition, the number of participants with primary nonresponse, secondary nonresponse, or intolerance to each biologic treatment will be summarized. Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention.

All baseline use of CD-specific concomitant medications (including 5-aminosalicylic acids [5-ASAs], Corticosteroids, Immunomodulators (6-MP/AZA/MTX), and antibiotics) will be summarized by treatment group for the LTE Efficacy analysis set. Baseline is defined as Week 0.

6.6. Appendix 6 Medical History

A summary of medical history of interest (not for W192 DBL), as well as a summary of Crohn's disease history and Crohn's disease conditions of interest, will be summarized for the LTE efficacy analysis set.

6.7. Appendix 7 Intervention Compliance

Randomized treatment versus actual treatment will be summarized using the LTE efficacy analysis set.

6.8. Appendix 8 Adverse Events of Special Interest and Other Events of Interest

There are two AEs of Special Interest: Tuberculosis and Malignancy. Preferred terms will be updated in the DPS with any MedDRA version updates.

AEs of special interest (AESI) and other events of interest:

Events of Interest	MedDRA Terms	Scope
Infections	SOC Infections and infestations	
Opportunistic Infections	OPPORTUNISTIC INFECTIONS (SMQ)	Narrow
Tuberculosis (AESI)	HLT Tuberculous infections	
Malignancies (AESI)	MALIGNANT TUMOURS (SMQ) NonMelanoma Skin Cancer (NMSC) events identified from: BASAL CELL CARCINOMA; SQUAMOUS CELL CARCINOMA.	Narrow
Major Adverse Cardiovascular Event (MACE) • Cardiovascular death • Nonfatal myocardial infarction (MI) • Nonfatal stroke Events meeting these criteria for MACE underwent clinical review by a blinded physician independent of the study team.	AEs where the Preferred Term is featured in the global standard SMQ dataset where (SMQ='CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS (SMQ)' and SUB_SMQ1='CENTRAL NERVOUS SYSTEM HAEMORRHAGES AND CEREBROVASCULAR CONDITIONS (SMQ)' and SUB_SMQ2='ISCHAEMIC CENTRAL NERVOUS SYSTEM VASCULAR CONDITIONS (SMQ)') OR (SMQ='ISCHAEMIC HEART DISEASE (SMQ)' and SUB_SMQ1='MYOCARDIAL INFARCTION (SMQ)') and SCOPE='NARROW'.	Narrow
Hepatic Disorders	SMQ='HEPATIC DISORDERS (SMQ)' and SUB_SMQ1='DRUG RELATED HEPATIC DISORDERS - COMPREHENSIVE SEARCH (SMQ)' and SCOPE='NARROW	Narrow
Venous thromboembolism (VTE)	PTs of: 1.Axillary vein thrombosis 2.Brachiocephalic vein thrombosis 3.Budd-Chiari syndrome 4.Deep vein thrombosis 5.Deep vein thrombosis postoperative 6.Embolism venous 7.Hepatic vein thrombosis 8.Homans' sign positive 9.Inferior vena cava syndrome 10.Jugular vein thrombosis 11.Mahler sign	

	12.May-Thurner syndrome 13.Mesenteric vein thrombosis 14.Obstetrical pulmonary embolism 15.Ovarian vein thrombosis 16.Paget-Schroetter syndrome 17.Pelvic venous thrombosis 18.Penile vein thrombosis 19. Peripheral vein thrombosis 20.Peripheral vein thrombus extension 21.Post procedural pulmonary embolism 22.Postpartum venous thrombosis 23.Pulmonary embolism 24.Pulmonary infarction 25.Pulmonary microemboli 26.Pulmonary thrombosis 27.Pulmonary venous thrombosis 28.Renal vein thrombosis 29.Spermatic vein thrombosis 30.Splenic vein thrombosis 31.Subclavian vein thrombosis 32.Thrombosis corpora cavernosa 33.Vena cava embolism 34.Vena cava thrombosis 35.Venous thrombosis 36.Venous thrombosis in pregnancy 37.Venous thrombosis limb 38.Visceral venous thrombosis For the Final Analysis DBL, the additional PT of Subclavian vein embolism is added for VTE search, resulting from the MedDRA v27.0 upgrade.	
Anaphylactic Reaction	PTs of Anaphylactic Reaction, Anaphylactic Shock, Anaphylactoid Reaction, Anaphylactoid Shock, and Type I Hypersensitivity.	
Serum-sickness	PTs of Serum sickness and Serum sickness-like reaction.	
Injection site reaction		
Infusion-related AE		
Suicidal Ideation and Behavior (SIB)	SUICIDE/SELF-INJURY (SMQ)	Narrow

6.9. Appendix 9 Medications of Special Interest

No medications of special interest have been identified.

6.10. Appendix 10 Laboratory Toxicity Grading

Hematology Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
Hemoglobin (g/dL)	Increase	>0 - 2 + ULN	>2 - 4 + ULN	>4 + ULN	
Hemoglobin (g/dL)	Decrease	<LLN - 10.0	<10.0 - 8.0	<8.0	
Lymphocytes (/mm3)	Increase		>4000 - 20,000	>20,000	
Lymphocytes (/mm3)	Decrease	<LLN - 800	<800 - 500	<500 - 200	<200
Neutrophils (/mm3)	Decrease	<LLN - 1500	<1500 - 1000	<1000 - 500	<500
Platelets (/mm3)	Decrease	<LLN - 75,000	<75,000 - 50,000	<50,000 - 25,000	<25,000
Total WBC count (/mm3)	Increase			>100,000	
Total WBC count (/mm3)	Decrease	<LLN - 3000	<3000 - 2000	<2000 - 1000	<1000
Chemistry Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
Albumin (g/L)	Decrease	≥30 - <LLN	≥20 - <30	<20	
Corrected Calcium (mmol/L)	Increase	>ULN - ≤2.9	>2.9 - ≤3.1	>3.1 - ≤3.4	>3.4
Corrected Calcium (mmol/L)	Decrease	≥2.0 - <LLN	<2.0 - ≥1.75	<1.75 - ≥1.5	<1.5
Creatinine	Increase	>ULN - ≤1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Glucose (mmol/L)	Decrease	<LLN - 3.0	<3.0 - 2.2	<2.2 - 1.7	<1.7
Potassium (mmol/L)	Increase	>ULN - ≤5.5	>5.5 - 6.0	>6.0 - 7.0	>7.0
Potassium (mmol/L)	Decrease		<LLN - 3.0	<3.0 - 2.5	<2.5
Sodium (mmol/L)	Increase	>ULN - 150	>150 - 155	>155 - 160	>160
Sodium (mmol/L)	Decrease	<LLN - 130		<130 - 120	<120

Liver Function Test	**ULN Thresholds**
ALT/AST	> 1 x to < 3 x ULN
	≥ 3 x to < 5 x ULN
	≥ 5 x ULN to < 8 x ULN
	≥ 8 x ULN
Total Bilirubin	> 1 to < 2 x ULN
	≥ 2 x ULN
Alkaline Phosphatase	> 1 to < 2 x ULN
	≥ 2 to < 4 x ULN
	≥ 4 x ULN

6.11. Appendix 11 Prohibited Changes in CD Medications Prior to Week 48 (ICE Category 6) Applicable to Over-Time Estimands (OT)

ICE CATEGORY 6 FOR ALL ESTIMANDS OTHER THAN SES-CD RELATED ENDPOINTS

(i) Prohibited medications

Initiation of the following prohibited medications after Week 0 due to worsening Crohn's disease:

a. Immunomodulatory agents other than AZA, 6-MP, or MTX (including, but not limited to, 6 TG, cyclosporine, mycophenolate mofetil, tacrolimus, and sirolimus).
b. Immunomodulatory biologic agents (including, but not limited to, TNF antagonists, natalizumab, ustekinumab, rituximab, vedolizumab). Ustekinumab is permitted in this study only in participants randomly assigned to ustekinumab and only as stipulated in this protocol.
c. Experimental Crohn's disease medications (including, but not limited to, upadacitinib, filgotinib, ozanimod, etrolizumab, brazikumab, mirakizumab [formerly LY-3074828], risankizumab, GS 5745).
d. Thalidomide or related agents.

(ii) Corticosteroids

The occurrence of the following changes in corticosteroid usage during induction treatment (ie, before week 12), OR, during maintenance treatment (ie, between week 36 and week 48, including changes initiated before week 36 and continued after week 36, unless otherwise specified).

a. Initiation of oral corticosteroids (including budesonide and beclomethasone dipropionate), parenteral, or rectal corticosteroids due to - worsening Crohn's disease.
b. Increase in the dose of oral corticosteroids (including budesonide and beclomethasone dipropionate), as specified below, above the baseline dose due to worsening Crohn's disease.
    i. Oral corticosteroids ≥ 5 mg/day (prednisone equivalent)
    ii. Oral budesonide ≥ 3 mg/day
    iii. Oral beclomethasone dipropionate ≥ 5 mg/day
c. Initiation of oral corticosteroids (including budesonide and beclomethasone dipropionate) due to reasons other than worsening Crohn's disease for more than 7 days during induction treatment, OR, for more than 28 days during maintenance treatment.
d. Increase in the dose of oral corticosteroids (including budesonide and beclomethasone dipropionate), as specified below, above the baseline dose due to reasons other than worsening Crohn's disease for more than 7 days during induction treatment, OR, for more than 28 days during maintenance treatment.
    i. Oral corticosteroids ≥ 5 mg/day (prednisone equivalent)
    ii. Oral budesonide ≥ 3 mg/day
    iii. Oral beclomethasone dipropionate ≥ 5 mg/day

(iii) Immunomodulator agents
   a. Initiation of oral 6-MP/AZA due to worsening Crohn's disease.
   b. Initiation of oral, subcutaneous, or intramuscular MTX due to worsening Crohn's disease.
   c. Increase in the dose of oral 6-MP/AZA above the baseline dose due to worsening Crohn's disease.
   d. Increase in the dose of oral, subcutaneous, or intramuscular MTX above the baseline dose due to worsening Crohn's disease (within the same route).

(iv) 5-ASA
Initiation or increase of oral 5-ASA compounds due to worsening of Crohn's disease.

(v) Antibiotics
Initiation or change of antibiotics due to worsening Crohn's disease.

ICE CATEGORY 6 FOR SES-CD RELATED ENDPOINTS

An initiation of any of the following prohibited medications after Week 0 due to worsening Crohn's disease:

- Immunomodulatory agents other than AZA, 6-MP, or MTX (including, but not limited to, 6-TG, cyclosporine, mycophenolate mofetil, tacrolimus, and sirolimus).
- Immunomodulatory biologic agents (including, but not limited to, TNF antagonists, natalizumab, ustekinumab, rituximab, vedolizumab). Ustekinumab is permitted in this study only in participants randomly assigned to ustekinumab and only as stipulated in this protocol.
- Experimental Crohn's disease medications (including, but not limited to, upadacitinib, filgotinib, ozanimod, etrolizumab, brazikumab, mirakizumab [formerly LY-3074828], risankizumab, GS-5745).
- Thalidomide or related agents.

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