Janssen Research & Development

Statistical Analysis Plan
Amendment 2

A Phase 3 Study of the Efficacy, Safety, and Pharmacokinetics of Ustekinumab as Open label Intravenous Induction Treatment Followed by Randomized Double blind Subcutaneous Ustekinumab Maintenance in Pediatric Participants with Moderately to Severely Active Crohn's Disease
UNITI-Jr

Protocol CNTO1275CRD3004; Phase 3

STELARA (ustekinumab)

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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
1.0	12 April 2021	Not Applicable	Initial release
2.0 (draft)	05 May 2022	Section 1.1.1 and Section 1.1.2: Updated Global and US-specific secondary and other endpoints	Clarification and align with protocol
		Section 1.2: Updated sample size and study enrollment strategy	Address FDA's comments
		Section 1.2: Added PK interim analysis in study design, and minor modifications	New analysis, clarification and align with protocol
		Section 3: Updated sample size, study enrollment strategy, and the precision calculation	Address FDA's comments
		Section 4: Updated analysis sets	Clarification and new analysis sets
		Sections 5.1: Added statement for the statistical method used to construct the 95% CI of a proportion	Address FDA's comments
		Section 5.1: Specified randomized intervention groups will be used in both efficacy analyses and safety analyses.	Clarification
		Section 5.2: Minor modifications	Clarification
		Section 5.3.2.2: Modified Global Primary Estimand 1: all ICEs are addressed using composite strategy except for the ICE "Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)", which is addressed using hypothetical strategy	Address FDA's comments
		Section 5.3.2.3.1: Changed Global Supplementary Estimand 1 from hypothetical estimand to treatment policy estimand	Address FDA's comments
		Deleted Global Supplementary Estimand 2 (composite strategy, Previous Section 5.3.2.3.2)	Delete this estimand since it is the same as the updated primary estimand
		Section 5.3.2.3.2: Changed the prior Global Primary Estimand 1 to Global Supplementary Estimand 2	Address FDA's comments
		Section 5.3.2.5: Modified US-specific Primary Estimand 1: all ICEs are addressed using composite strategy except for the ICE "Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)", which is addressed using hypothetical strategy	Address FDA's comments
		Section 5.3.2.6.1: Changed US-specific Supplementary Estimand 1 from hypothetical estimand to treatment policy estimand	Address FDA's comments
		Deleted US-specific Supplementary Estimand 2 (Previous Section 5.3.2.6.2)	Delete this estimand since it is the same as the updated primary estimand.

SAP Version	Approval Date	Change	Rationale
		Section 5.3.2.6.2: Changed the prior US-specific Primary Estimand 1 to US-specific Supplementary Estimand 2	Address FDA's comments
		Section 5.3.3.2: • Section 5.3.3.2.1: Updated analysis method corresponding to the updated Global Supplementary Estimand 1 • Section 5.3.3.2.3: Added analysis method for Global Supplementary Estimand 3	Address FDA's comments
		Section 5.3.3.4: Added adjusted risk difference for US-specific Primary Estimand analysis	Address FDA's comments
		Section 5.3.3.5: • Section 5.3.3.5.1: Updated analysis method corresponding to the updated US-specific Supplementary Estimand 1 • Section 5.3.3.5.3: Added analysis method for US-specific Supplementary Estimand 3	Address FDA's comments
		• Section 5.3.3.6.3: Added US-specific Sensitivity Analysis 3: tipping point analysis	Address FDA's comments
		Section 5.3.3.7: Added US-specific supportive analyses • Section 5.3.3.7.1: Added US-specific Supportive Analysis 1: a frequentist approach to compare the proportion of pediatric participants on ustekinumab in clinical remission at Week M-44 with that of the historical proportion of adults on placebo that is obtained using trials with participant-level adult data • Section 5.3.3.7.2: Added US-specific Supportive Analysis 2: a Bayesian approach to compare the proportion of pediatric participants on ustekinumab in clinical remission at Week M-44 with that of a historical proportion of adults on placebo that is obtained using trials with participant-level adult data and trials with study-level data	
		Section 5.4.1 and Section 5.4.2: Minor modifications on secondary endpoints	Align with the updated objectives
		Section 5.4.3: Deleted some definitions	Align with the updated objectives
		Section 5.4.4.1: Updated Global secondary estimands for ICE handling strategies	To be consistent with the updated Global Primary Estimand
		Deleted Global Supplementary Estimands for Global Secondary Endpoints (previous Section 5.4.4.2)	Deleted as these are the same as the updated main secondary estimands

SAP Version	Approval Date	Change	Rationale
		Section 5.4.4.2: Updated US-specific secondary estimands for ICE handling strategies	To be consistent with the updated US-specific Primary Estimand
		Deleted US-specific Supplementary Estimands for US-specific Secondary Endpoints (previous Section 5.4.4.4)	Deleted as these are the same as the updated main secondary estimands
		Section 5.4.5: Minor modifications	Clarifications
		Section 5.5.1: • Section 5.5.1.1: Changed histologic assessment analyses as exploratory to be reported in a separate report • Section 5.5.1.3: Added BMI as a tertiary endpoint • Section 5.5.1.4: Added shift table for nutritional parameters • Section 5.5.1.6: Updated other endpoints	Clarification and new analysis
		Section 5.5.2: Updated endpoint definitions • Section 5.5.2.1: Clarified histologic assessments • Section 5.5.2.4: Added BMI • Section 5.5.2.7: Updated definitions for endpoints based on sPCDAI • Section 5.5.2.8: Deleted CDAI sustained clinical remission definition • Section 5.5.2.9: Updated definitions for endpoints based on SES-CD and endpoints based on SEMA-CD	Clarification and new analysis
		Section 5.5.3: Updated ICE handling strategies	To be consistent with the updated Primary Estimands
		Deleted prior Section 5.6.1 “Efficacy Endpoints at Week M-44 for all Participants (FAS)”	Clarification
		Section 5.6.2 and Section 5.6.3 updated analysis sets and some minor modifications	Clarification
		Deleted prior Section 5.6.4 “Supplementary Analyses of Efficacy Endpoints by Local vs. Central Laboratories”	Clarification
		Section 5.6.4: Added supplementary analysis using PCDAI diary data	New analysis
		Section 5.6.5: Updated ICE handling strategies	To be consistent with the updated Primary Estimands
		Section 5.6.7: Updated ICE handling strategies	Clarification
		Section 5.7: Deleted some analysis sets and minor modifications	Clarification
		Section 5.7.1: Added new listing for subjects who missed doses through Week M-44	New listing added
		Section 5.7.2: Updated analysis sets, added one subgroup analysis, and other minor modifications	Clarification and new analysis

SAP Version	Approval Date	Change	Rationale
		Section 5.7.3.1: Added shift tables for clinical lab tests, updated ALT/AST categories, and added an analysis of Hy's law abnormality	Clarification and new analysis
		Section 5.8.1: Updated the analysis set for PK analysis	Clarification
		Section 5.8.2: Updated the analysis set for Immunogenicity analysis	Clarification
		Section 5.8.7: Added analysis of dietary therapies in other analyses	New analysis
		Section 5.8.8: Added new subgroup – biologic washout period duration; updated categories for CD disease duration	Clarification and new analysis
		Section 5.9.1: Added PK interim analysis	New analysis
		Section 5.11: Specified analysis set	Clarification
		Section 6.1: Updated list of abbreviations	Added additional list of abbreviations
		Section 6.3: Added additional analysis and minor modification	Clarification and new analysis
		Section 6.5: Minor clarification and updated analysis set	Clarification
		Section 6.12: Previous subsection 6.12.1 was relocated to Section 6.15.2	Clarification
		Section 6.17: Added Appendix 17 for Bayesian approach details	FDA requested analysis
		Section 6.18: Minor modifications	Align with protocol
		Section 7: Updated references	Clarification
2.0	13 November 2023	Section 1: Updated the introduction text and Section numbers to include interim analysis for the EMA submission	Interim analysis for the EMA submission
		Section 1.2: Added a paragraph for the DBL for the analysis for the EMA submission and minor edits on the definitions of other DBLs	Interim analysis for the EMA submission
		Section 1.2.5.2: Added a paragraph describing the unblinding plan for the analysis for the EMA submission	Interim analysis for the EMA submission
		Section 3: Added sample size justification for the analysis for the EMA submission	Interim analysis for the EMA submission
		Section 4: Added analysis sets for the analysis for the EMA submission	Interim analysis for the EMA submission
		Section 5: Clarified the structure of Section 5	Clarification
		Section 5.5.2.5: Updated IMPACT-III to include the transformed scores and added analyses for the 4-domain IMPACT-III scoring system.	Clarification and new analysis
		Section 5.8.1: Clarified some PK analyses	Clarification
		Section 5.8.2: Clarified some immunogenicity analyses	Clarification
		Section 5.9.2: Added analysis for EMA submission;	Interim analysis for the EMA submission

SAP Version	Approval Date	Change	Rationale
		Section 6.11: Minor modifications and clarification	To align with CRF wording and to clarify definitions of some ICEs to be consistent with the treatment failure rules used across Janssen's clinical trials in Crohn's disease
		Section 6.15.1 Revised criteria to identify studies for the meta-analysis.	Revised criteria to identify studies for the meta-analysis to be more inclusive, and resulting in more than 1 study each of patient level and study level data, respectively.
		Section 6.16 (Appendix 16 Point Estimates and 95% CI Based on Various Biologic Failure Rate) was deleted	No longer relevant
		Section 6.16: Revised Bayesian model.	Revised Bayesian model to account for more than 1 study with patient-level and study-level data, respectively.
		Section 6.17: Minor modifications	Added timing of summaries for the substudy participants
3.0	21 August 2024	Sections 4 and 5.8.1: Deleted the text “as determined by the IWRS” where applicable; deleted “Immunogenicity Randomized Analysis Set” (no longer needed)	Clarification
		Sections 5.2, 5.7, and 6.4: Updated the text to clarify that any final safety visit data occurring prior to the Week M-44 DBL will not be included in the analysis for the Week M-44 DBL where applicable	Clarification
		Section 5.3.3.7: Fixed the typos	Typos
		Section 5.3.2.6.3: Added US-Specific Supplementary Estimand 3: difference from the Primary estimand is that the condition “within 90 days prior to endpoint assessment date” used to determine the use of immunomodulator in ICE 3 is removed	New analysis to address FDA’s comment:
		Section 5.3.2.6.4: Added US-Specific Supplementary Estimand 4: difference from the Primary estimand is that the clinical response at Week I-8 that is used to define Population will be determined by IWRS.	New analysis
		Section 5.5.1.6: Added text to clarify the definition for corticosteroid-free clinical remission over time	Clarification
		Sections 5.5.1.6 and 5.5.2.11: Added mucosal inflammation noninvasive index (MINI) score (continuous and categorical) as tertiary endpoints	New analysis
		Section 5.6.3: Specified that the observed data would be used for the efficacy analyses for participants who are qualified for dose adjustments	Clarification

SAP Version	Approval Date	Change	Rationale
		Section 5.7.1: Added analysis for the summary of study intervention duration, number of administrations, and cumulative dose	Clarification
		Section 5.8.2: Changed 2-fold increase to 4-fold increase in the definition for treatment-boosted anti-ustekinumab antibodies	New definition
		Section 5.8.8 and Section 6.3: Added a category "inactive [0-2]" for endoscopic disease severity per SES-CD score	Clarification
		Section 6.3: Clarified the analysis set to be used in the analysis of demographics and baseline characteristics; Updated the region categories for Israel	Clarification

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, data handling conventions and statistical methods for all planned analyses in protocol CNTO1275CRD3004, including analysis specifications for the European Medicines Agency (EMA) submission for participants with body weight ≥40 kg (Section 5.9.2) and the Exposure Optimization Substudy (Section 6.17).

Analyses of data for the Maintenance Week 44 (Week M-44) database lock (DBL) will be described through Section 5.8. The PK interim analyses will be described in Section 5.9.1. Analyses of data for the main study final DBL will be described in Section 5.10. The interim analysis for the EMA submission for participants with body weight ≥40 kg will be described in Section 5.9.2. Analysis of data for the Exposure Optimization Substudy will be described in Section 5.11.

1.1. Objectives and Endpoints

The primary objective and primary endpoint in this study is to assess clinical remission. Please note the assessment timepoint for the primary objective and primary endpoint will be different for countries outside of the United States (global timepoint at Induction Week 8 [Week I-8]) and the United States (US-specific timepoint at Week M-44).

The objectives and primary and secondary endpoints found in Section 1.1.1 refer to the global objectives and endpoints.

The objectives and primary and secondary endpoints found in Section 1.1.2 refer to the US-specific objectives and endpoints.

The objectives and endpoints for the Exposure Optimization Substudy will be described in Section 6.17.

1.1.1. Global Objectives and Endpoints

Global Objectives	Global Endpoints
Primary	
• To evaluate the efficacy of ustekinumab dosing in inducing clinical remission in pediatric participants with moderately to severely active Crohn's disease.	The primary endpoint is clinical remission at Week I-8.
• To evaluate the safety profile of ustekinumab in pediatric participants with moderately to severely active Crohn's disease.	• Adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation of study intervention, and AEs of interest (eg, infections). • Clinical laboratory, hematology and chemistry.

Global Objectives	Global Endpoints
	• Reactions temporally associated with an intravenous (IV) infusion (induction period) and subcutaneous (SC) injection-site reactions (maintenance period).
• To evaluate ustekinumab exposure (pharmacokinetics [PK]).	• Serum ustekinumab concentrations.
Secondary	
• To evaluate the efficacy of IV ustekinumab during the induction period.	• Clinical remission at Week I-6 as assessed by short Pediatric Crohn's Disease Activity Index (sPCDAI). • Clinical response at Week I-8. • Clinical response at Week I-6 as assessed by sPCDAI. • Endoscopic response at Week M-8* as assessed by Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) • Clinical response at Week M-8* *These endpoints are evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction.
• To evaluate the efficacy of SC ustekinumab during the maintenance period among participants who were in clinical response in induction.	• Clinical remission at Week M-44. • Endoscopic response at Week M-44 as assessed by SES-CD. • Clinical response at Week M-44. • Corticosteroid-free clinical remission at Week M-44. • Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8.
Other	
• To evaluate the effects of ustekinumab on the following factors: – Histologic assessments – Serum and fecal biomarkers – Growth	• Histologic assessments based on the Global Histology Activity Score (GHAS), Geboes score, and Robarts Histopathology Index (RHI). Change from baseline in: • C-reactive protein (CRP) concentrations. • Fecal calprotectin and fecal lactoferrin levels.

Global Objectives	Global Endpoints
– Nutritional parameters	• Height, weight, and body mass index (BMI) (measured with age and sex-specific z-scores) at Weeks I-8 and M-44 • 25-hydroxyvitamin D, methyl malonic acid (MMA), and iron levels at Weeks M-4 and M-44.
• To evaluate the effect of ustekinumab on Crohn's disease-related quality of life (QoL)	• Change from baseline in IMPACT-III scores at Week M-44 for participants ≥10 years of age at Week I-0.

1.1.2. US-specific Objectives and Endpoints

US-Specific Objectives	US-Specific Endpoints
Primary	
• To evaluate the efficacy of ustekinumab dosing in maintaining clinical remission in pediatric participants with moderately to severely active Crohn's disease.	The primary endpoint is clinical remission at Week M-44. This endpoint will be assessed among participants who are in clinical response at Week I-8.
• To evaluate the safety profile of ustekinumab in pediatric participants with moderately to severely active Crohn's disease.	• AEs, SAEs, AEs leading to discontinuation of study intervention, and AEs of interest (eg, infections). • Clinical laboratory, hematology and chemistry. • Reactions temporarily associated with an IV infusion (induction period) and SC injection-site reactions (maintenance period).
• To evaluate ustekinumab exposure (PK).	• Serum ustekinumab concentrations
Secondary	
• To evaluate the efficacy of IV ustekinumab during the induction period.	• Clinical remission at Week I-8. • Clinical remission at Week I-6 as assessed by sPCDAI. • Clinical response at Week I-8. • Clinical response at Week I-6 as assessed by sPCDAI. • Endoscopic response at Week M-8* as assessed by SES-CD • Clinical response at Week M-8* *These endpoints are evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction.

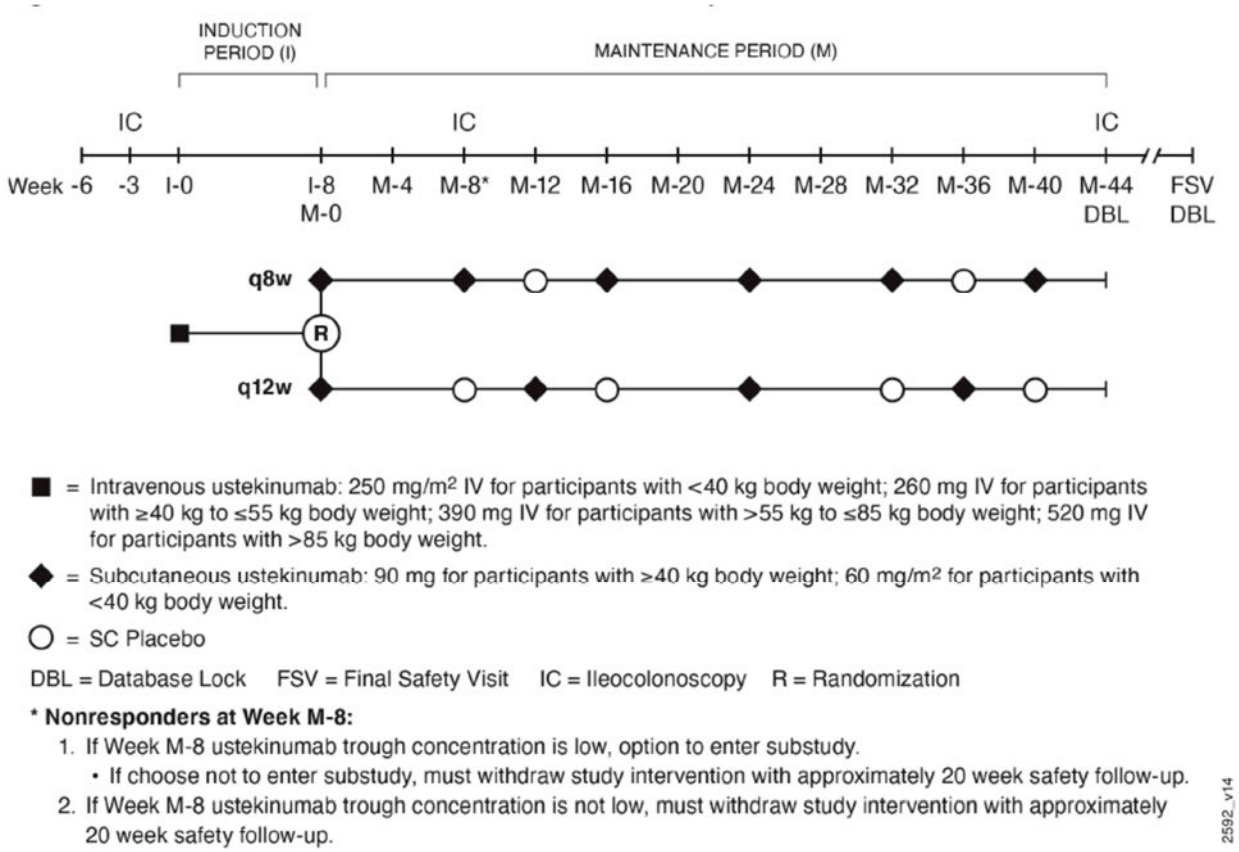
US-Specific Objectives	US-Specific Endpoints
• To evaluate the efficacy of SC ustekinumab during the maintenance period among participants who were in clinical response in induction.	• Endoscopic response at Week M-44 as assessed by SES-CD • Clinical response at Week M-44 • Corticosteroid-free clinical remission at Week M-44 • Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8
Other • To evaluate the effects of ustekinumab on the following factors: – Histologic assessments – Serum and fecal biomarkers – Growth – Nutritional parameters	• Histologic assessments based on the GHAS, Geboes score, and RHI. Change from baseline in: • CRP concentrations. • Fecal calprotectin and fecal lactoferrin levels. • Height, weight, and BMI (measured with age and sex-specific z-scores) at Weeks I-8 and M-44. • 25-hydroxyvitamin D, MMA, and iron levels at Weeks M-4 and M-44.
• To evaluate the effect of ustekinumab on Crohn's disease-related QoL	• Height, weight, and BMI (measured with age and sex-specific z-scores) at Weeks I-8 and M-44.
• To evaluate the effect of ustekinumab on Crohn's disease-related QoL	• Change from baseline in IMPACT-III scores at Week M-44 for participants ≥10 years of age at Week I-0.

1.2. Study Design

This is a Phase 3, multicenter, interventional study consisting of an open-label induction period with a single IV ustekinumab dose followed by a maintenance period with a randomized, double-blind, parallel group 2-arm study design, exploring 2 different SC ustekinumab maintenance dose regimens. Participants will be 2 to <18 years of age with moderately to severely active Crohn's disease (defined by a Pediatric Crohn's Disease Activity Index [PCDAI] score >30). Participants must have demonstrated an inadequate response and/or intolerance to biologic therapy (ie, TNFα antagonists or vedolizumab) and/or conventional therapies (ie, IV or oral corticosteroids or the immunomodulators azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]) or be dependent upon corticosteroids.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



Approximately 90 participants will be enrolled in the study with at least 24 participants <40 kg including at least 5 participants <30 kg. Participants must weigh ≥10 kg to enroll in the study. Approximately 90% of the enrolled participants were induction responders from the preliminary data of the current study (out of the 29 randomized, 27 were induction responders). Hence, it is expected that approximately 80 participants will be induction responders.

In the induction period, all participants will receive a single open-label IV administration of ustekinumab at Week I-0. For participants ≥40 kg, dosing will be based on a weight-tiered induction dose which is the same as the approved adult dosing regimen. For participants <40 kg, dosing will be body surface area (BSA)-adjusted.

For participants with body weight <40 kg:

- 250 mg/m^2 IV

For participants with body weight ≥40 kg:

- 260 mg IV for participants with ≥40 kg to ≤55 kg body weight
- 390 mg IV for participants with >55 kg to ≤85 kg body weight
- 520 mg IV for participants with >85 kg body weight

In the maintenance period, all participants who complete the Week I-8 visit will be randomized at Week M-0 in a blinded fashion to a 1:1 ratio stratified by response status at Week I-8 (induction responder and induction nonresponder) and weight (<40 kg, ≥40 kg) to receive 1 of 2 SC dose regimens:

- **Ustekinumab q8w:** 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight. Participants will receive ustekinumab at Weeks M-0, M-8, M-16, M-24, M-32, and M-40 and matching placebo at Weeks M-12 and M-36 to maintain the blind.
- **Ustekinumab q12w:** 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight. Participants will receive ustekinumab at Weeks M-0, M-12, M-24, and M-36 and matching placebo at Weeks M-8, M-16, M-32, and M-40 to maintain the blind.

Ustekinumab doses from Week M-0 through Week M-40 will be based on the participants' weight and height obtained at that visit or based on participant weight and height at the last on-site visit. If a study participant's weight falls below 10 kg after Week I-8, the study intervention must be withheld until their body weight is ≥10 kg. If participants miss 2 consecutive doses of ustekinumab because of body weight below the 10 kg limit, the study intervention should be discontinued.

During the maintenance period, at the Weeks M-0 and M-8 study visits, study intervention administrations will be performed (or supervised) at the study site by a study-site staff member. The study staff member will provide training on study intervention administration, proper syringe disposal, and injection-site monitoring. At Week M-12, Week M-24, Week M-36, and Week M-40, participants or the participant's caregiver will have the option to conduct study visits remotely and to administer study intervention at home.

At Week M-8, the following early escape criterion options apply, where induction nonresponders who do not achieve clinical response based on the PCDAI by Week M-8 (ie, a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30) have 1 or 2 options:

- Option 1: must be discontinued from study intervention.
- Option 2: Wait to determine if the participant has low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit) whereby the participant will be eligible for enrollment in a 16-week, open-label Exposure Optimization Substudy with dose interval adjustment to every 4 weeks (see Appendix 17). If the participant does not have low exposure, they will be discontinued from study intervention.

Beginning at Week M-8 for induction responders and beginning at Week M-16 for delayed responders (induction nonresponders who are in clinical response at Week M-8), participants who experience loss of response (LOR) (Section 1.2.2) may be eligible for an immediate dose adjustment (Section 1.2.3). If the participant has an 8-week trough serum ustekinumab concentration of <1.4 µg/mL in addition to the LOR during the maintenance period, the participant will be eligible to enroll in a 16-week, open-label Exposure Optimization Substudy with dosing interval adjustment to q4w (see Appendix 17). If determined to be medically appropriate in the judgment of the investigator, participants who meet the Early Escape criteria may receive approved

rescue therapies (Section 1.2.4) while they await the Week M-8 ustekinumab trough level result to determine eligibility for the Exposure Optimization Substudy. Dose adjustments (including enrollment in the Exposure Optimization Substudy) can occur until the Week M-44 dosing visit.

Participants will be followed for AEs and SAEs for up to 20 weeks after the last study intervention administration.

The following concomitant medications/therapies for Crohn's disease are allowed at the start of this study: oral 5-ASAs, oral corticosteroids, immunomodulators (ie, 6-MP, AZA, MTX), and single antibiotics for the treatment of Crohn's disease. These treatments must be stable for 2 to 4 weeks before the first administration of study intervention at Week I-0. If there is a concern for drug toxicity, dose reduction can always occur.

In general, concomitant medications for Crohn's disease should remain stable (without initiation or increase in dose) through Week M-44. However, the following medication/therapy changes after Week I-0 are allowed:

- For participants receiving immunomodulators at Week M-0, the dose may be discontinued at any time during the study at the discretion of the investigator, though it is preferred that they be continued through Week M-44.
- For participants on an oral 5-ASA or single antibiotic for the treatment of Crohn's disease at Week I-0, the 5-ASA or antibiotic can be discontinued at any time during the course of the study, though preferably after Week M-44.
- For participants receiving oral corticosteroids (including budesonide or beclomethasone dipropionate) at Week I-0, the steroids may be tapered beginning at Week I-0. For those participants continuing to receive corticosteroids on entry into the maintenance period, corticosteroid tapering must be initiated at Week M-0 for induction responders and at Week M-8 for delayed responders as follows:

Recommended tapering schedule for oral prednisone-equivalent corticosteroids:

- Participants receiving >20 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until 0 mg/day.
- Participants receiving ≤20 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.

Tapering of budesonide or beclomethasone dipropionate should follow local clinical practice.

Participants may transiently (ie, for ≤4 weeks) use increased doses of corticosteroids for reasons other than Crohn's disease activity (eg, stress doses of corticosteroids for surgery, asthma flare, adrenocortical insufficiency).

Participants in response, who complete participation at Week M-44, or complete the 16 weeks follow-up post Exposure Optimization Substudy (whichever is longer) and are less than 18 years old may be eligible for inclusion into a separate long term extension (LTE) and continue to receive

SC ustekinumab at the dose they were receiving on completion of the maintenance period. Details will be provided in a separate protocol.

If participants do not participate in the LTE study, they will continue safety follow-up for approximately 20 weeks after the administration of last study intervention, including participants from the substudy. The study will end when the last participant has either completed Week M-44 and transitioned into the LTE study, completed their final safety visit (approximately 20 weeks after the administration of last study intervention), completed the Exposure Optimization Substudy (approximately 16 weeks), or terminated study participation, whichever is later.

The primary endpoint is:

- **Global** - clinical remission at Week I-8
- **US-specific** - clinical remission at Week M-44. This endpoint will be assessed among participants who are in clinical response at Week I-8.

Efficacy, PK, biomarkers, and safety will be assessed according to the Schedule of Activities (SoA, Protocol, Section 1.3).

Four DBLs are planned for this study:

1. **DBL1**: A DBL to support the interim analysis for the EMA submission for randomized participants with body weight ≥40 kg will occur when at least 36 randomized participants with body weight ≥40 kg at Week I-0 and Week M-0 have received at least 1 administration of study intervention during maintenance and have completed the Week M-44 visit, or terminated the main study participation prior to Week M-44. Participants who meet this criterion and who had PK samples collected at the Week I-0, M-0, and M-8 visits will be included in the PK analysis. All available data from each participant will be included in the DBL, including data from the Exposure Optimization Substudy for participants who participated in the substudy and completed assessments through Week M-44.
2. **DBL2:** The primary outcome DBL will occur at Week M-44 after all participants have either completed their Week M-44 visit or terminated the main study participation prior to Week M-44.
3. **DBL3:** A third DBL will occur when all participants who are not participating in the LTE have completed their final safety visit (20 weeks after the last administration of study intervention).
4. **DBL4:** A fourth DBL will be conducted after all participants have completed the Exposure Optimization Substudy, including their final safety visit.

Additional DBLs other than the ones specified above may be performed. If the third and fourth DBLs will take place around the same time, the two DBLs may be combined.

A PK interim analysis to evaluate the ustekinumab dosage and safety for participants <40 kg (as measured at Week I-0) will be performed when about 20 participants <40 kg from both CNTO1275CRD3004 and CNTO1275PUC3001 studies (combined) complete the Week M-8 visit (Section 5.9.1).

An external Data Monitoring Committee (DMC), consisting of at least one medical expert in the relevant therapeutic area and at least one statistician, will be established to monitor safety data on an ongoing basis until all participants reach the Week M-44 visit or terminate the study prior to Week M-44 (Section 5.9.2) for both the pediatric ustekinumab Inflammatory Bowel Disease [IBD] studies (CNTO1275PUC3001 [pediatric ulcerative colitis] and CNTO1275CRD3004) or for participants in the Exposure Optimization Substudy, completion of the Week 16 visit or termination of study participation, whichever is longer. In addition, the DMC members along with an unblinded internal sponsor PK expert (independent of study) will review the results of the PK interim analysis to evaluate the ustekinumab dosage and safety for participants <40 kg (as measured at week I-0) (Section 5.9.1). The DMC responsibilities, authorities, and procedures will be documented in the joint DMC charter for CNTO1275PUC3001 and CNTO1275CRD3004.

1.2.1. Early Escape Criteria

At Week M-8, the following early escape criterion applies:

- Induction nonresponders who do not achieve clinical response based on the PCDAI by Week M-8 (ie, a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30) will have 1 of 2 options:

  1. Must be discontinued from blinded study intervention and then complete a safety follow-up visit approximately 20 weeks after the last administration of study intervention and discontinue the study.

  OR

  2. Wait to determine if induction nonresponders have low exposure and would like to participate in the optional substudy:

     – If a participant is documented to have low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit), the participant will be eligible for enrollment in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to q4w (See Appendix 17). If determined to be medically appropriate in the judgment of the investigator, participants who meet the Early Escape criteria may receive approved rescue therapies (Section 1.2.4) while they await the Week M-8 ustekinumab trough level result to determine eligibility for the Exposure Optimization Substudy.

     – Induction nonresponders who do not have low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit) must be discontinued from study intervention and complete a safety follow-up visit approximately 20 weeks after the last administration of study intervention.

1.2.2. Loss of Response During the Maintenance Period

All participants randomized into the maintenance period will be assessed for LOR. During home study visits, participants who experience LOR will be transitioned to a study site visit to complete their current visit.

For the purpose of this protocol, participants in the maintenance period who meet the following criteria will be considered to have LOR:

1. An increase in the PCDAI >12.5 above the reference PCDAI score, or an increase in the short Pediatric Crohn's Disease Activity Index [sPCDAI] ≥10 above the reference sPCDAI score, at 2 consecutive visits at least 7 days apart, the reference baseline being Week M-0 for induction responders and Week M-8 for delayed induction responders.

AND

2. The PCDAI score is >30 or the sPCDAI score is >30 at 2 consecutive visits at least 7 days apart.

Note: Participants for whom LOR is suspected will need to provide a stool sample for enteric pathogen testing, which will include a stool culture and a Clostridioides difficile test. In case of a positive test, a participant can be considered as having LOR if still showing symptoms that meet the criteria, after having received a standard treatment course for the enteric pathogen infection.

Participants who have LOR will be eligible for a dose adjustment (Section 1.2.3), those who have LOR and have documented low ustekinumab exposure will be eligible for the Exposure Optimization Substudy.

1.2.2.1. Loss of Response and Low Exposure During the Maintenance Period

If the participant has an 8-week trough serum ustekinumab concentration of <1.4 g/mL in addition to the LOR during the maintenance period, they will have the option to enroll in an open-label Exposure Optimization Substudy (for details, see Section 6.17). If the participant chooses not to enroll in the substudy, they can be withdrawn from study participation at the discretion of the investigator.

1.2.3. Dose Adjustment During the Maintenance Period

Beginning at Week M-8 for induction responders and beginning at Week M-16 for delayed responders, participants who experience LOR (Section 1.2.2) may be eligible for an immediate dose adjustment as follows:

- Participants who are randomized to ustekinumab q12w and have LOR will be eligible for a dose adjustment to ustekinumab q8w.
- Participants who are randomized to ustekinumab q8w and who experience LOR will remain on ustekinumab q8w (a sham adjustment).

At the first scheduled visit that participants experience LOR, they will have a dose adjustment and transition to q8w dosing without any placebo injections. For the first dose, participants may receive a study intervention 4 weeks after the prior study intervention if LOR occurs between their scheduled study intervention injections in order to maintain study blinding.

Participants who experience LOR and undergo dose adjustment or sham dose adjustment will proceed to visits every 4 weeks until clinical response or sPCDAI clinical response is achieved. The LOR visit and all subsequent visits after LOR must be conducted at the study site.

Participants who have lost response will be assessed 16 weeks after dose adjustment. At that time, those participants who are not in clinical response or sPCDAI clinical response will be withdrawn from study intervention and return for their final safety visit (approximately 20 weeks after the administration of the last study intervention).

Participants who experience LOR and have low ustekinumab exposure may be eligible to participate in an optional Exposure Optimization Substudy with q4w dosing and safety visits (see Appendix 17) or be withdrawn from study participation at the discretion of the investigator.

If a participant experiences LOR, is dose adjusted (or sham dose adjusted) to ustekinumab q8w, achieves response, and subsequently experiences a second LOR with documented low ustekinumab exposure, the participant may be eligible for the optional Exposure Optimization Substudy (Appendix 17).

1.2.4. Rescue Medication

If determined to be medically appropriate in the judgment of the investigator, dose adjustment should precede institution of Crohn's disease-specific therapies in participants meeting study-specific LOR criteria.

Rescue therapies include:

- Oral and rectal corticosteroids
- Oral and rectal 5-ASA compounds
- Antibiotics for Crohn's disease-specific therapy (more than one antibiotic for Crohn's disease-specific therapy is prohibited)
- Immunomodulators (6-MP, AZA, or MTX)

If the above medical therapies are initiated or medication doses increased based on medical necessity after meeting LOR criteria, participants can continue study intervention and should continue to attend all study visits and have all assessments. Prohibited changes to Crohn's disease medication are defined in Section 6.11.

Rescue therapies for oral corticosteroids are limited to 2 courses of corticosteroids (for further details, Section 4.1.4. of the Protocol).

1.2.5. Randomization and Blinding

Randomization at Week M-0 will be used to minimize bias in the assignment of participants to treatment groups and to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups.

The maintenance blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

1.2.5.1. Randomization

Central randomization will be implemented in this study. At Week M-0, participants (induction responders and induction nonresponders) will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

The randomization will be balanced by using permuted block randomizations and will be stratified by response status at Week I-8 (induction responder/induction nonresponder) and weight (<40 kg, ≥40 kg). Clinical response status at Week I-8 will be determined by the PCDAI score.

The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant.

1.2.5.2. Blinding

To maintain the study blind during the maintenance period, the study intervention container will have a label containing the study name, study intervention number, and reference number. The label will not identify the study intervention in the container. The vial number will be entered in the electronic case report form (eCRF) when the study intervention is dispensed. Placebo injections will be used, and they will be identical in appearance to ustekinumab.

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

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

Notes:

- If a participant has documented LOR and the investigator wishes to evaluate if the participant would be eligible for the Exposure Optimization Substudy, the site will be informed of the participant's exposure (ie, low [<1.4 µg/mL] or normal).

- If a participant's ustekinumab trough concentration at the end of the Exposure Optimization Substudy (after at least 3 doses) is >7.2 µg/mL, the site will be informed and the participant will not be able to continue q4w dosing, but may continue q8w dosing in the LTE. (For details on the Exposure Optimization Substudy, refer to Appendix 17).

If an investigative site requests specific ustekinumab trough concentration data, they will be provided to the site after the Week M-44 analyses have been completed.

Treatment assignment blinding will be maintained for investigative sites and participants participating in this protocol until the Week M-44 analyses for the maintenance period have been completed.

Generally, the sponsor personnel will remain blinded to maintenance treatment assignment until after the primary outcome DBL following the Week M-44 visit, with the exception of a PK sponsor representative independent of study conduct to review the PK interim analysis (see Section 5.9.1 for further details). In addition, a prespecified sponsor unblinded group will have access to the data and be unblinded to prepare for the EMA submission for the participants with body weight ≥40 kg at the interim analysis (Further details is provided in the unblinding plan).

Under normal circumstances, the blind during the maintenance period should not be broken until the Week M-44 analyses of the maintenance period have been completed. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant. In such cases, the investigator may in an emergency determine the identity of the ustekinumab treatment regimen by contacting the IWRS. While the responsibility to break the treatment regimen code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate Section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Additionally, a given participant’s treatment assignment may be unblinded to the sponsor, the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and site personnel to fulfill regulatory reporting requirements for suspected unexpected serious adverse reactions (SUSARs). If a participant is unblinded to the site, the information must be entered in the appropriate Section of the eCRF and in the participant's source documents.

A separate code break procedure will be available for use by the sponsor’s Global Medical Safety group to allow for unblinding of individual participants to comply with specific requests from regulatory or health authorities.

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

2. STATISTICAL HYPOTHESES

The **Global** primary hypothesis, used for countries outside of the United States, is:

The primary hypothesis is that ustekinumab is an effective therapy in pediatric participants with moderately to severely active Crohn's disease. A determination of the efficacy of ustekinumab for the treatment of pediatric Crohn's disease will be made based on the totality of evidence from an assessment of the primary and secondary endpoints. This totality of evidence will be presented descriptively.

The **US-specific** primary hypothesis is:

The primary hypothesis is that ustekinumab is an effective therapy in pediatric participants with moderately to severely active Crohn's disease. A determination of the efficacy of ustekinumab for the treatment of pediatric Crohn's disease will be made based on the totality of evidence from an assessment of the primary and secondary endpoints. This totality of evidence will include a descriptive comparison of the proportion of pediatric participants in clinical remission at Week M-44 relative to a historical adult placebo control (see Section 5.3).

3. SAMPLE SIZE DETERMINATION

Approximately 90 participants will be enrolled in the study with at least 24 participants <40 kg including at least 5 participants <30 kg. Participants must weigh ≥10 kg to enroll in the study. Approximately 90% of the enrolled participants were induction responders from the preliminary data of the current study (27 induction responders out of 29 randomized participants observed). Hence, the study is expected to enroll approximately 80 induction responders who are randomized.

Given that success will be evaluated by the totality of the data, such a sample size is considered sufficient to determine efficacy under the extrapolation concept for both the global objectives and the US-specific objectives.

The sample size determination for the EMA submission for participants with body weight ≥40 kg is provided in Section 3.1.The sample size determination for the **Global** primary endpoint is provided in Section 3.2.

The sample size determination for the **US-specific** primary endpoint is provided in Section 3.3.

3.1. Sample Size Determination for the EMA Submission for Participants ≥40 kg

Optimal design analysis was performed for this study using Fisher Information Matrix (FIM)-based methods to determine the appropriate sample size needed to adequately characterize ustekinumab PK in pediatric CD participants ≥40 kg. Based on the pediatric investigation plan (PIP) commitment, at least 24 participants with body weight <40 kg are planned to be enrolled in this study. Thus, the number of participants with body weight ≥40 kg may not be expected to exceed 66 (for a total of 90). Accordingly, optimization analyses for the subgroup of participants with body weight ≥40 kg were performed with the assumption that 66 participants will provide the

maximum information obtainable in the study. From the FIM optimization analysis, no substantial PK information is expected to be gained if the number of pediatric participants with body weight ≥40 kg increases from 36 to 66. With 36 participants, approximately 92% of the information needed to characterize ustekinumab PK is obtained when compared with the information obtained from 66 participants. Accordingly, 36 participants with body weight ≥40 kg would adequately characterize the PK of ustekinumab in this subgroup.

3.2. Sample Size Determination for the Global Primary Endpoint

With a sample size of 90 participants enrolled and assuming 90% of the participants in this study are biologic failures, the precision (ie, half width of the 95% confidence interval [CI]) in estimating the true proportion of pediatric participants in clinical remission at Week I-8 is 8.7% (assuming the proportion of participants in clinical remission is 22.8% at Week I-8 [based on a weighted average from the biologic-failure population from the ustekinumab adult study CNTO1275CRD3001 (20.9%; ~6 mg/kg treatment group) and from the non-biologic-failure population from the ustekinumab adult study CNTO1275CRD3002 (40.2%; ~6 mg/kg treatment group)]).

Table 2: Precision (%) for Various Proportions of Biologic Failures for the Global Primary Endpoint

Proportion of biologic failures (%)	Weighted average of participants in clinical remission (%)	Precision (%)
90	22.8	8.7
75	25.7	9.1
50	30.6	9.5

3.3. Sample Size Determination for the US-Specific Primary Endpoint

It should be noted that this study is not powered to show any differences between maintenance treatment regimens. Approximately 90% of the enrolled participants were induction responders from the preliminary data of the current study (27 induction responders out of 29 randomized participants observed). Hence, with a sample size of 90 participants enrolled, approximately 80 participants (40 in each group) who are clinical responders at Week I-8 and 10 participants who are induction nonresponders at Week I-8 would be expected to enter the randomized maintenance portion of the study.

Assuming 90% of the participants in this study are biologic failures, with a sample size of 90 participants enrolled and with the expectation that 80 participants will be clinical responders at Week I-8, the precision (ie, half width of the 95% confidence interval [CI]) in estimating the true proportion of pediatric participants in clinical remission at Week M-44 is 10.85% (assuming a clinical remission rate of 43.2% at Week M-44 [based on a weighted average from the biologic-failure population from the adult study CNTO1275CRD3003 (41.1%; 90 mg q8w treatment group) and from the non-biologic-failure population from the adult study CNTO1275CRD3003 (62.5%; 90 mg q8w treatment group)]).

Table 3: Precision (%) for Various Proportions of Biologic Failures for the US-specific Primary Endpoint

Proportion of biologic failures (%)	Weighted average of participants in clinical remission (%)	Precision (%)
90	43.2	10.85
75	46.5	10.93
50	51.8	10.95

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
All Enrolled Analysis Set	All participants who sign the informed consent/assent form (ICF).
Full Analysis Set (FAS)	All participants who received an administration of study intervention in induction at Week I-0.
Full Randomized Analysis Set (FASR)	All participants who were randomized in the maintenance period of the study and received at least 1 administration of study intervention during maintenance.
Full Clinical Responder Analysis Set (FASCR)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and received at least 1 administration of study intervention during maintenance.
All Responder Analysis Set (FASRES)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab therapy at Week I-8 or Week M-8 and received at least 1 administration of study intervention during maintenance.
Safety Analysis Set	All participants who received an administration of study intervention in induction at Week I-0.
Safety Randomized Analysis Set (SASR)	All participants who were randomized into the maintenance period of the study and received at least 1 administration of study intervention during maintenance.
Safety Clinical Responder Analysis Set (SASCR)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and received at least 1 administration of study intervention during maintenance.
PK Analysis Set (PKAS)	All participants who received an administration of ustekinumab in induction at Week I-0 and have at least one postbaseline blood sample collection in induction.
PK Randomized Analysis Set (PKASR)	All participants who were randomized into the maintenance period of the study, received at least 1 administration of ustekinumab during maintenance, and have at least one post-Week M-0 blood sample collection in maintenance.
PK Clinical Responder Analysis Set (PKASCR)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and have received at least 1 administration of ustekinumab during maintenance, and have at least one post-Week M-0 blood sample collection in maintenance.
PK All Responder Analysis Set (PKASRES)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab therapy at Week I-8 or at Week M-8, and have received at least 1 administration of ustekinumab during maintenance, and have at least one post-Week M-0 blood sample collection in maintenance.

Analysis Sets	Description
Immunogenicity Analysis Set (IAS)	All participants who received an administration of study intervention in induction at Week I-0 and have appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 sample collection in induction).
Immunogenicity Clinical Responder Analysis Set (IASCR)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8, received at least 1 administration of ustekinumab during maintenance, and have appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 post Week M-0 sample collection in maintenance).
Immunogenicity All Responder Analysis Set (IASRES)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab therapy at Week I-8 or at Week M-8, and have received at least 1 administration of ustekinumab during maintenance, and have appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 post Week M-0 sample collection in maintenance).
Substudy Analysis Set (SSAS)	All participants who entered the exposure optimization substudy and received at least 1 administration of study intervention during the substudy
EMA Randomized Analysis Set for Participants with Body Weight ≥40 kg (ERAS)	All participants who had body weight ≥40 kg at Week I-0 and Week M-0, received at least 1 administration of study intervention during maintenance, and completed Week M-44 visit or terminated the main study prior to Week M-44 at the EMA DBL Includes participants who entered the substudy.
EMA PK Analysis Set for Participants with Body Weight ≥40 kg (PKERAS)	All participants who had body weight ≥40 kg at Week I-0 and Week M-0, received at least 1 administration of study intervention during maintenance, had PK samples collected at Week I-0, Week M-0, and Week M-8, and completed Week M-44 visit or terminated the main study prior to Week M-44 at the EMA DBL

5. STATISTICAL ANALYSES

The statistical analyses in this SAP will include all analyses from Week I-0 through the final safety visit, including the analyses for the Exposure Optimization Substudy.

Section 5.1 through Section 5.8 provide the analyses through the DBL2 (ie, the primary outcome DBL); Section 5.9.2 provides the analyses for DBL1 (ie., the DBL to support the IA for the EMA submission for participants with body weight ≥40 kg); Section 5.10 provides the analyses for DBL3 (ie, when all participants who are not participating in the LTE have completed final safety visit); and Section 5.11 provides the analyses for DBL4 (Exposure Optimization Substudy).

5.1. General Considerations

In general, baseline is defined as the last observation prior to or at the time of the first study intervention, unless otherwise specified.

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, interquartile range (IQ), minimum and maximum, as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Unless otherwise specified, the Wilson score method will be used to construct the 95% CI for binary endpoints where a proportion and the

respective 95% CI are reported. Graphical data displays (eg, line plots) may also be used to summarize the data.

Unless otherwise specified, the endoscopic subscore as obtained during the central review of the video endoscopy will be used for all efficacy analyses involving ileocolonoscopy in this section.

Unless otherwise specified, all efficacy and safety analyses during maintenance will be based on the randomized study intervention.

5.1.1. Visit Windows

Unless otherwise specified, nominal visits will be used for all by visit analyses.

5.1.2. Pooling Algorithm for Analysis Centers

Unless otherwise specified, data from all investigational centers/sites will be pooled for analyses.

5.1.3. Reference Date and Study Day

The Reference Date is the date of the first study intervention. If the date of the first study intervention is missing or the first study intervention is not done, then the Reference Date equals the corresponding visit date (ie, Week I-0 visit date).

Study Day 1 or Day 1 refers to the reference date (there is no Study Day 0). All efficacy and safety assessments at all visits will be assigned a day relative to this date.

5.2. Participant Disposition

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants who received study intervention at Week I-0
- Participants randomized at Week M-0
- Participants who discontinued study intervention
  - Reasons for discontinuation of study intervention (including discontinuation due to COVID-19 related reasons)
- Participants who terminated study prematurely
  - Reasons for termination of study (including termination for COVID-19 related reasons)
- Participants who entered into the substudy

The above categories will include summaries through Week I-8 and from Week M-0 through Week M-44 (through the last visit not including the Final Safety Visit).

The number (%) of participants with a dose adjustment during the maintenance period from Week M-0 through Week M-44 will be summarized for the Safety Randomized Analysis Set (SASR).

A listing of participants will be provided through Week M-44 (through the last visit not including the Final Safety Visit) for the following categories:

- Participants who discontinued study intervention (including discontinuation due to COVID-19 related reasons)
- Participants who terminated study participation prematurely (including termination for COVID-19 related reasons)
- Participants who were unblinded during the maintenance study period
- Participants who entered into the substudy
- Participants who dose adjusted

5.3. Primary Endpoint Analysis

Note the assessment timepoint for the primary endpoint will be different for countries outside of the United States (global timepoint of Week I-8) and the United States (US-specific timepoint of Week M-44). The primary endpoint is:

- **Global**: Clinical remission at Week I-8
- **US-specific**: Clinical remission at Week M-44. This endpoint will be evaluated among participants who are in clinical response at Week I-8.

5.3.1. Definition of Endpoint(s)

Clinical remission: PCDAI score ≤10 points

PCDAI Score

The assessment of remission and response in children with Crohn's disease will be evaluated with the PCDAI (Appendix 13; Section 6.13; Hyams 1991, 2006). The PCDAI is a validated, patient-reported and clinician-administered composite index designed for use in children ages 3.5 to 19 years old with Crohn's disease. Longitudinal studies have demonstrated that the PCDAI is a reliable and valid assessment and is responsive to changes of disease activity. Based on clinical study, cut-offs for disease severity and a definition of clinically meaningful change have been established (Hyams 1991, 2006). The 11-item PCDAI covers 5 general disease activity domains: symptom history scores (3 items: abdominal pain, stool frequency; and general well-being); laboratory scores (3 items: hematocrit [HCT],%; erythrocyte sedimentation rate [ESR], mm/hr; albumin, g/dL); growth scores (2 items: weight and height), physical examination scores (2 items: abdomen and perirectal disease), and extraintestinal manifestations.

Body weight is measured to assess weight status (weight gain, stable weight or weight loss) and is used to calculate the composite score for the PCDAI, and will be measured to the nearest 0.1 kg, in duplicate.

Both height and height velocity are used to calculate the PCDAI composite score. Height will be measured and recorded in cm using a stadiometer graduated in centimeters or millimeters, with a

horizontal measuring block. Height velocity will be calculated. Based on the height velocity, the Height at Follow-up will be scored using Table 5 and Table 6 in the document "A Case-Based Monograph Focusing on Pediatric IBD)" (Bousvaros 2009).

$$Height\ velocity = \frac{Current\ Height - \ Previous\ Height\ (cm)}{Time\ (Year)}$$

The PCDAI score will be completed during the induction and maintenance periods of the study according to the timepoints specified in the Schedule of Activities. All items are summed to derive the total score. The total PCDAI score ranges from 0 to 100 with higher scores indicating greater disease activity. A PCDAI score ≤10 points is considered to be indicative of clinical remission, and clinical response is defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30. (Hyams, 1991, 2006; Best 1976).

The total PCDAI score should only be calculated when ≥3 of the 5 components are available in full (ie, all subcomponents are complete) from the visit where the PCDAI is to be measured. If fewer than 3 components are completely available, then the PCDAI cannot be calculated based on the information collected at the visit. Conditional on ≥3 of the 5 component scores being available in full from the visit where the PCDAI is to be measured, in general when the value of a subcomponent within each of the 5 components is missing, the closest previous subcomponent value (of the PCDAI or sPCDAI [Section 5.5.2.7]) will be used.

5.3.2. Estimands

5.3.2.1. Global Estimands

Primary Trial Objective: To evaluate the efficacy of ustekinumab dosing in inducing clinical remission in pediatric participants with moderately to severely active Crohn's disease.

Estimand Scientific Question of Interest: What is the proportion of participants considered to have benefited from ustekinumab at Week I-8, as measured by clinical remission at Week I-8, administered together with the protocol-allowed background standard-of-care medication?

5.3.2.2. Global Primary Estimand 1

a. **Study intervention:**
   - Ustekinumab (experimental treatment/intervention)

b. **Population:** Participants who are 2 to <18 years of age with moderately to severely active Crohn's disease.

c. **Variable**: Clinical remission at Week I-8. Participants that have intercurrent events (ICEs) 1-3, and 5 below are not considered to be in clinical remission at Week I-8.

d. **Summary measure (Population-level summary)**: Proportion of participants in clinical remission at Week I-8.

e. **ICEs and their corresponding strategies:**

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved clinical remission (PCDAI score ≤10 points) after this event; the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Composite Strategy:** Same as above
4. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data after the event occurred.
5. Discontinued study intervention due to reasons other than ICEs 2 or 4 as described above	**Composite Strategy:** Same as above

5.3.2.3. Global Supplementary Estimands

5.3.2.3.1. Global Supplementary Estimand 1 (Treatment policy estimand)

a. **Study intervention:** Same as Global Primary Estimand 1.

b. **Population:** Same as Global Primary Estimand 1.

c. **Variable**: Clinical remission at Week I-8.

d. **Summary measure (Population-level summary)**: Same as Global Primary Estimand 1.

e. **ICEs and their corresponding strategies:**

The ICEs are the same as the Global Primary Estimand 1 but differ in the strategies for handling said events.

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Treatment Policy Strategy:** The ICE does not affect the outcome, and the data collected at and after the event will be used for analysis, if available.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Treatment Policy Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Treatment Policy Strategy:** Same as above

ICEs	Strategy for Addressing ICEs and Its Description
4. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Treatment Policy Strategy:** Same as above
5. Discontinued study intervention due to reasons other than ICEs 2 or 4 as described above	**Treatment Policy Strategy:** Same as above

Difference from Global Primary Estimand 1: The strategy to address all ICEs is that the data collected at and after the event will be used for analysis, if available (ie, treatment policy strategy).

5.3.2.3.2. Global Supplementary Estimand 2

a. **Study intervention:** Same as Global Primary Estimand 1

b. **Population:** Same as Global Primary Estimand 1

c. **Variable**: Clinical remission at Week I-8. Participants that have ICEs 1-3 below are not considered to be in clinical remission at Week I-8.

d. **Summary measure (Population-level summary)**: Same as Global Primary Estimand 1

e. **ICEs and their corresponding strategies:**

The ICEs are the same as the Global Primary Estimand 1 but differ in the strategies for handling said events.

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved clinical remission (PCDAI score ≤10 points) after this event; the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Composite Strategy:** Same as above
4. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data after the event occurred.
5. Discontinued study intervention due to reasons other than ICEs 2 or 4 as described above	**Treatment Policy Strategy:** The ICE does not affect the outcome, and the data collected at and after the event will be used for analysis, if available.

Difference from Global Primary Estimand 1: ICE 5 is addressed using the treatment policy strategy.

5.3.2.4. US-Specific Estimands

Primary Trial Objective: To evaluate the efficacy of ustekinumab dosing in maintaining clinical remission in pediatric participants with moderately to severely active Crohn's disease.

Estimand Scientific Question of Interest: What is the proportion of participants considered to have benefited from ustekinumab at Week M-44, administered together with the protocol-allowed background standard-of-care medication, where benefit is measured by clinical remission at Week M-44?

5.3.2.5. US-Specific Primary Estimand 1

a. **Study intervention:**

- Ustekinumab (experimental treatment/intervention) SC q8w and SC q12w

b. **Population:** Participants who are 2 to <18 years of age with moderately to severely active Crohn's disease who are in clinical response at Week I-8.

c. **Variable**: Clinical remission at Week M-44. Participants that have ICEs 1-5, and 7 below are not considered to be in clinical remission at Week M-44.

d. **Summary measure (Population-level summary)**: Proportion of participants in clinical remission at Week M-44 for both study intervention regimens combined.

e. **ICEs and their corresponding strategies:**

ICEs	**Strategy for Addressing ICEs and Its Description**
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved clinical remission (PCDAI score ≤10 points) after this event, the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Composite Strategy:** Same as above
4. Rescue medication used (initiation or increase above baseline) for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders (for details, see Section 6.12)	**Composite Strategy:** Same as above
5. Eligible for dose adjustment (ie, met criteria for loss of response) after Week M-8 (including both study intervention regimens)	**Composite Strategy:** Same as above

ICEs	Strategy for Addressing ICEs and Its Description
6. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data after the event occurred.
7. Discontinued study intervention due to reasons other than ICEs 2 or 6 as described above	**Composite Strategy:** Same as above

5.3.2.6. US-Specific Supplementary Estimands

5.3.2.6.1. US-Specific Supplementary Estimand 1 (Treatment policy estimand)

a. **Study intervention:** Same as US-specific Primary Estimand 1.

b. **Population:** Same as US-specific Primary Estimand 1.

c. **Variable**: Clinical remission at Week M-44.

d. **Summary measure (Population-level summary)**: Same as US-specific Primary Estimand 1.

e. **ICEs and their corresponding strategies:**

The ICEs are the same as the US-specific Primary Estimand 1 but differ in the strategies for handling said events.

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Treatment Policy Strategy:** The ICE does not affect the outcome, and the data collected at and after the event will be used for analysis, if available.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Treatment Policy Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Treatment Policy Strategy:** Same as above
4. Rescue medication used (initiation or increase above baseline) for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders (for details, see Section 6.12)	**Treatment Policy Strategy:** Same as above
5. Eligible for dose adjustment (ie, met criteria for loss of response) after Week M-8 (including both study intervention regimens)	**Treatment Policy Strategy:** Same as above
6. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Treatment Policy Strategy:** Same as above
7. Discontinued study intervention due to reasons other than ICEs 2 or 6 as described above	**Treatment Policy Strategy:** Same as above

Difference from US-Specific Primary Estimand 1: The strategy to address all ICEs is that the data collected at and after the event will be used for analysis, if available (ie, treatment policy strategy).

5.3.2.6.2. US-Specific Supplementary Estimand 2

a. **Study intervention:** Same as US-specific Primary Estimand 1.

b. **Population:** Same as US-specific Primary Estimand 1.

c. **Variable**: Clinical remission at Week M-44. Participants that have ICEs 1-5 below are not considered to be in clinical remission at Week M-44.

d. **Summary measure (Population-level summary)**: Same as US-specific Primary Estimand.

e. **ICEs and their corresponding strategies:**

The ICEs are the same as the US-specific Primary Estimand 1 but differ in the strategies for handling said events.

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved clinical remission (PCDAI score ≤10 points) after this event, the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Composite Strategy:** Same as above
4. Rescue medication used (initiation or increase above baseline) for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders (for details, see Section 6.12)	**Composite Strategy:** Same as above
5. Eligible for dose adjustment (ie, met criteria for loss of response) after Week M-8 (including both study intervention regimens)	**Composite Strategy:** Same as above
6. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data after the event occurred.
7. Discontinued study intervention due to reasons other than ICEs 2 or 6 as described above	**Treatment Policy Strategy:** The ICE does not affect the outcome, and the data collected at and after the event will be used for analysis, if available.

Difference from US-Specific Primary Estimand 1: ICE 7 is addressed using the treatment policy strategy.

5.3.2.6.3. US-Specific Supplementary Estimand 3

a. **Study intervention:** Same as US-specific Primary Estimand 1.

b. **Population:** Same as US-specific Primary Estimand 1.

c. **Variable**: Same as US-specific Primary Estimand 1.

d. **Summary measure (Population-level summary)**: Same as US-specific Primary Estimand.

e. **ICEs and their corresponding strategies:**

The ICEs are the same as the US-specific Primary Estimand 1 with one exception: for ICE 3, the condition "within 90 days prior to endpoint assessment date" used to determine the use of immunomodulator agents is removed. The strategies for handling the ICEs are the same as the US-specific Primary Estimand 1.

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved clinical remission (PCDAI score ≤10 points) after this event, the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Composite Strategy:** Same as above
4. Rescue medication used (initiation or increase above baseline) for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders (for details, see Section 6.12)	**Composite Strategy:** Same as above
5. Eligible for dose adjustment (ie, met criteria for loss of response) after Week M-8 (including both study intervention regimens)	**Composite Strategy:** Same as above
6. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data after the event occurred.
7. Discontinued study intervention due to reasons other than ICEs 2 or 6 as described above	**Composite Strategy:** Same as above

Difference from US-Specific Primary Estimand 1: For ICE3, the condition "within 90 days prior to endpoint assessment date" used to determine the use of immunomodulator agents is removed.

5.3.2.6.4. US-Specific Supplementary Estimand 4

a. **Study intervention:** Same as US-specific Primary Estimand 1.

b. **Population:** Participants who are 2 to <18 years of age with moderately to severely active Crohn's disease who are in clinical response at Week I-8. The clinical response at Week I-8 is determined by IWRS.

c. **Variable**: Same as US-specific Primary Estimand 1.

d. **Summary measure (Population-level summary)**: Same as US-specific Primary Estimand.

e. **ICEs and their corresponding strategies:** Same as US-specific Primary Estimand.

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved clinical remission (PCDAI score ≤10 points) after this event, the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Composite Strategy:** Same as above
4. Rescue medication used (initiation or increase above baseline) for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders (for details, see Section 6.12)	**Composite Strategy:** Same as above
5. Eligible for dose adjustment (ie, met criteria for loss of response) after Week M-8 (including both study intervention regimens)	**Composite Strategy:** Same as above
6. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data after the event occurred.
7. Discontinued study intervention due to reasons other than ICEs 2 or 6 as described above	**Composite Strategy:** Same as above

Difference from US-Specific Primary Estimand 1: the clinical response at Week I-8 that is used to define Population will be determined by IWRS.

5.3.3. Analysis Methods for the Primary Estimands

5.3.3.1. Global Primary Estimand 1 Analysis

Data used in the global primary analysis include all values for estimating the clinical remission status at Week I-8 for all participants in the Full Analysis Set (FAS) (ie, all participants who received an administration of study intervention at Week I-0).

There is only 1 treatment at this point. For the Global primary analysis, the Global Primary Estimand 1, will be targeted.

The proportion of participants who are in clinical remission at Week I-8, and its respective 95% CI will be provided.

The 95% CI for the proportion of pediatric participants in clinical remission at Week I-8 will be descriptively compared with a 95% CI among adult participants with Crohn's disease who received ustekinumab induction therapy (~6 mg/kg) in the CNTO1275CRD3001 and CNTO1275CRD3002 studies.

After accounting for the ICEs, participants who have a missing PCDAI score will be considered not to have achieved clinical remission at Week I-8.

5.3.3.2. Global Supplementary Analyses

5.3.3.2.1. Global Supplementary Analysis 1 (Treatment policy estimand)

The global primary endpoint will be analyzed using Global Supplementary Estimand 1 (Treatment policy estimand). A similar analysis, including the handling of missing PCDAI scores, will be conducted as described for the Global Primary Estimand 1 (Section 5.3.3.1).

5.3.3.2.2. Global Supplementary Analysis 2

The global primary endpoint will be analyzed using Global Supplementary Estimand 2. The same analysis will be conducted as described for the Global Primary Estimand 1 (Section 5.3.3.1), including the handling of missing PCDAI scores.

5.3.3.3. Global Sensitivity Analysis

To examine the robustness of the primary endpoint analysis, the following sensitivity analyses will be performed. The sensitivity analyses will be evaluated using the Global Primary Estimand 1 (Section 5.3.2.2).

5.3.3.3.1. Global Sensitivity Analysis 1

Global Sensitivity Analysis 1 (Observed case): excludes participants who have a missing PCDAI score at Week I-8 after accounting for ICEs prior to Week I-8.

5.3.3.3.2. Global Sensitivity Analysis 2

Global Sensitivity Analysis 2: After accounting for the ICEs, missing PCDAI scores will be imputed using multiple imputation methods. The imputation model will include PCDAI subscores at Week I-0 as covariates. One hundred imputed datasets will be created using the Markov chain Monte Carlo method, assuming missing at random (MAR) and a multivariate normal distribution. For each multiple-imputed data set, each participant's clinical remission status at Week I-8 will be calculated. The results from the 100 data sets will be aggregated over the 100 imputations according to Rubin (1987, 1996), and the proportion of participants in clinical remission at Week I-8 and its 95% CI will be provided.

5.3.3.4. US-Specific Primary Estimand 1 Analysis

Data used in the primary analysis include all values for estimating the clinical remission status at Week M-44 for all participants in the Full Clinical Responder Analysis Set (FASCR) (ie, all participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and received at least 1 administration of study intervention during maintenance). After accounting for the ICEs, participants who have missing PCDAI score will be considered not to have achieved clinical remission at Week M-44.

The proportion of participants who are in clinical remission at Week M-44 and its 95% CI will be provided overall. This will also be summarized for the individual maintenance intervention groups with 95% Cis. In addition, the difference in the proportion of participants who are in clinical remission at Week M-44 between the maintenance intervention groups will be estimated using the Cochran-Mantel-Haenszel (CMH) method adjusting for weight at baseline (<40 kg, ≥40 kg). The corresponding 95% CI for the difference will be provided based on the Wald statistics (CMH weights).

The 95% CI for the proportion of pediatric participants in the combined maintenance interventions who are in clinical remission at Week M-44 will be descriptively compared with a 95% CI among adult participants with Crohn's disease in clinical remission (defined using the CDAI) who received ustekinumab maintenance therapy (90 mg q8w) in the CNTO1275CRD3003 study.

In addition, the 95% CI for the proportion of pediatric participants in the combined maintenance interventions who are in clinical remission at Week M-44 will be descriptively compared with a 95% CI for a historical adult placebo control for clinical remission (defined using the CDAI) at Week M-44, which will be based on a meta-analysis of placebo clinical remission rates using historical randomized adult Crohn's disease studies with sufficiently similar characteristics (ie, similar design and study populations).

Appendix 15 illustrates the criteria used to pick these studies from the Certara Clinical Outcomes database. Confidence intervals based on other confidence levels (eg, 70% or 80%) may also be explored. As appropriate, other studies may be included in the meta-analysis.

5.3.3.5. US-Specific Supplementary Analysis

5.3.3.5.1. US-Specific Supplementary Analysis 1 (Treatment policy estimand)

The US-specific primary endpoint will be analyzed using US-specific Supplementary Estimand 1 (Treatment policy estimand). Similar analyses, including the missing PCDAI data handling rules, will be conducted as described for the US-specific Primary Estimand (Section 5.3.3.4).

5.3.3.5.2. US-Specific Supplementary Analysis 2

The US-specific primary endpoint will be analyzed using US-specific Supplementary Estimand 2. Similar analyses, including the handling of missing PCDAI scores, will be conducted as described for the US-specific Primary Estimand 1 (Section 5.3.3.4).

5.3.3.6. US-Specific Sensitivity Analysis

To examine the robustness of the primary endpoint analysis, the following sensitivity analyses will be performed. The sensitivity analyses will be evaluated using the US-specific Primary Estimand 1 (Section 5.3.2.5).

5.3.3.6.1. US-Specific Sensitivity Analysis 1

US-specific Sensitivity Analysis 1 (Observed case): excludes participants who have a missing PCDAI score at Week M-44 after accounting for ICEs prior to Week M-44.

5.3.3.6.2. US-Specific Sensitivity Analysis 2

US-specific Sensitivity Analysis 2: After accounting for ICEs, missing PCDAI scores will be imputed using multiple imputation methods. The imputation model will include PCDAI subscores at Week I-0, Week M-0, and Week M-44, and maintenance treatment intervention as covariates. A hundred imputed datasets will be created using the Markov chain Monte Carlo method, assuming MAR and a multivariate normal distribution. For each multiple-imputed data set, each participant's clinical remission status at Week M-44 will be calculated. The results from the 100 data sets will be aggregated over the 100 imputations according to Rubin (1987, 1996) and the proportion of participants in clinical remission at Week M-44 and its 95% CI will be provided.

5.3.3.6.3. US-Specific Sensitivity Analysis 3

US-specific Sensitivity Analysis 3: To comprehensively evaluate the robustness of departures from the missing data assumption (MAR) used in the US-specific Primary Estimand 1 analysis, a tipping point analysis via exhaustive scenarios will be performed. For subjects with missing remission status at Week M-44, remission status will be imputed in an increasing manner by participant. Specifically, for each participant, a remission/non-remission status will be imputed starting with the scenario where all participants being in non-remission up to the scenario where all participants are in remission. This would include all possible scenarios of remission status for all missing data. The 95% Cis for the proportion of pediatric participants (combined ustekinumab) who are in clinical remission at Week M-44 using the Wilson Score method will be provided for all possible scenarios. The lower bound of the 95% Cis will be descriptively compared with the upper bound

of the 95% CI for the historical adult placebo control for clinical remission at Week M-44 mentioned in Section 5.3.3.4.

5.3.3.7. US-Specific Supportive Analysis

5.3.3.7.1. US-Specific Supportive Analysis 1

The historical proportion of adults on placebo in clinical remission at Week M-44 will be estimated using participant-level data of the adult studies. The data from participants who were in clinical response in ustekinumab induction therapy and randomized to placebo will be used in the analysis. A logistic regression model will be fitted with the clinical remission status at Week M-44 as the dependent variable and the following variables as covariates: biologic failure status (biologic-failure, non-biologic-failure), CRP (≤3 mg/L, >3 mg/L), and oral corticosteroids (receiving, not receiving). Using covariate data from the pediatric participants (combined ustekinumab), the predicted clinical remission status at Week M-44 for a "pediatric covariate-adjusted placebo intervention group" will be calculated based on covariate parameters from the logistic regression model. The estimate and the corresponding 95% CI for the proportion of participants in clinical remission in the pediatric covariate-adjusted placebo intervention group will be constructed. This will be descriptively compared with the 95% CI of the proportion of pediatric participants in the combined maintenance interventions who are in clinical remission at Week M-44 in the FASCR.

5.3.3.7.2. US-Specific Supportive Analysis 2

A Bayesian approach will be used to compare the proportion of pediatric participants on ustekinumab in clinical remission at Week M-44 in the combined maintenance interventions and a historical proportion of adults on placebo in clinical remission at Week M-44. A Bayesian logistic model will be used to obtain the covariate adjusted remission rate to account for potential difference in the participants of the current CNTO1275CRD3004 pediatric study (combined ustekinumab) and in the participants of the adult studies (ie, only participants who were in clinical response in ustekinumab induction therapy and randomized to placebo). The following covariates will be used if they are significantly associated with the outcome measure in the adult studies: biologic failure status (biologic-failure, non-biologic-failure), CRP (≤3 mg/L, >3 mg/L), and oral corticosteroids (receiving, not receiving). The adult placebo proportion in clinical remission will be modeled using the weighted average of the covariate-adjusted remission rate based on the studies with the subject-level data and the studies with the study-level data. The posterior distribution of the difference in outcome measures between the treatment groups and its corresponding 95% credible interval (CrI) will be constructed to make inference. If the lower bound of the CrI is greater than 0, then it is assumed that the proportion of pediatric participants on ustekinumab in clinical remission at Week M-44 is higher than that of adult participants on placebo intervention. Details are in Appendix 16.

5.3.4. Subgroups

The consistency of treatment effect for the Global and US-specific primary endpoints will be evaluated for the subgroups defined in Section 5.8.8, using the Global and US-specific Primary Estimands and associated analyses, respectively.

5.4. Secondary Efficacy Endpoints Analysis

Global secondary endpoints are provided in Section 5.4.1.

US-specific secondary endpoints are provided in Section 5.4.2.

The endpoints for Global and US-specific are the same with one exception. The only difference is:

- Clinical remission at Week I-8 is a secondary endpoint for US-specific endpoints.
- Clinical remission at Week M-44 is a secondary endpoint for global endpoints.

as they were primary endpoints for global and US-specific endpoints, respectively.

5.4.1. Global Secondary Endpoints

The following secondary endpoints will be evaluated during the induction period:

1. Clinical remission at Week I-6 as assessed by sPCDAI.
2. Clinical response at Week I-8.
3. Clinical response at Week I-6 as assessed by sPCDAI.
4. Endoscopic response at Week M-8* as assessed by SES-CD.
5. Clinical response at Week M-8*.

*These endpoints are evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction.

The following secondary endpoints will be evaluated at Week M-44. These endpoints will be evaluated for participants who are clinical responders at Week I-8.

1. Clinical remission
2. Endoscopic response as assessed by SES-CD
3. Clinical response
4. Corticosteroid-free clinical remission
5. Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8

5.4.2. US-Specific Secondary Endpoints

The following secondary endpoints will be evaluated during the induction period:

1. Clinical remission at Week I-8
2. Clinical remission at Week I-6 as assessed by sPCDAI
3. Clinical response at Week I-8
4. Clinical response at Week I-6 as assessed by sPCDAI
5. Endoscopic response at Week M-8* as assessed by SES-CD
6. Clinical response at Week M-8*

*These endpoints are evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction.

The following secondary endpoints will be evaluated at Week M-44. These endpoints will be evaluated for participants who are clinical responders at Week I-8.

1. Endoscopic response as assessed by SES-CD
2. Clinical response
3. Corticosteroid-free clinical remission
4. Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8.

5.4.3. Definition of Endpoints

5.4.3.1. PCDAI Score

Refer to Section 5.3.1 for the definition of PCDAI score.

Clinical remission: PCDAI score ≤10 points.

Clinical response: A reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30.

Corticosteroid-free clinical remission: PCDAI score ≤10 points and not receiving corticosteroids for at least 90 days prior to Week M-44.

5.4.3.2. Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) Score

SES-CD score: To explore the potential utility of endoscopic improvement endpoints in children, 3 ileocolonoscopies will be performed, one at screening, another at Week M-8, and one at Week M-44 within approximately 3 weeks prior to these timepoints. All ileocolonoscopies will be videotaped and read by a central reader who will also provide the SES-CD assessment (process defined in a separate Imaging Charter). Endoscopic response will be assessed using the SES-CD (Adler 2019).

The SES-CD is a scoring system developed to provide a more granular evaluation of endoscopic disease severity in patients with Crohn's disease (Kerur 2020). It is constructed based on the evaluation of 4 endoscopic components across 5 predefined ileocolonic segments. The 4 endoscopic components within each segment are: (1) the presence/size of ulcers, (2) the proportion of mucosal surface covered by ulcers, (3) the proportion of mucosal surface affected by any other lesions, and (4) 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 4. The total SES-CD score ranges from 0 to 56.

Table 4: 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:

To calculate the SES-CD score at a visit, the sum of the segments that were present at the visit will be used. For segments that were present at baseline but missing post-baseline, the baseline score for the missing segment(s) will be carried forward. In the event that a segment is missing at baseline but non-missing at post-baseline, the non-missing post-baseline score is not used in the calculation of SES-CD.

Endoscopic response: A reduction in the SES-CD score of ≥50% or SES-CD score ≤2 in participants with a baseline SES-CD score of ≥3.

5.4.4. Secondary Estimands

5.4.4.1. Global Secondary Estimands

5.4.4.1.1. Global Secondary Estimands During Induction

The following describes the attributes for the Global Secondary Estimands 1-5 during induction:

a. Study intervention: Same as Global Primary Estimand 1

b. Population: Same as Global Primary Estimand 1.

c. Variables and Summary measure (Population-level summary):

Table 5: Variables and Summary Measure (Population-level Summary) for Each Global Secondary Estimand During Induction

Global Secondary Estimand	Variable	Summary measure (Population-level summary)
1	Clinical remission at Week I-6. Participants that have ICEs 1-3, and 5 below are not considered to be in clinical remission at Week I-6.	Proportion of participants in clinical remission at Week I-6 as assessed by sPCDAI
2	Clinical response at Week I-8. Participants that have ICEs 1-3, and 5 below are not considered to be in clinical response at Week I-8.	Proportion of participants in in clinical response at Week I-8
3	Clinical response at Week I-6. Participants that have ICEs 1-3, and 5 below are not considered to be in clinical response at Week I-6.	Proportion of participants in clinical response at Week I-6 as assessed by sPCDAI
4	Endoscopic response at Week M-8. Participants that have ICEs 1-3, and 5 below at Week I-8 are not considered to be in endoscopic response at Week M-8.*	Proportion of participants with endoscopic response at Week M-8 as assessed by SES-CD
5	Clinical response at Week M-8. Participants that have ICEs 1-3, and 5 below at Week I-8 are not considered to be in clinical response at Week M-8.*	Proportion of participants with clinical response at Week M-8

* These endpoints are evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction.

d. ICEs and Corresponding Strategies:

The ICEs and corresponding strategies for all global secondary estimands during induction are the same as those used for the Global Primary Estimand 1 (at Week I-8), and are as follows:

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved remission nor response after this event; the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Composite Strategy:** Same as above
4. Discontinued study intervention due to COVID-19 related reasons	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data after the event occurred.
5. Discontinued study intervention due to reasons other than ICEs 2 or 4 as described above	**Composite Strategy:** Same as above

5.4.4.1.2. Global Secondary Estimands During Maintenance

The following describes the attributes of the Global Secondary Estimands 6-10 at Week M-44:

a. Study intervention: Same as US-specific Primary Estimand 1.

b. Population: Same as US-specific Primary Estimand 1.

c. Variables and Summary Measure (Population-level Summary):

Table 6: Variables and Summary Measure (Population-level Summary) for Each Global Secondary Estimand During Maintenance

Global Secondary Estimand	Variable	Summary measure (Population-level summary)
6	Clinical remission at Week M-44. Participants that have ICEs 1-5, and 7 below are not considered to be in clinical remission at Week M-44	Proportion of participants in clinical remission at Week M-44
7	Endoscopic response at Week M-44. Participants that have ICEs 1-5, and 7 below are not considered to be in endoscopic response at Week M-44	Proportion of participants in endoscopic response at Week M-44 as assessed by SES-CD
8	Clinical response at Week M-44. Participants that have ICEs 1-5, and 7 below are not considered to be in clinical response at Week M-44	Proportion of participants in clinical response at Week M-44
9	Corticosteroid-free clinical remission at Week M-44. Participants that have ICEs 1-5, and 7 below are not considered to be in corticosteroid-free clinical remission at Week M-44	Proportion of participants with corticosteroid-free clinical remission at Week M-44

Table 6: Variables and Summary Measure (Population-level Summary) for Each Global Secondary Estimand During Maintenance

Global Secondary Estimand	Variable	Summary measure (Population-level summary)
10	Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8. Participants that have ICEs 1-5, and 7 below are not considered to be in clinical remission at Week M-44	Proportion of participants with clinical remission at Week M 44 among participants who are in clinical remission at Week I-8

d. ICEs and their corresponding strategies:

The ICEs and corresponding strategies for all global secondary estimands at Week M-44 are the same as those used for the US-specific Primary Estimand 1 (at Week M-44), and are as follows:

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved these global secondary endpoints after this event; the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.11)	**Composite Strategy:** Same as above
4. Rescue medication used (initiation or increase above baseline) for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders (for details, see Section 6.12)	**Composite Strategy:** Same as above
5. Eligible for dose adjustment (ie, met criteria for loss of response) after Week M-8 (including both study intervention regimens)	**Composite Strategy:** Same as above
6. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data after the event occurred.
7. Discontinued study intervention due to reasons other than ICEs 2 or 6 as described above	**Composite Strategy:** Same as above

5.4.4.2. US-Specific Secondary Estimands

5.4.4.2.1. US-Specific Secondary Estimands During Induction

The following describes the attributes for the US-specific secondary estimands during induction:

a. Study intervention: Same as Global Primary Estimand 1.

b. Population: Same as Global Primary Estimand 1.

c. Variables and Summary measure (Population-level Summary):

Table 7: Variables and Summary Measure (Population-level Summary) for Each US-Specific Secondary Estimand During Induction

US-Specific Secondary Estimand	Variable (Endpoint)	Population-level summary
1	Clinical remission at Week I-8. Participants that have ICEs 1-3, and 5 below are not considered to be in clinical remission at Week I-8.	Proportion of participants in clinical remission at Week I-8
2	Clinical remission at Week I-6. Participants that have ICEs 1-3, and 5 below are not considered to be in clinical remission at Week I-6.	Proportion of participants in clinical remission at Week I-6 as assessed by sPCDAI
3	Clinical response at Week I-8. Participants that have ICEs 1-3, and 5 below are not considered to be in clinical response at Week I-8.	Proportion of participants in clinical response at Week I-8.
4	Clinical response at Week I-6. Participants that have ICEs 1-3, and 5 below are not considered to be in clinical response at Week I-6.	Proportion of participants in clinical response at Week I-6 as assessed by sPCDAI
5	Endoscopic response at Week M-8. Participants that have ICEs 1-3, and 5 below at Week I-8 are not considered to be in endoscopic response at Week M-8. *	Proportion of participants with endoscopic response at Week M-8 as assessed by SES-CD
6	Clinical response at Week M-8. Participants that have ICEs 1-3, and 5 below at Week I-8 are not considered to be in clinical response at Week M-8.*	Proportion of participants with clinical response at Week M-8

*These endpoints are evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction.

d. ICEs and Corresponding Strategies:

The ICEs and corresponding strategies for all US-specific secondary estimands during induction are the same as those used for the Global Primary Estimand 1 (at Week I-8) (Section 5.3.2.2).

5.4.4.2.2. US-Specific Secondary Estimands During Maintenance

The following describes the attributes for the US-specific secondary estimands at Week M-44:

a. Study intervention: Same as US-specific Primary Estimand 1.

b. Population: Same as US-specific Primary Estimand 1.

c. Variables and Population-level Summary:

Table 8: Variables and Summary Measure (Population-level Summary) for Each US-Specific Secondary Estimand During Maintenance

US-Specific Secondary Estimand	Variable (Endpoint)	Population-level summary
7	Endoscopic response at Week M-44. Participants that have ICEs 1-5, and 7 below are not considered to be in endoscopic response at Week M-44.	Proportion of participants in endoscopic response at Week M-44 as assessed by SES-CD
8	Clinical response at Week M-44. Participants that have ICEs 1-5, and 7 below are not considered to be in clinical response at Week M-44.	Proportion of participants in clinical response at Week M-44
9	Corticosteroid-free clinical remission at Week M-44. Participants that have ICEs 1-5, and 7 below are not considered to be in corticosteroid-free clinical remission at Week M-44.	Proportion of participants in corticosteroid-free clinical remission at Week M-44
10	Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8. Participants that have ICEs 1-5, and 7 below are not considered to be in clinical remission at Week M-44.	Proportion of participants in clinical remission at Week M-44 among participants who are in clinical remission at Week I-8

d. ICEs and Corresponding Strategies:

The ICEs and corresponding strategies for all US-specific secondary estimands at Week M-44 are the same as those used for the US-specific Primary Estimand 1 (at Week M-44) (Section 5.3.2.5).

5.4.5. Analysis Methods for the Estimands for the Secondary Endpoints

5.4.5.1. Main Estimators (Analyses) for the Estimands

5.4.5.1.1. During Induction

The analysis population for secondary endpoints during induction includes all participants who received one administration of study administration at Week I-0 (FAS). For endpoints at Week M-8 specified above where the objective is to evaluate endpoint due to induction, the Full Randomized Analysis Set (FASR) will be used. For the secondary endpoints during induction, the proportion of participants who meet the endpoint will be summarized, and a 95% CI will be provided.

After accounting for ICEs, participants who have missing data for the endpoints during induction will be considered not to have achieved their respective endpoints.

5.4.5.1.1.1. Additional Induction Secondary Endpoint Analyses

For the secondary endpoints during induction, the 95% CI for the proportion of pediatric participants who are in remission or response during induction will be descriptively compared with a 95% CI among adult participants with Crohn's disease who received ustekinumab induction therapy (~6 mg/kg) in the CNTO1275CRD3001 and CNTO1275CRD3002 studies, separately.

5.4.5.1.2. Maintenance Period Secondary Endpoints

The analysis population for the Week M-44 endpoints includes all participants who were randomized in the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and received at least one administration of study intervention during maintenance (FASCR). For the secondary endpoints at Week M-44, the proportion of participants who meet the endpoint at Week M-44 will be summarized overall, and 95% CIs will be provided. This will also be summarized for the individual maintenance intervention groups with 95% CIs. In addition, an estimate of the difference between maintenance treatment arms will be provided along with the 95% CI for the difference.

After accounting for ICEs, participants who have missing data for the endpoint at Week M-44 will be considered not to have achieved their respective endpoint.

5.4.5.1.2.1. Additional US-Specific Secondary Endpoint Analyses

The secondary endpoints (defined based on the PCDAI) at Week M-44 will be descriptively compared with the proportion (and 95% CI) of adult participants who met the endpoint (defined based on the CDAI) at Week M-44 in the CNTO1275CRD3003 study among participants who were clinical responders at Week I-8 (90 mg q8w treatment group). In addition, for the US-specific secondary endpoints, a 95% CI for the adult placebo rate from studies reporting these endpoints will be provided to assess the effect of ustekinumab compared with a historical placebo.

5.5. Tertiary/Exploratory Efficacy Endpoints Analysis

The following denote endpoints to address the other objectives from the protocol.

5.5.1. Tertiary/Exploratory Endpoints

5.5.1.1. Other Objective 1: To Evaluate the Effects of Ustekinumab on Histological Assessments

Histologic assessment (based on GHAS, Geboes score, and RHI) analyses are considered exploratory and will be summarized in separate technical reports.

5.5.1.2. Other Objective 2: To Evaluate the Effects of Ustekinumab on Serum and Fecal Biomarkers

The other endpoints to address the objective above are the following:

1. Baseline, postbaseline values and the change from baseline in CRP concentrations at Weeks I-3, I-6, I-8, M-8, M-24, and M-44.
2. Baseline, postbaseline values and the change from baseline in fecal calprotectin and lactoferrin concentrations at Weeks I-3, I-6, I-8, M-8, M-24, and M-44.
3. Normalization of CRP concentration (≤3 mg/L) through Week I-8 and during the maintenance period through Week M-44 among participants with abnormal CRP concentration (>3 mg/L) at Week I-0.
4. Normalization of fecal calprotectin (≤250 mg/kg) and lactoferrin (≤7.24 µg/g) concentration through Week I-8 and during the maintenance period through Week M-44 among participants with abnormal fecal calprotectin (>250 mg/kg) and lactoferrin (>7.24 µg/g) at Week I-0.

5.5.1.3. Other Objective 3: To Evaluate the Effects of Ustekinumab on Growth

The other endpoints to address the objective above are the following:

Baseline, postbaseline values, and the change from baseline in parameters of growth (age and sex-specific z-scores for height, weight, and BMI) at Weeks I-8 and M-44.

5.5.1.4. Other Objective 4: To Evaluate the Effects of Ustekinumab on Nutritional Parameters

The other endpoints to address the objective above are the following:

Baseline, postbaseline values, and the change from baseline in 25 hydroxyvitamin D, MMA and iron at Weeks M-4 and M-44.

Shift tables will be provided summarizing the shift in nutritional parameters from baseline through Week M-44 over time with respect to abnormality criteria (low, normal, high).

5.5.1.5. Other Objective 5: To Evaluate the Effect of Ustekinumab on Crohn's Disease-related Quality of Life (QoL)

The other endpoints to address the objective above are the following:

Change from baseline in IMPACT-III scores at Week M-44 for participants ≥10 years of age at Week I-0. These will be performed for the regular scores, for the 4-factor model scores, and the transformed scores (range of 0-100). The Well-being and Emotional domains will also be summarized separately.

5.5.1.6. Other Endpoints

The other endpoints include:

1. PCDAI, sPCDAI, and CDAI score related endpoints over time through Week M-44.
    a. Clinical remission
    b. Clinical remission based on PCDAI <10
    c. Clinical response
    d. Clinical-biomarker response
    e. Corticosteroid-free clinical remission. Note that corticosteroid-free clinical remission at a visit is defined as PCDAI score ≤10 points and not receiving corticosteroids for at least 30 days prior to that visit for all visits except for Week M-44. For Week M-44, the same definition as specified in Section 5.4.3.1 is used. The same definition for "corticosteroid-free" will be used to determine sPCDAI and CDAI score related corticosteroid-free clinical remission.
    f. Clinical remission among participants who are in clinical remission at Week I-8
    g. Change from baseline (Week I-0) in the PCDAI, sPCDAI, and CDAI scores
    h. Components of the PCDAI, sPCDAI, and CDAI scores
2. Clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44 among participants who received corticosteroids at Week I-0.
3. SES-CD and SEMA-CD score related endpoints at Week M-8 * and Week M-44:
    a. Endoscopic response
    b. Endoscopic remission
    c. Clinically meaningful endoscopic improvement
    d. Change from baseline (Week I-0) in SES-CD and SEMA-CD score
    e. Shift tables based on categorical SEMA-CD scores
4. Endoscopic improvement at Week M-8 * and Week M-44
5. Fistula assessments at Weeks I-0, I-8, M-8, M-16, M-32, and M-44, among participants with fistulas at baseline.
    a. Fistula response
    b. Complete fistula response
6. Crohn's disease-related hospitalizations and surgeries
7. Mucosal Inflammation Noninvasive Index (MINI)
    a. Change from baseline in the MINI index over time through Week M-44
    b. MINI index categories over time through Week M-44: MINI<8, MINI<7, or MINI<6

* These endpoints at Week M-8 will be evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction

5.5.2. Endpoint Definitions

5.5.2.1. Histology

Histologic assessments will be performed using biopsy samples collected during video ileocolonoscopy (see endoscopy manual for biopsy details). Histologic assessments will be conducted by a central reader who is blinded to treatment groups and visit. The GHAS (D'Haens 1998), Geboes score (Geboes 2000), and RHI (Mosli 2017) will be used to evaluate histologic improvements and healing.

5.5.2.2. C-Reactive Protein

C-reactive protein has been demonstrated to be useful as a marker of inflammation in patients with IBD. (Daniluk 2019; Gibson 2018; Keefer 2006; Solem 2005; Vermeire 2004) In Crohn's disease, elevated CRP concentrations have been associated with severe clinical activity, elevated sedimentation rate, and active disease as detected by colonoscopy. CRP will be assayed using a validated, high sensitivity CRP assay.

5.5.2.3. Fecal Calprotectin and Fecal Lactoferrin

Fecal calprotectin and fecal lactoferrin have been demonstrated to be sensitive and specific markers of intestinal inflammation and response to treatment in patients with IBD. (Langhorst 2012) Stool samples for fecal calprotectin and lactoferrin concentrations will be collected from all participants. Assays for fecal calprotectin and lactoferrin concentrations will be performed using a validated method. Additional tests may also be performed on the stool samples for additional markers related to intestinal inflammation and treatment response.

5.5.2.4. Height, Weight, and BMI z-Scores

Age and sex-specific z-scores for height, weight, and BMI will be used to assess growth. The z-score is a measure of how many standard deviations a value is from the mean of the data (WHO, 1995). For population-based assessment, including surveys and nutritional surveillance, the z-score is widely recognized as the best system for analysis and presentation of anthropometric data because of its advantages compared to the other methods (Wendler 2019). At the individual level, there is recognition that z-score is the most appropriate descriptor of malnutrition. The z-score system expresses the anthropometric value as a number of standard deviations or z-scores below or above the reference mean or median value. For population-based uses, a major advantage is that a group of z-scores can be subjected to summary statistics such as the mean and standard deviation.

The z-score scale is linear and therefore a fixed interval of z-scores has a fixed height difference in cm, weight difference in kg, or BMI difference in kg/m^2, for all children of the same age. Z-scores have the same statistical relation to the distribution of the reference around the mean at all ages, which makes results comparable across age groups and indicators. Z-scores are also

sex-independent, thus permitting the evaluation of children's growth status by combining sex and age groups. These characteristics of z-scores allow further computation of summary statistics such as means, standard deviations, and standard error to classify a population's growth status.

5.5.2.5. IMPACT-III

Disease-related health QoL measures will be assessed in participants who are ≥10 years of age at Week I-0 using the validated IMPACT-III questionnaire. The questionnaire is self-administered and comprises 35 questions and is validated and applicable for children and adolescents ≥10 years of age with IBD. The IMPACT-III will be administered to participants either at home prior to the study visits or at the study site at Weeks I-0 and M-44. The recall period is 2 weeks and the questionnaire takes approximately 10 minutes. The questionnaire's 35 questions cover the following 6 domains: Bowel symptoms (7 items); Systemic symptoms (3 items); Emotional functioning (7 items); Social functioning (12 items); Body image (3 items); Tests and treatments (3 items), with a 5-point Likert response options from 1 to 5 for each question. The total score, which is the sum of responses from all 35 questions, ranges from 35 to 175 (Otley 2002, 2006) with a higher score indicating better quality of life. The instrument has been shown to be valid, reliable, and able to detect change in disease-related QoL in pediatric and adolescent studies in IBD (Hyams 2007a, 2007b; Ogden 2008; Otley 2002, 2006).

Consistent with the developers scoring methodology (Otley 2002, 2006), in addition to deriving an IMPACT-III total score (range from 35 to 175), the sponsor will generate transformed scores, which are derived as follows: the original five Likert response options per question will be linearly transformed to a range of 0-100 (5:100; 4:75; 3:50; 2:25; and 1:0); to obtain a total score, responses from all 35 questions are summed, and divided by the number of questions answered; domain scores can be obtained by summing the responses for each question within a domain, and dividing by the total number of questions answered within the domain. In a recent study (Grant, MacIntyre, Kappelman, Otley, 2020), the developer sought to confirm the structural validity of the IMPACT-III, which included a series of exploratory and confirmatory factor analyses. The developer confirmed that that a 4-factor model of the IMPACT-III (i.e., general well-being [12 items], social [11-items] and emotional functioning [7 items], and perceptions of body-image [4 items]) presented improved model fit, as compared to the original 6-factor and exploratory 5-factor model. The developer further noted that the 4-factor model was conceptually more parsimonious.

It is important to note that the new/alternative domain structure is based on the current IMPACT version and does not represent any changes to the content or wording of the questionnaire items. Furthermore, the developer recommends the scoring algorithm for the total score should remain consistent or unchanged. Finally, the developer encouraged other clinical researchers to assess the updated 4-factor structure of the IMPACT-III. Consistent with these recommendations, the Sponsor will seek to confirm the suitability of the traditional 6-factor scoring methodology as well as the updated 4-factor model. The proposed additional domain groupings and aggregation for assessment include the following:

Well-being domain comprised of IMPACT-III questions 1, 3, 4, 6, 9, 10, 17, 21, 28, 32, 34, and 35. Social domain comprised of questions 11, 16, 18, 19, 20, 23, 24, 25, 26, 27, and 30. Emotional domain comprised of questions 2, 5, 8, 12, 13, 14, and 22. Body image domain comprised of questions 7, 15, 29, and 33.

The total score and the transformed scores mentioned above will be used in scoring.

5.5.2.6. PCDAI Score

Refer to Section 5.3.1 for the definition of PCDAI score.

Clinical-biomarker response: A reduction from baseline in the PCDAI score of ≥12.5 points, total PCDAI score not more than 30 points, and ≥50% reduction from baseline in CRP, fecal calprotectin, or fecal lactoferrin.

5.5.2.7. sPCDAI Score

The sPCDAI, a shorter version of the PCDAI, will also be used to evaluate remission and response in some situations. The sPCDAI is composed of the following 6 PCDAI items: abdominal pain, general well-being, weight, stool frequency, abdominal exam, and extraintestinal manifestations (Kappelman 2011; Turner 2012).

- Abdominal pain (0, 10, 20)
- Stool frequency* (0, 5, 10)
- Patient general well-being (0, 10, 20)
- Extra-intestinal manifestations (0, 5, 10)
- Abdominal mass and tenderness (0, 5, 10)
- Body weight (0, 10, 20)

Each of the components is scored as 0, 5, 10, or 20 depending on the component, with higher scores for more severe disease activity, and the sPCDAI summary score ranges from 0 to 90.

The sPCDAI score will be completed during the induction and maintenance periods of the study according to the timepoints specified in the SoA (Protocol, Section 1.3). The sPCDAI may be used if laboratory test values are not available including for those participants who lose response. During home visits an abdominal examination will not be conducted and will be computed without the abdominal exam item. The 6-item sPCDAI score ranges from 0 (no disease activity) to 90 (severe disease activity), with higher scores indicating more active disease.

The sPCDAI score should only be calculated when ≥3 of the 6 components are available in full (ie, all subcomponents are complete) from the visit where the PCDAI will be measured. If fewer than 3 components are completely available, then the PCDAI cannot be calculated based on the information collected at the visit. Conditional on ≥3 of the 6 component scores being available in full from the visit where the sPCDAI is to be measured, in general when the value of a

subcomponent within each of the 6 components is missing, the closest previous subcomponent value will be used.

sPCDAI clinical remission: sPCDAI score ≤10 points

sPCDAI clinical response: A reduction from baseline in the sPCDAI score of ≥10.

sPCDAI corticosteroid-free clinical remission: sPCDAI score ≤10 points and not receiving corticosteroids for at least 90 days prior to Week M-44.

sPCDAI clinical-biomarker response: A reduction from baseline in the sPCDAI score of ≥10 points, a total sPCDAI < 30 and ≥50% reduction from baseline in CRP, fecal calprotectin, or fecal lactoferrin.

5.5.2.8. CDAI Score

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 (Sandborn 2008, 2012). 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 patient-reported aspects of the CDAI will be evaluated by the parents for participants who cannot self-report.

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.

The use of the CDAI will be assessed for all participants at timepoints specified in the SoA and will more directly facilitate the extrapolation of results from the current study of ustekinumab in pediatric Crohn's disease to results obtained in the Phase 3 program with ustekinumab in adult Crohn's disease (CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003).

Clinical remission: a CDAI score of <150 points.

Clinical response: a reduction from baseline in the CDAI score of ≥100 points or CDAI <150 points.

CDAI corticosteroid-free clinical remission: A CDAI score <150 and not receiving corticosteroids for at least 90 days prior to Week M-44.

CDAI clinical-biomarker response: A reduction from baseline in the CDAI score of ≥100 points or CDAI score <150 points and ≥50% reduction from baseline in CRP, fecal calprotectin or fecal lactoferrin.

5.5.2.9. Endoscopic Assessment, SES-CD, and SEMA-CD Scores

Refer to Section 5.4.3.2. for the definition of the **SES-CD score**.

The below definitions are only based on the SES-CD score:

Endoscopic remission: A SES-CD score ≤2 in participants with a baseline SES-CD score of ≥3.

Clinically meaningful endoscopic improvement: A reduction in SES-CD of ≥3 points from baseline in participants with a baseline SES-CD score of ≥3.

Endoscopic response: A reduction in the SES-CD score of ≥50% or SES-CD score ≤2 in participants with a baseline SES-CD score of ≥3.

In addition, endoscopic reports will be evaluated using the Simplified Endoscopic Mucosal Assessment for Crohn's disease (**SEMA-CD**) (Adler 2019).

The SEMA-CD is a novel endoscopic scoring index designed to assess the severity of mucosal involvement in the ileum and colon in Crohn's disease.

The SEMA-CD uses a simple Likert-like scale to rate the severity of mucosal involvement in the ileum and colon. Scores range from 0 to 20, where 0 indicates inactive Crohn's disease activity (endoscopic remission) and 20 indicates the worst disease severity for each bowel region (ileum and colon). The colon score is multiplied by the number of involved colonic segments and summed with the ileum score (Table 9).

When applying the SEMA-CD, the colon will be considered as a continuous assessment, and a score of 0 to 4 is selected based upon the worst feature within the entire colon. The selection of colonic segments involved should consist of all diseased segments, even if they are of a less severe description, but not including non-diseased segments. For example, if the ascending colon is

considered severe, and the transverse and descending colon are considered mild and the rectum is in endoscopic remission (non-diseased); then a score of 4 (severe) is assigned, and 3 colon segments are recorded (ascending, transverse and descending) for the SEMA-CD Colon segment score of 12 (severity 4 x 3 segment). The final score is calculated by summing the total scores for the colon and ileum.

Clinically meaningful cut scores for the SEMA-CD have not been established. For this study we will test mucosal activity categories as an exploratory measure. Initially, the SEMA-CD scores will be defined as follows:

0 = inactive

1 = minimal

2 – 4 = mild

5 – 9 = moderate

10 >= severe disease

Table 9: Scoring of the Simplified Endoscopic Mucosal Assessment for Crohn's Disease

Points	Ileum	Colon	Description
0	Endoscopic remission	Endoscopic remission	Normal
1	Minimal disease	Minimal disease	No more than a few aphthous ulcers Otherwise normal
2	Mild disease	Mild disease	Scattered aphthous ulcers or small ulcers No large ulcers (i.e. no ulcers >2cm) Narrowing, ok if it can be passed
3	Moderate disease	Moderate disease	Scattered large ulcers or widespread small ulcers Multiple passable stenoses No non-passable stricture or visible fistulas
4	Severe disease	Severe disease	Widespread large ulcers Non-passable stricture or visible fistula
-	Not assessed	Not assessed	

Colonic segments involved	❑ Ascending	❑ Transverse	❑ Descending	❑ Rectum

Note: Strictures of the ileocecal valve should be considered in the *ileum* score. Non-intubation of ileum without stricture should be considered "not assessed".

The below definitions are based on the SEMA-CD score:

Endoscopic remission: A SEMA-CD score of ≤1 in participants with a baseline SEMA-CD score of ≥2.

Clinically meaningful endoscopic improvement: A reduction in SEMA-CD of ≥2 points from baseline in participants with a baseline SEMA-CD score of ≥2.

Endoscopic response: A reduction in SEMA-CD from baseline of ≥50% or SEMA-CD score ≤1 in participants with a baseline SEMA-CD score of ≥2.

The below definition is based on assessment of mucosal ulcerations:

Endoscopic improvement: The complete absence of any mucosal ulcerations among participants who presented with an ulceration in at least 1 ileocolonic segment at induction baseline.

5.5.2.10. Fistula Assessment

For participants with fistulizing disease, fistula closure will be assessed. Enterocutaneous fistulas (eg, perianal and abdominal) will be considered no longer draining (ie, closed) when there is absence of drainage despite gentle compression. Rectovaginal fistulas will be considered closed based on either physical examination or absence of relevant symptoms (eg, passage of rectal material or flatus from the vagina).

Fistula response: A fistula response is defined as a ≥50% reduction in the number of draining fistulas among participants with 1 or more fistulas at baseline.

Complete fistula response: Complete fistula closure of all draining fistulas among participants with 1 or more fistulas at baseline.

5.5.2.11. Mucosal Inflammation Noninvasive Index (MINI)

The MINI index was developed and validated by Cozijnsen et al. (Cozijnsen 2020) to non-invasively assess mucosal inflammation in children with CD. The MINI index is calculated using stooling item from the PCDAI, fecal calprotectin, ESR, and CRP. The maximal score of MINI is 25 points and minimal minus 3 points. The scoring algorithm is shown in the table below.

Item	Points
Stool (the stooling item from the PCDAI)	
0-1 Normal or liquid stools, no blood	0
≤2 Semiformed with small blood, or 2-5 liquid	4
Gross bleeding, or ≥6 liquid, or nocturnal diarrhea	8
Fecal calprotectin	
<50 ug/g	-3
50-99.9 ug/g	0
100-299.9 ug/g	5
300-599.9 ug/g	7
600-899.9 ug/g	9
≥900 ug/g	12
3. ESR and CRP*	
ESR <10 mm/h and CRP <5 mg/L	0

Item	Points
30 > ESR ≥10 mm/h or 10 > CRP ≥5mg/L	1
50 > ESR ≥30 mm/h or 30 > CRP ≥10mg/L	2
ESR ≥50 mm/h or CRP ≥30 mg/L	5
MINI Sum	**-3 to 25**

* 1) While it is possible to score the MINI index with either CRP or ESR, both are preferred. 2) Score the highest of CRP or ESR.

The below dichotomized categories of the MINI index are based on a different cut-off value:

- MINI index <8
- MINI index <7
- MINI index <6

5.5.3. Estimands and Analyses of Tertiary/Exploratory Endpoints

Data will be summarized using descriptive statistics (Section 5.1) through Week I-8 using the FAS. Data will be summarized overall and by intervention group using descriptive statistics (Section 5.1) from Week M-0 through Week M-44 using the FASCR. For endpoints at Week M-8 specified above where the objective is to evaluate response due to induction, the FASR will be used.

Dichotomous endpoints *

1. Through Week I-8: The Global Primary Estimand 1 approach specified for the Global primary endpoint Section 5.3.2.2 and Section 5.3.3.1, respectively, will be used. After accounting for the ICEs, participants who have a missing data will be considered not to have achieved the endpoint at that timepoint.
2. Week M-0 through Week M-44: The US-specific Primary Estimand 1 approach specified for the US-Specific Primary Endpoint 1 Section 5.3.2.5 and Section 5.3.3.4, respectively will be used. After accounting for the ICEs, participants who have missing data will be considered not to have achieved the endpoint at that timepoint.

* No imputation will be performed for missing Crohn's disease-related hospitalizations and surgeries, ie, the missing values will remain as missing. In addition, no ICE will be applied.

Continuous endpoints

1. Through Week I-8: ICEs 1-5 from the Global Primary Estimand 1 will be targeted (Section 5.3.2.2). Participants with ICEs 1-3, and 5 prior to a visit will be considered to have no change from baseline for that endpoint at that visit and subsequent visits. Participants with ICE 4 will have their data assumed missing after the ICE 4 occurred.
2. Week M-0 through Week M-44: ICEs 1-7 from the US-specific Primary Estimand 1 will be targeted (Section 5.3.2.5). Participants with ICEs 1-5, and 7 prior to a visit will be considered to have no change from baseline for that endpoint at that visit and subsequent visits. Participants with ICE 6 will have their data assumed missing after the ICE 6 occurred.

5.6. Supplementary Analyses

5.6.1. Key Efficacy Endpoints by Baseline Subgroups

Key efficacy endpoints (the primary and secondary endpoints) will be summarized by:

- Baseline age (2 to 11 years, including 2-5 and 6-11 years, 12-17 years)
- Baseline weight (<40 kg, including <30 kg and 30-40 kg, ≥40 kg)

Efficacy endpoints through Week I-8 will be summarized based on the FAS. Efficacy endpoints during the maintenance period through Week M-44 will be summarized based on the FASCR by treatment intervention. In addition, efficacy endpoints during the maintenance period through Week M-44 will also be summarized overall based on the All Responder Analysis Set (FASRES) (eg, clinical responders, delayed responders).

5.6.2. Efficacy Endpoints for All Responders (Clinical Responders at Week M-0 and Delayed Responders at Week M-8 Combined)

The following endpoints will be summarized overall by the FASRES (clinical responders and delayed responders combined):

1. Clinical remission at Week M-44, as assessed by the PCDAI scores.
2. Endoscopic response at Week M-44.
3. Clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44.
4. Clinical response at Week M-44, as assessed by the PCDAI scores.
5. Clinical remission through Week M-44 as assessed by the PCDAI scores, for participants who are in clinical remission at Week I-8.
6. Baseline and postbaseline values and the change from baseline in the PCDAI score from Week I-0 through Week M-44.

5.6.3. Efficacy Endpoints for Participants Who Qualified for Dose Adjustments

The following efficacy analysis will also be summarized overall where participants who dose adjusted from q8w → q8w and q12w → q8w for FASRES. All analyses will be based on the observed data. Missing data will not be imputed and no ICE rules will be applied.

1. Clinical remission at Week M-44, as assessed by the PCDAI score.
2. Endoscopic response at Week M-44.
3. Clinical response at Week M-44, as assessed by the PCDAI score.
4. Change in PCDAI score at Week M-44 from baseline.
5. Change in PCDAI score at Week M-44 from before dose adjustment.
6. Change in PCDAI at 16 weeks after dose adjustment from baseline.

7. Change in PCDAI at 16 weeks after dose adjustment from before dose adjustment.
8. Clinical response at 16 weeks after dose adjustment, as assessed by the PCDAI score.
9. Clinical remission at 16 weeks after dose adjustment, as assessed by the PCDAI score.

5.6.4. Supplementary Analyses of Efficacy Endpoints using PCDAI Diary Data

For PCDAI, the total score will be calculated in the same way as described in Section 5.3.3.1, with the only exception of symptom history scores (including 3 items: abdominal pain, stool frequency; and general well-being) that will be calculated based on the diary data as the average of the daily scores over the 7 days prior to the visit for each item.

The following PCDAI related endpoints will be summarized over time through Week I-8 using the FAS and from Week M-0 through Week M-44 using the FASCR:

1. Change from baseline in scores
2. Clinical response
3. Clinical remission

5.6.5. Sensitivity Analyses of Primary and Secondary Endpoints Due to COVID-19 Assessment

In the primary estimand, data issues due to COVID-19 have already been addressed. The following are alternative data handling approaches to address COVID-19 data related issues. The following additional sensitivity analyses will be performed for all primary and secondary endpoints at Week I-8 and Week M-44:

1. All participants with missing data due to COVID-19 related reasons will be excluded from the clinical response, clinical remission, and endoscopic response analyses.

Note that participants who have had ICEs 1-3, and 5 prior to Week I-8 analyses and ICEs 1-5, and 7 prior to Week M-44 analyses, respectively, will be considered to be a nonresponder in these analyses, regardless of any missing data.

5.6.6. Supplementary Analyses of the Ratio of Pediatric Participants to Adult Participants

1. Ratio of the proportion of pediatric participants in clinical remission at Week I-8 over the proportion of adult participants in clinical remission at Week I-8 in the ustekinumab ~6 mg/kg intervention group from study CNTO1275CRD3001 and CNTO1275CRD3002.
2. Ratio of the proportion of pediatric participants in clinical remission at Week M-44 over the proportion of the adult participants in clinical remission at Week M-44 in the ustekinumab 90 mg SC q8w intervention group from study CNTO1275CRD3003.

5.6.7. Supplementary Analysis Methods

The analyses below apply to endpoints from Section 5.6.1 to Section 5.6.6 above.

No statistical comparisons will be made. Unless otherwise specified, data will be descriptively summarized through Week I-8 using the FAS, and data will also be descriptively summarized overall and by intervention group from Week M-0 through Week M-44 using the FASCR. For endpoints at Week M-8 specified above where the objective is to evaluate response due to induction, the FASR will be used.

Dichotomous endpoints

1. Through Week I-8: The Global Primary Estimand 1 approach specified for the Global primary endpoint Section 5.3.2.2 and Section 5.3.3.1, respectively, will be used. After accounting for the ICEs, participants who have a missing data will be considered not to have achieved the endpoint at that timepoint.
2. Week M-0 through Week M-44: The US-specific Primary Estimand 1 approach specified for the US-Specific Primary Endpoint 1 Section 5.3.2.5 and Section 5.3.3.4, respectively will be used. After accounting for the ICEs, participants who have missing data will be considered not to have achieved the endpoint at that timepoint.

Continuous endpoints

1. Through Week I-8: ICEs 1-5 from the Global Primary Estimand 1 will be targeted (Section 5.3.2.2). Participants with ICEs 1-3, and 5 prior to a visit will be considered to have no change from baseline for that endpoint at that visit and subsequent visits. Participants with ICE 4 will have their data assumed missing after the ICE 4 occurred.
2. Week M-0 through Week M-44: ICEs 1-7 from the US-specific Primary Estimand 1 will be targeted (Section 5.3.2.5). Participants with ICEs 1-5, and 7 prior to a visit will be considered to have no change from baseline for that endpoint at that visit and subsequent visits. Participants with ICE 6 will have their data assumed missing after the ICE 6 occurred.

5.7. Safety Analyses

Safety through Week I-8 will be summarized for the Safety Analysis Set. Safety during the maintenance period (ie, from Week M-0 through Week M-44[through the last visit not including the Final Safety Visit]), will be summarized for the SASR and will be based on the randomized treatment group. Participants who dose adjust will be counted in the treatment group they were randomized to at Week M-0.

Selected safety analysis during the maintenance period will also be summarized for the:

- Safety Clinical Responder Analysis Set (SASCR)

Safety will be assessed by summarizing the frequency and type of AEs, and laboratory parameters (hematology and chemistry).

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

5.7.1. Extent of Exposure

The number and percentage of participants who receive IV study intervention will be summarized by visit for the Safety Analysis Set. The number and percentage of participants who receive SC study intervention will be summarized by visit during the maintenance period from Week M-0 to Week M-44 for the SASR.

Descriptive statistics will be presented for the following parameters:

- Study intervention duration (weeks), defined as (date of last dose of study intervention – date of first dose of study intervention) +1
- Number of administrations
- Number of infusions
- Number of injections
- Cumulative total dose (mg)

The average follow-up time (weeks) and average exposure (number of administrations) will be summarized in the AE tables through Week I-8 and during the Maintenance period from Week M-0 through Week M-44 (through the last visit not including the Final Safety Visit).

Participants who missed a dose due to COVID-19 reasons will also be summarized by the SASR during the maintenance.

A listing of participants will be provided for the following:

- Participants who missed doses through Week M-44 (including missed doses due to COVID-19 related reasons)

5.7.2. Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention is considered to be treatment emergent adverse event (TEAE). If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported TEAEs will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized through Week I-8 for the

Safety Analysis Set and from Week M-0 through Week M-44 overall and by intervention group for the SASR. TEAEs will be tabulated by descending frequency in the combined column during maintenance of the System Organ Class (SOC) and then by preferred term within the SOC.

Summary tables will be provided for the following TEAEs:

1. AEs
2. Serious AEs (SAEs)
3. AEs leading to discontinuation of study intervention
4. AEs reasonably related to study intervention
5. AEs of severe intensity
6. Infections, serious infections, infections requiring oral and/or parenteral antimicrobial treatment
7. AEs temporally associated with the infusion of study intervention (Week I-0)
8. Injection-site reactions (Week M-0 through Week M-44)

These summary tables will provide the count and percentage of participants with 1 or more of the specified TEAEs by treatment group, SOC and preferred term.

AEs, SAEs, serious infections, and AEs leading to discontinuation of study intervention will also be summarized during the maintenance period (ie, from Week M-0 through Week M-44 [through the last visit not including the Final Safety Visit]) for the SASCR.

In addition, AEs, SAEs, serious infections, and AEs leading to discontinuation of study intervention will also be summarized from Week I-0 through Week M-44 (through the last visit not including the Final Safety Visit), for the:

- SASCR
- Safety Analysis Set

A summary of key safety events (death, discontinuation of study intervention because of 1 or more adverse events, AEs, SAEs, infections, serious infections, neoplasms [malignant], AEs temporally associated with the infusion of study intervention at Week I-0) for the Safety Analysis Set and during Maintenance Week M-0 through Week M-44 will be provided overall and by treatment intervention for the SASR. Injection-site reactions will be summarized during maintenance.

Key safety events through Week I-8 will also be summarized for the Safety Analysis Set by:

1. baseline age [2 to 11 years, including 2-5 years and 6-11 years, 12-17 years]
2. baseline weight (<40 kg, including <30 kg and 30-40 kg, ≥40 kg)
3. baseline immunomodulator status
4. baseline corticosteroid status
5. prior biologic washout period duration (≥5 half-lives, <5 half-lives)

Key safety events during the maintenance period from Week M-0 through Week M-44 (through the last visit not including the Final Safety Visit), will be summarized for the SASR by:

1. baseline age [2 to 11 years, including 2-5 years and 6-11 years, 12-17 years]
2. baseline weight (<40 kg, including <30 kg and 30-40 kg, ≥40 kg)
3. responder status (clinical responders at Week M-0, delayed responders at Week M-8, and non-responders at Week M-0 and Week M-8)
4. dose adjustment (q8w → q8w, q12w → q8w)
5. dose adjustment and no dose adjustment
6. prior biologic washout period duration (≥5 half-lives, <5 half-lives)

In addition to the summary tables, listings will be provided from Week I-0 through Week M-44 (through the last visit not including the Final Safety Visit) using the Safety Analysis Set, for participants who:

1. Had SAEs
2. Had AEs leading to discontinuation of study intervention
3. Had AEs related to COVID-19 reasons

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 (CSR).

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.

Definitions

- A reasonably-related AE is defined as any event with a relationship to study intervention of 'Related' on the AE eCRF page or if the relationship to study intervention is missing.
- An AE that is temporally associated with the infusion of study intervention is one that occurs during or within 1 hour after the infusion, with the exception of laboratory abnormalities.
- 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.

5.7.3. Additional Safety Assessments

5.7.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the Safety Analysis Set and the SASR.

Descriptive statistics will be presented for selected chemistry and hematology laboratory tests at scheduled time points. Change from baseline through Week I-8 for the Safety Analysis Set will be summarized for chemistry and hematology tests. Change from baseline from Week M-0 through

Week M-44 for the SASR will be summarized for chemistry and hematology tests and displayed by intervention group.

The laboratory data to be summarized is as follows:

- **Hematology assessments** will include but are not limited to the following: hemoglobin, hematocrit, platelet count, and white blood cell count with differential.

- **Blood chemistry assessments** will include but are not limited to the following: sodium, potassium, chloride, blood urea nitrogen, creatinine, alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total and direct bilirubin, alkaline phosphatase, calcium, phosphate, albumin, CRP.

Shift tables will be provided for selected laboratory parameters (hematology: hemoglobin, hematocrit, platelets, and white blood cell count with differential; chemistry: ALT, AST, total bilirubin, albumin, and CRP) summarizing the shift in laboratory values from baseline over time with respect to abnormality criteria (low, normal, high) through Week I-8 for the Safety Analysis Set, and during the maintenance period from Week M-0 through Week M-44 for the SASR.

The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0) will be used in the summary of laboratory data (Grades 0 to 4). The proportion of participants with each post-baseline maximum toxicity grade for clinical laboratory tests will be summarized by study intervention group. Participants with toxicity grades ≥ 2 will be listed. The laboratory tests not included in Section 6.10 will not be presented in the corresponding toxicity tables or listings.

Further, the proportion of participants with maximum ALT/AST (relative to ULN) will be provided for the categories:

- ≤1x upper limit of normal (ULN)
- >1xULN
  - 1 and ≤ 3xULN
  - > 3 and ≤ 5xULN
  - > 5 and ≤ 20xULN
  - > 20xULN

In addition, the following summaries will be performed:

1. Summary of maximum postbaseline total bilirubin relative to ULN
2. Number and percentage of participants who met the criteria of possible Hy's law (ie, ALT or AST ≥3xULN, and total bilirubin ≥2xULN (>35% direct) or international normalized ratio [INR] >1.5)

Change from baseline is defined to be the assessment at the postbaseline visit minus the assessment at Week I-0. Summaries of laboratory data will be completed using all the available laboratory data at the time point of interest without imputing missing data.

5.7.3.2. Vital Signs and Physical Examination Findings

Change from baseline of the vital sign parameters (weight, height, pulse, and blood pressure [systolic and diastolic]) will be collected and summarized for the Safety Analysis Set through Week I-8. In addition, safety data during the maintenance period will also be summarized for the SASR and will be based on the randomized treatment group.

Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented. Abnormalities considered clinically relevant by the investigator will be reported as AEs.

5.8. Other Analyses

5.8.1. Pharmacokinetics

PK analyses will be performed on the PK analysis set (PKAS), defined as participants who have received at least 1 dose of ustekinumab and have at least 1 post initial dose blood sample drawn for PK analysis.

Descriptive statistics (N, mean, SD, median, range, and IQ range) will be used to summarize ustekinumab serum concentrations at each sampling time point. PK data may be displayed graphically, such as median, or mean +/- SD PK ustekinumab concentrations over time by intervention group.

Serum ustekinumab concentrations will be summarized overall through Week I-8 for the PKAS. Serum ustekinumab concentrations from Week I-0 through Week M-44 will be summarized by intervention group for PK All Responder Analysis Set (PKASRES) (responder, delayed responder).

For summary statistics of serum ustekinumab concentrations, concentration values below the limit of quantification will be treated as zero. No imputation for missing concentration data will be performed. The proportion of participants with concentration below the lowest quantifiable concentrations at each visit will also be summarized through Week I-8 for the PKAS and during maintenance from Week M-0 through Week M-44 for the PKASCR.

Once a participant meets one of the following dosing deviation criteria, the participant's data will be excluded from the by-visit data analyses from that point onwards.

Dosing deviation criteria:

1. Received an incomplete/incorrect infusion (Week I-0).
2. Received an incorrect SC dose (Maintenance Period).
3. Missed an administration.

4. Received an additional SC dose of ustekinumab.
5. Received commercial ustekinumab.

In addition, during induction PK samples taken outside the scheduled visit window (±4 days) will be excluded from the summary tables at that visit. After the Week I-8 visit, if the PK sampling time deviates by more than 10 days, the ustekinumab concentration at this visit will be excluded from the by-visit data analyses.

Serum ustekinumab concentrations will also be summarized through Week I-8 by:

1. Baseline age [2 to 11 years, including 2-5 years, 6-11 years, 12-17 years]
2. Baseline weight (<40 kg, including <30 kg and 30-40 kg, ≥40 kg)
3. Clinical response status at Week I-8
4. Baseline immunomodulator status

There will be a descriptive comparison of PK data of the adult studies (CNTO1275CRD3001, CNTO1275CRD3002 [Adult PK Induction combined; ~6 mg/kg treatment group]) with PK data of the pediatric Study (CNTO1275CRD3004) at Week I-8.

In addition to the summary tables the following plots will also be provided for ustekinumab participants:

1. Plot of serum ustekinumab concentrations over time through Week I-8 by baseline body weight (<40 kg, ≥ 40 kg)
2. Plot of serum ustekinumab concentrations over time through Week I-8
3. Participants by study (CNTO1275CRD3001, CNTO1275CRD3002 (Adult PK Induction combined; ~6 mg/kg treatment group) and CNTO1275CRD3003 (Adult PK Maintenance; 90 mg q8w treatment group), CNTO1275CRD3004).

Serum ustekinumab concentrations will also be summarized during maintenance through Week M-44 for the PK Randomized Analysis Set (PKASR) for participants who dose adjusted.

A population PK analysis approach will be used to determine ustekinumab PK parameters. Relevant covariates will be evaluated for their effect on ustekinumab PK where appropriate.

Additional PK data from other studies may be used to supplement the population PK analysis in pediatric participants with Crohn's disease. The results of the population PK analysis will be provided in a separate report from the clinical study report.

5.8.1.1. Pharmacokinetics and Efficacy

To determine the influence of ustekinumab concentration on the efficacy of ustekinumab, the primary and secondary endpoints will be summarized by ustekinumab concentration quartiles at Week I-8 and at steady state trough, as appropriate.

Descriptive comparisons of the adult studies (CNTO1275CRD3001, CNTO1275CRD3002, CNTO1275CRD3003) with the pediatric study (CNTO1275CRD3004) for the summary of key

efficacy endpoints by ustekinumab concentration quartiles at Week I-8 and at steady state trough will be performed. Graphical displays may be used to summarize the data.

Further, the primary and secondary endpoints may also be summarized by ustekinumab concentrations using medians or appropriate quantiles.

In addition to the tables, the following plots will also be provided.

1. Bar chart of median improvement from baseline in the PCDAI scores at Week I-8 will be summarized by ustekinumab concentration quartiles (micrograms/mL) at Week I-8 for the PKAS population.
2. Bar chart of median improvement from baseline in the PCDAI scores at Week M-44 will be summarized by ustekinumab concentration quartiles (micrograms/mL) at Week M-24 for the PKASCR population.

5.8.2. Immunogenicity

Sample anti-drug antibody (ADA) status and sample titer as well as the cumulative "participant ADA status" and peak titer through the visit will be coded and provided by the sponsor's bioanalytical group.

Participants evaluable for immunogenicity are defined as having at least one postdose ADA time point collected for anti-ustekinumab antibody detection.

Participants with treatment-emergent anti-ustekinumab antibodies include participants with treatment-induced anti-ustekinumab antibodies and treatment-boosted anti-ustekinumab antibodies.

Participants with treatment-induced anti-ustekinumab antibodies have an anti-ustekinumab antibody-negative sample prior to ustekinumab administration and at least one anti-ustekinumab antibody-positive sample after ustekinumab.

Participants with treatment-boosted anti-ustekinumab antibodies have an anti-ustekinumab antibody-positive sample prior to ustekinumab administration and at least one anti-ustekinumab antibody-positive sample after ustekinumab with a 4-fold increase in titer over baseline.

In participants who have a positive ADA titer prior to ustekinumab administration, if ADA titer remains the same after intervention or if ADA titer reduces or ADA disappears, the participant is classified as "treatment-emergent ADA negative". Participants that are unavailable for treatment-emergent ADA following intervention will be classified as "participants with baseline samples only", ie, no appropriate sample is available after intervention.

The anti-ustekinumab antibodies summary and analysis will be based on the observed data; therefore no imputation of missing data will be performed. Note: participant status is through each visit, thus, participant status and peak titers may change as the study progresses over time. Therefore, the 'participant ADA status' at a visit represents the cumulative ADA status through that visit.

The summary of participants with baseline positive samples is taken from the sample status at baseline. There is no participant level status at baseline.

Incidence of antibody (evaluable, treatment-emergent ADA positive, treatment-emergent ADA negative) status and neutralizing antibodies (NAbs) to ustekinumab will be summarized overall through Week I-8 by the Immunogenicity Analysis Set (IAS). Summaries for Week I-0 through Week M-44 will be provided by intervention group, irrespective of dose adjustment for the Immunogenicity All Responder Analysis Set (IASRES**)** (clinical responder, delayed responder).

In addition, antibody to ustekinumab status (positive/negative) through Week I-8 and through Week M-44 will also be summarized by study (CNTO1275CRD3001, CNTO1275CRD3002 [Adult PK Induction combined; ~6 mg/kg treatment group], CNTO1275CRD3003 [Adult PK Maintenance; 90 mg q8w treatment group], and CNTO1275CRD3004).

In addition, listings of participants with baseline positive ADA samples, participants who are classified as positive for treatment-emergent anti-ustekinumab antibodies and participants who discontinue the study by anti-ustekinumab antibodies status as well as graphical representation of median serum ustekinumab concentration by antibody status may be presented.

The peak titer for participants positive for treatment-emergent anti-ustekinumab antibodies will be grouped by Peak Titer categories, eg, ≤1:10, 10 to 100, 100 to 1000, >1000, if needed.

Incidence of treatment-emergent positive antibody across Peak Titer categories might be summarized.

Additional relationships between treatment-emergent anti-ustekinumab antibodies status (positive or negative) and ustekinumab concentration may be assessed, if sufficient number of ustekinumab participants are positive for anti-ustekinumab antibodies.

5.8.3. Pharmacodynamics

Blood, fecal and mucosal biopsy samples will be collected at visits indicated in the SoA of the protocol. Changes in the concentration of individual serum markers from baseline to the selected post treatment time points will be summarized. Differential expression of RNA in whole blood, mucosal biopsies and microbiome analyses will be performed. Biomarker analyses are considered exploratory and will be summarized in separate technical reports.

5.8.4. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between serum concentrations of ustekinumab and the efficacy measures and/or relevant pharmacodynamic (PD) endpoints may be explored graphically when appropriate. If any visual pattern is observed, additional analysis may be conducted if deemed necessary.

Results of PK/PD analyses will be presented in a separate technical report, if conducted.

5.8.5. Biomarkers

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 cut-off date will not be analyzed, and therefore, excluded from the biomarker analysis.

Changes in serum protein analytes, fecal biomarkers, and biopsy RNA obtained over time will be summarized for the induction period and summarized by treatment group for the maintenance period. Associations between baseline levels and changes from baseline in select markers and response to treatment will be explored. Proprietary algorithms and standard statistical techniques will be used to identify markers exhibiting significantly different changes in their levels between samples and/or between groups of samples.

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

5.8.6. Health Economics

Not Applicable.

5.8.7. Other Variables and/or Parameters

Change from baseline through Week I-8 of dietary therapies will be summarized for the Safety Analysis Set. Change from baseline during the maintenance period from Week M-0 through Week M-44 of dietary therapies will be summarized for the SASR and displayed by intervention group. Shift tables will be provided summarizing the shift in number of dietary therapies from baseline through Week I-8 and during the maintenance period from Week M-0 through Week M-44.

5.8.8. Definition of Subgroups

The consistency of treatment effect for the primary endpoint will be evaluated for subgroups based on demographic, Crohn’s disease characteristics, Crohn’s disease-related concomitant medication usage, and Crohn’s-related medication history using the Primary Estimand(s) (Global or US-specific Primary Estimands).

For each of these subgroups, the proportion of participants in clinical remission at Week I-8 (Global primary endpoint) or clinical remission at Week M-44 (US-specific primary endpoint) and the associated 95% confidence interval will be provided.

The subgroups for subgroup analysis include the following:

Table 10: Demographic Subgroups

Subgroup	Definition
Region	• Asia [Israel, Japan] • Eastern Europe [Poland, Hungary] • Rest of World [United States, Germany, UK, and Belgium]
Age Group	• 2-11 years (including 2-5, 6-11) • 12-17 years
Weight group	• <40 kg • >= 40kg
Race	• White • Non-white
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino
Sex	• Male • Female

Table 11: Clinical Disease Characteristics at Baseline Subgroups

Subgroup	Definition
Clinical Disease Characteristics at Baseline	
Crohn's disease duration	• <=1 year • 1-<5 years • ≥5 years
Involved gastrointestinal areas	• Ileum only • Colon Only • Ileum and Colon
Severity of Crohn's disease by PCDAI Score	• Not Severe: ≤ 40, • Severe: >40
Severity of Crohn's disease by CDAI Score	• < median CDAI score • >= median CDAI score
Endoscopic disease severity per SES-CD score	• < 6 (or <4 for ileal disease only) • >= 6 (or >= 4 for ileal disease only) and • Inactive [0-2] • Mild [3-6] • Moderate [7-16] • Severe [>16]
CRP	• ≤3 mg/L • >3 mg/L
Fecal calprotectin	• ≤250 mg/kg • >250 mg/kg
Fecal lactoferrin	• ≤7.24 µg/g • >7.24 µg/g

Table 12: Concomitant Medication Use at Week 0

Subgroup	Definition
Concomitant Medication Use at Week 0	
Oral corticosteroids, including budesonide and beclomethasone dipropionate	• Yes • No
5-ASA compounds	• Yes • No
6-MP/AZA/MTX	• Yes • No

Table 13: Crohn's disease-related Medication History

Subgroup	Definition
Crohn's disease-related Medication History	
Biologic failures vs. non-biologic failures	• Yes • No
Biologic washout period duration	• ≥5 half-lives • <5 half-lives

5.9. Interim Analyses / DMC

An independent DMC will monitor safety data and the PK interim analysis assessment during the study.

5.9.1. PK Interim Analysis

A PK interim analysis to evaluate the ustekinumab dosage and safety for participants <40 kg (as measured at Week I-0) will be performed when at least 20 participants from both CNTO1275CRD3004 and CNTO1275PUC3001 studies (combined) weighing <40 kg complete the Week M-8 visit. Available PK data from participants ≥40 kg who completed the Week M-8 visit from both CNTO1275CRD3004 and CNTO1275PUC3001 studies and PK data from the adult Stelara UC/CD studies will also be included (for reference purposes) in this PK interim analysis. Serum ustekinumab concentrations will be summarized for this purpose. The DMC members along with an unblinded internal sponsor PK expert independent of the study conduct will be reviewing the results of the analysis to evaluate the ustekinumab dosage and safety for participants.

Details of the PK interim analysis will be included in the DMC SAP.

5.9.2. Interim Analysis of Data for the EMA submission for Participants ≥40 kg (DBL1)

An interim analysis to support the EMA submission will be based on at least 36 randomized participants who had body weight ≥40 kg at Week I-0 and Week M-0 and had completed the Week M-44 visit or terminated study participation prior to Week M-44.

The analysis set will be the EMA randomized analysis set for participants with body weight ≥40 kg (ERAS) for all other analyses, except for PK analyses, where the PKERAS will be used.

For participants who entered the Exposure Optimization Substudy, the data from the main study and the data from Exposure Optimization Substudy will be summarized separately.

5.9.2.1. Participant Dispositions

Participant disposition will be summarized the same as described in Section 5.2.

5.9.2.2. Protocol Deviations

The following listings will be provided from Week I-0 through the DBL1:

- List of participants with major protocol deviations.
- List of participants who did not meet study selection criteria by category.
- List of participants who had a protocol deviation in study intervention administration.

5.9.2.3. Efficacy Analyses

All efficacy analyses that are specified in Section 5.3 to Section 5.5 will be performed with exception of the US-specific endpoints analyses. All other supplementary analyses that are described in Section 5.6 will not be performed.

In addition, data permitting, analysis of key efficacy endpoints may be performed by responder status (clinical responder, delayed responder, non-responder).

5.9.2.4. Safety Analyses

All safety analyses that are specified in Section 5.7 will be performed.

5.9.2.5. Other Analyses

Analyses of PK and immunogenicity (Section 5.8.1 and Section 5.8.2) will be performed. Data permitting, subgroup analysis (Section 5.8.8) may be performed. All other analyses that are described in Section 5.8 will not be performed.

5.9.2.6. Exposure Optimization Substudy Analyses

For participants who entered the substudy, the data from substudy will be summarized separately. Analysis and endpoints in Section 5.11 and Section 6.17.4 (Appendix 17) will be summarized or listed over time.

5.9.3. DMC or Other Review Board

The independent DMC will monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in the study, including data from the Exposure Optimization Substudy. The external Data Monitoring Committee (DMC) will monitor safety data on an ongoing basis for both the ustekinumab pediatric IBD studies (CNTO1275PUC3001 and CNTO1275CRD3004).

None of the DMC members will be participating in the study; they will be independent of the sponsor. The independent DMC consists of 2 medical experts in relevant therapeutic areas and 1 statistician and are to be specified before study initiation. The major function of the DMC is to monitor the safety of the study intervention and provide recommendations for placing the study on hold or stopping the study in the event of serious safety concerns.

The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. Any safety concerns will be communicated to the sponsor Committee Chairperson.

Periodic safety reviews will occur as outlined in the DMC Charter. The first DMC meeting will occur approximately 4 months after the first participant is dosed with study intervention. Subsequent meetings will occur approximately every 3 months until the last meeting which will be through the Week M-44 database lock or for participants in the Exposure Optimization Substudy, completion of their 16-week dosing administration or termination of study participation, whichever is longer.

Serious adverse events will be reported to the DMC members on an ongoing basis. The DMC will have access to the unblinded data and review tabulated safety summaries (if appropriate) and any additional safety data that the DMC may request.

The content of the safety summaries, the content of the PK interim analysis, the DMC roles and responsibilities and the general procedures (including communication plan) and their possible recommendations on study conduct will be defined and documented in the joint DMC charter for CNTO1275PUC3001 and CNTO1275CRD3004.

5.10. Analyses for DBL3 (When All Participants who are not Participating in LTE Have Completed Final Safety Visit)

5.10.1. Participant Dispositions

A listing of participants who terminated study participation will be provided from the Week M-44 DBL through the final safety visit.

5.10.2. Protocol Deviations

A listing of participants with major protocol deviations will be provided from the Week M-44 DBL through the final safety visit.

5.10.3. Adverse Events

A listing of participants with AEs will be provided from the Week M-44 DBL through the final safety visit.

5.11. Analyses for DBL4 (Exposure Optimization Substudy)

Details about the Exposure Optimization Substudy are described in Section 6.17. Analyses will be performed among all participants in the Substudy Analysis Set (SSAS). Participants data will be summarized overall and by treatment group (q12w→q4w, q8w→q4w)

5.11.1. Participant Dispositions

A listing of participants will be provided for the following categories:

1. Participants who discontinued study intervention
2. Participants who terminated study participation

5.11.2. Protocol Deviations

A listing of participants will be provided for the following categories:

- List of participants with major protocol deviations

5.11.3. Efficacy

Change in the PCDAI score from initiation of the q4w dose regimen through to Week M-44 (or through 16 weeks of q4w exposure, whichever is longer).

Serum CRP, fecal calprotectin/fecal lactoferrin through 16 weeks of **a**dministration will be summarized by treatment group (q12w → q4w, q8w → q4w, and combined ustekinumab).

Efficacy endpoints in Section 6.17.4 (Appendix 17) will be summarized over time.

5.11.4. Adverse Events

Summary tables during the substudy will be provided for TEAEs:

- AEs
- SAEs
- AEs leading to discontinuation of study intervention
- Infections, serious infections, infections requiring oral and/or parenteral antimicrobial treatment
- Injection-site reactions

A listing of participants with SAEs and AEs leading to discontinuation of study intervention will be provided.

5.11.5. Laboratory

Change from initiation of the q4w dose regimen in selected laboratory analytes (ie, hematology, chemistry,) through 16 Weeks of administration will be summarized by treatment group (q12w → q4w, q8w → q4w, and combined ustekinumab).

5.11.6. PK

PK will be summarized by treatment group (q12w→ q4w, q8w → q4w, and combined ustekinumab).

5.11.7. Immunogenicity

Immunogenicity will be summarized by treatment group (q12w → q4w, q8w→q4w, and combined ustekinumab).

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT/SGPT	Alanine Aminotransferase
AST/SGOT	Aspartate Aminotransferase
AZA	Azathioprine
BMI	Body Mass Index
BSA	Body Surface Area
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CrI	Credible Interval
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Data Base Lock
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ERAS	EMA Randomized Analysis Set
FAS	Full Analysis Set
FASCR	Full Clinical Responder Analysis Set
FASR	Full Randomized Analysis Set
FASRES	All Responder Analysis Set
FIM	Fisher information matrix
GGT	Gamma-Glutamyl Transferase
GHAS	Global Histology Activity Score
IAS	Immunogenicity Analysis Set
IASCR	Immunogenicity Clinical Responder Analysis Set
IASR	Immunogenicity Randomized Analysis Set
IASRES	Immunogenicity All Responder Analysis Set
IBD	Inflammatory Bowel Disease
ICE	Intercurrent Current Event
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMPACT-III	A Quality of Life Questionnaire for Children with Inflammatory Bowel Disease
INR	International Normalized Ratio
IQ	Interquartile
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
Kg	Kilogram
LLOQ	Lower Limit of Quantification
LOR	Loss of Response
LTE	Long Term Extension
MAR	Missing At Random

MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methyl Malonic Acid
MTX	Methotrexate
Nab	Neutralizing Antibodies
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
PCDAI	Pediatric Crohn's Disease Activity Index
PD	Pharmacodynamic
PIP	Pediatric Investigation Plan
PK	PHARMACOKINETIC
PKAS	PK Analysis Set
PKASCR	PK Clinical Responder Analysis Set
PKASR	PK Randomized Analysis Set
PKASRES	PK All Responder Analysis Set
PKERAS	EMA PK Analysis Set
q12w	Every 12 Weeks
q4w	Every 4 Weeks
q8w	Every 8 Weeks
QoL	Quality of Life
RHI	Robarts Histopathology Index
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SASCR	Safety Clinical Responder Analysis Set
SASR	Safety Randomized Analysis Set
SC	Subcutaneous
SD	Standard Deviation
SEMA-CD	Simplified Endoscopic Mucosal Assessment for Crohn's Disease
SES-CD	Simplified Endoscopic Activity Score for Crohn's Disease
SoA	Schedule of Activities
sPCDAI	Short Pediatric Crohn's Disease Activity Index
SSAS	Substudy Analysis Set
TEAE	Treatment-Emergent Adverse Event
TNFα	Tumor Necrosis Factor Alpha
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
US	United States
Week I-8	Induction Week 8
Week M-44	Maintenance Week 44
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Not Applicable.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized by intervention group, and overall. In addition, the distribution of participants by region, country, and site ID will be presented unless otherwise noted.

Table 14 presents a list of the demographic variables that will be summarized by intervention group and overall for the FAS and the Safety Analysis Set if the Safety Analysis Set is different from the FAS.

Table 14: Demographic 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)	
Weight z-score	
Height (cm)	
Height z-score	
Body Mass Index (BMI) (kg/m^2)	
BMI z-score	
Categorical Variables	
Age(2-5 years, 6 11 years, 12-17 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Region (Asia [Israel, Japan]; Eastern Europe [Poland, Hungary]; Rest of World [United States, Germany, UK and Belgium]	

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

Table 15 presents a list of the baseline disease characteristics variables that will be summarized by intervention group and overall for the FAS and the Safety Analysis Set if the Safety Analysis Set is different from the FAS.

Table 15: CD Disease Characteristics Variables

Continuous Variables:	**Summary Type**
CD disease duration (years)	Descriptive statistics (N, mean, SD, median and range [minimum and maximum], and IQ range).
Age at diagnosis (years)	
PCDAI, sPCDAI, CDAI Score	
Simple Endoscopic Score for Crohn's Disease (SES-CD), and SEMA-CD score	
CRP concentration	
Fecal calprotectin and Lactoferrin concentrations	
IMPACT III	
Categorical Variables	
Location of disease (Ileum, Colon, Ileum and Colon)	
Severity of disease by PCDAI Score (Not Severe: ≤ 40, Severe: >40)	

Table 15: CD Disease Characteristics Variables

Continuous Variables:	**Summary Type**
Endoscopic disease severity per SES-CD score (Inactive [0-2], Mild [3-6], Moderate [7-16], Severe [>16]) and < 6 (or <4 for ileal disease only), >= 6 (or >= 4 for ileal disease only)	Frequency distribution with the number and percentage of participants in each category.
SEMA-CD score: 0 = inactive; 1 = minimal; 2 - 4 = mild; 5 - 9 = moderate; 10 = severe disease	
Abnormal CRP (>3 mg/L)	
Abnormal fecal calprotectin (≥250 mg/kg)	
Abnormal fecal lactoferrin (>7.24 µg/g)	
Fistula (Peri-anal, Rectovaginal, None)	

In addition, summaries by age (2 to 11 years, including 2 to5 years and 6 to 11 years, 12 to 17 years), and weight (<40 kg, including <30 kg and 30-40 kg, >= 40 kg) categories will be provided separately for demographics and baseline disease characteristics variables.

In addition, selected summaries of demographics and baseline characteristics will be also provided for the FASCR and FASRES.

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category (Section 6.4.1).

Protocol deviations will be summarized overall for the FAS through Week I-8, and by treatment group and overall for the FASR (from Week M-0 through Week M-44 [through the last visit not including the Final Safety Visit]).

In addition to the summary tables, the following listings will be provided from Week I-0 through Week M-44 (through the last visit not including the Final Safety Visit):

- List of participants with major protocol deviations
- List of participants who did not meet study selection criteria by category
- List of participants who had a protocol deviation in study intervention administration

6.4.1. Major Protocol Deviations

Participants with major protocol deviations will be identified prior to the Week M-44 database lock and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received incorrect IV dose during induction
- Received incorrect dose during maintenance
- Other
  - Missed visit/assessment due to COVID-19

In these summaries a participant can be included in more than 1 deviation category.

6.4.2. Inclusion/Exclusion Criteria Deviations

Participants who entered the study but did not meet the inclusion/exclusion selection will be grouped into the following 5 categories: Crohn's disease criteria, medication criteria, laboratory criteria, medical history criteria, and other.

In these summaries a participant can be included in more than 1 deviation category.

6.4.3. Study Administration Deviations

Protocol deviations in study intervention administrations includes missing doses, incorrect doses, and treatments administrated out of dosing windows.

In these summaries a participant can be included in more than 1 deviation category.

6.4.4. COVID-19 Related Missing Visits/Assessments

Protocol deviations due to COVID-19 related missing visits and assessments will be summarized.

6.5. Appendix 5 Prior and Concomitant Medications

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

Summaries of Crohn's disease-specific concomitant medications at baseline (Week I-0) will be presented by the FAS. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 Crohn's disease-specific concomitant medication. The following Crohn's disease-specific concomitant medications at baseline will be summarized (oral 5-ASAs, immunomodulators [6-MP/AZA/MTX], and oral corticosteroids [including budesonide and beclomethasone dipropionate]).

Summaries by age (2 to 11 years, [2-5 years and 6-11 years], 12-17 years), and weight (<40kg, [<30 kg and 30-40 kg], >=40 kg) categories will also be provided for the FAS.

In addition, summaries of Crohn's disease-related medication history (history of response to or tolerance of 6-MP/AZA/MTX and history of response to, tolerance of or dependence on corticosteroids) and Crohn's disease-related biologic medication history will be summarized overall for the FAS.

In addition, summaries of Crohn's disease medication history (participants who took medications for Crohn's disease and their length of exposure prior to Week I-0) will be provided.

In addition, summaries of Crohn's disease-specific concomitant medications, Crohn's disease-related medication history, and Crohn's disease medication history will be also provided for the FASRES (eg, clinical responders, delayed responders).

6.6. Appendix 6 Medical History

Past medical history and current diagnoses, opioid usage, alcohol and tobacco/nicotine status (nonsmoker, prior smoker, current smoker) will be summarized overall for the FAS.

6.7. Appendix 7 Intervention Compliance

Distribution of participants by study intervention lot will be provided based on the Safety Analysis Set and the SASR.

In addition, a listing of participants who were unblinded during the maintenance portion of the study will be provided.

6.8. Appendix 8 Adverse Events of Special Interest

Any newly identified malignancy, case of active TB, or opportunistic infection occurring after the first administration of study intervention(s) in participants in this clinical study will be presented in the CSR.

6.9. Appendix 9 Medications of Special Interest

Not Applicable

6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale used for lab assessments is based on CTCAE v5.0.

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

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

Hematology Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
Hemoglobin (g/dL)	Increase	>0 - 2 x ULN	>2 - 4 x ULN	>4 x 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**
ALT	Increase	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
AST	Increase	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Albumin (g/L)	Decrease	≥30 - <LLN	≥20 - <30	<20	

Alkaline Phosphatase	Increase	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin (total)	Increase	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
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 xULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 xULN
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	129 - 125	124 - 120	<120

ALT = Alanine Aminotransferase. AST = Aspartate Aminotransferase, LLN = Lower Limit Normal, ULN = Upper Limit Normal

6.11. Appendix 11 Prohibited changes in concomitant medications (Category 3 of the ICEs)

ICE category 3 for all estimands

Had prohibited changes in Crohn's disease medication as defined below:

Corticosteroids:

1. Increase above baseline in the prednisone equivalent dosage of oral corticosteroids (excluding budesonide and beclomethasone dipropionate) due to worsening Crohn's disease.
2. Increase above baseline in the dosage of oral budesonide or oral beclomethasone dipropionate due to worsening Crohn's disease.
3. No oral corticosteroids (excluding budesonide and beclomethasone dipropionate) at baseline and initiation of oral corticosteroids (excluding budesonide and beclomethasone dipropionate) after baseline due to worsening Crohn's disease within 90 days prior to endpoint assessment date.
4. No oral budesonide or oral beclomethasone dipropionate at baseline and initiation of oral budesonide or oral beclomethasone dipropionate due to worsening Crohn's disease within 90 days prior to endpoint assessment date.
5. An initiation of rectal corticosteroids after baseline due to worsening Crohn's disease within 90 days prior to endpoint assessment date.
6. Any switch from oral budesonide/oral beclomethasone dipropionate to other oral corticosteroids or parenteral corticosteroid due to worsening Crohn's disease within 90 days prior to endpoint assessment date.

5-ASA compounds:

1. Increase above baseline in the dosage of oral 5-ASA compounds (sulfasalazine, mesalamine, olsalazine, or balsalazide) due to worsening Crohn's disease.
2. No oral 5-ASA compounds at baseline and initiation of oral 5-ASA compounds after baseline due to worsening Crohn's disease.
3. Initiation of rectal 5-ASAs (foam, enema, or suppositories) after baseline due to worsening Crohn's disease.
4. Switch between one 5-ASA compound to another 5-ASA compound due to worsening Crohn's disease.

Immunomodulator agents:

1. Increase above baseline in the dosage of AZA/6-MP or MTX due to worsening Crohn's disease.
2. No AZA, 6-MP, or MTX at baseline and initiation of AZA, 6-MP, or MTX after baseline due to worsening Crohn's disease within 90 days prior to endpoint assessment date.
3. Switched from oral MTX to SC/Intramuscular route due to worsening Crohn's disease within 90 days prior to endpoint assessment date.

Protocol-prohibited medications:

Initiation of any of the following immunomodulatory agents after baseline due to worsening of Crohn's disease:

1. Immunomodulatory agents other than 6-MP, AZA, and MTX (including, but not limited to, 6-TG, cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus, thalidomide, tofacitinib, and other Janus kinase inhibitors).
2. More than one antibiotic initiated for the treatment of Crohn's disease.
3. Parenteral nutrition administered via a central line.
4. Initiation of excusive enteral nutrition as a primary therapy for Crohn's disease.
5. Biologic agents (including, but not limited to, TNFα antagonists, abatacept, anakinra, rituximab, vedolizumab, natalizumab, alemtuzumab, and visilizumab).
6. A biologic therapy targeted at IL-12 and/or IL-23 (eg, commercial ustekinumab, ustekinumab, risankizumab, brazikumab, tildrakizumab).
7. Investigational drugs.
8. A live virus or bacterial vaccine (see CNTO1275CRD3004 Protocol Section 5.3 [Lifestyle Considerations]).

6.12. Appendix 12 Rescue medications

Following a loss of response, any initiation or increase in the dose of 6-MP/AZA/MTX, oral budesonide, oral beclomethasone dipropionate, or other oral corticosteroids (prednisone equivalent) above the dose received at baseline will be considered a rescue medication. Any participant who uses rescue medication after losing response will be considered not to have achieved clinical response/remission after this event.

6.13. Appendix 13: Pediatric Crohn's Disease Activity Index (PCDAI)

HISTORY SCORE (Recall, 1 week)

Abdominal Pain:

None	_____ (0 points)
Mild - Brief, does not interfere with activities	_____ (5)
Mod/Severe – daily, longer lasting, affects activities, nocturnal	_____ (10)
	Total _____

Stools (per day):

0 – 1 liquid stools, no blood	_____ (0)
Up to 2 semi-formed with small blood or 2-5 liquid	_____ (5)
Gross bleeding or ≥ 6 liquid or nocturnal diarrhea	_____ (10)
	Total _____

Subject Functioning- General well-being

No limitation of activities, well	_____ (0)
Occasional difficulty in maintaining age appropriate activities, below par	_____ (5)
Frequent limitation of activity, very poor	_____ (10)
	Total _____

History Score _____ **(Max 30)**

****

LABORATORY SCORE

HCT(%)	**≤ 10 yrs:**	≥ 33	____ (0)	**Males 11-14:**	≥ 35	____ (0)
		28-32	____ (2.5)		30-34	____ (2.5)
		< 28	____ (5)		< 30	____ (5)
	Females 11-19	≥ 34	____ (0)	**Males 15-19:**	≥ 37	____ (0)
		29-33	____ (2.5)		32-36	____ (2.5)
		< 29	____ (5)		< 32	____ (5)
ESR (mm/hr)		< 20	____ (0)			
		20-50	____ (2.5)			
		> 50	____ (5)			
Albumin (g/dL)		≥ 3.5	____ (0)			
		3.1-3.4	____ (5)			
		≤ 3.0	____ (10)			

Laboratory Score_____**(Max 20)**

GROWTH SCORE

Weight

Weight gain or voluntary weight stable/loss	_____ (0 points)
Involuntary weight stable, weight loss 1-9 %	_____ (5)
Weight Loss ≥ 10 %	_____ (10)

Total _____

Height

At diagnosis (Refer to percentile chart):

< 1 channel decrease	_____ (0)
≥ 1 and < 2 channel decrease	_____ (5)
≥ 2 channel decrease	_____ (10)

OR **Total** _____

Follow-up (Refer to growth velocity chart):

Height velocity	≥ -1 SD	_____ (0)
Height velocity	< -1 SD and > -2 SD	_____ (5)
Height velocity	≤ -2 SD	_____ (10)

Total _____

Growth Score _____ **(Max 20)**

****

PHYSICAL EXAMINATION SCORE

Abdomen

No tenderness, no mass	_____ (0)
Tenderness or mass without tenderness	_____ (5)
Tenderness, involuntary guarding, definite mass	_____ (10)

Total _____

Perirectal disease

None, asymptomatic tags	_____ (0)
1-2 indolent fistula, scant drainage, no tenderness	_____ (5)
Active fistula, drainage, tenderness or abscess	_____ (10)

Total _____

Physical Examination Score _____ **(Max 20)**

****

Extraintestinal Manifestation SCORE

(Fever ≥ 38.5°C for 3 days over past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)

None	_____ (0)
One	_____ (5)
≥ Two	_____ (10)
	Total _____

HISTORY SCORE	_____
LABORATORY SCORE	_____
GROWTH SCORE	_____
PHYSICAL EXAMINATION SCORE	_____
EXTRAINTESTINAL MANIFESTATION SCORE	_____
TOTAL PCDAI SCORE	_____

6.14. Appendix 14: Crohn's Disease Activity Index (CDAI)

WORKSHEET

	Site Number	Subject Number
Protocol No. CNTO1275CRD3004 EudraCT No. 2019-004225-24 IND - 11632	Q 3 7 -	1

6.14.1. PATIENT DIARY CARD

Instructions:

1. Record each bowel movement after going to the bathroom.
2. Record scores for abdominal pain and well-being each day before going to bed (describe the average pain or well-being for that day).
3. If you have a fever on any day, enter the temperature if above over 100°F/ 37.8°C (oral) or 101°F/ 38.3° C (rectal)

		Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Date:								
1. Number of stools	a. normal stools							
	b. very soft/ liquid stools							
2. Abdominal pain (average) 0 = none 2 = moderate 1 = mild 3 = severe								
3. General well-being (average) 0 = generally well 1 = slightly under par 2 = poor 3 = very poor 4 = terrible								
4. Fever over 100°F/ 37.8°C (oral) or 101°F/ 38.3° C (rectal)								

5. In the past 24-hours, did you take any anti-diarrheal or opiate medication for diarrhea. Yes or No

Click the box next to all anti-diarrheal or opiate medications that you took in the last 24- hours:

Loperamide (Imodium)

Diphenoxylate (Lomotil, Lomocot)

Bismuth subsalicylate (Kaopectate, Pepto-Bismol)

Cholestyramine (Questran, Prevalite)

Codeine (Cocet, Tylenol with codeine, Vopac)

Eluxadoline (viberzi)

Other anti-diarrheal

Other opiate

6.15. Appendix 15 Placebo Meta-analysis Details

6.15.1. Identification of Studies

For the purpose of the meta-analyses for the placebo rate to be descriptively compared with the US-Specific Primary Endpoint, **Clinical Remission at Week M-44**, the studies will be chosen from published data (using the Certara Crohn's Disease Clinical Database), that meet the following inclusion and exclusion criteria:

INCLUSION

1. Phase 3 global clinical studies
2. Enrolled patients with moderate to severe Crohn's disease based Crohn's disease activity index (CDAI) score 220 - 450 or as determined by stool frequency and abdominal pain, at baseline
3. Placebo group at maintenance based on responders at the induction period.
4. Have clinical remission endpoint defined as CDAI ≤150 or CDAI <150 (without requiring sustained remission at multiple timepoints)
5. Have data from the placebo group at a timepoint that is approximately 1 year after treatment
6. Compounds under study which were approved for the treatment of Crohn's disease in adults

EXCLUSION

1. Studies where significant systematic concentrations are reported after 25 weeks (this may need to be determined by clinical review)

6.15.2. Method for Meta Analysis

The meta-analysis for the historical placebo control used the 'metafor' package in R. The meta-analytic models were fitted with the rma.uni() function.

For a set of i = 1, 2, …k independent studies, the random-effects model was fitted using DerSimonian-Laird (DL) random-effects model using the rma.uni ( ) function with:

rma(yi=p,sei=se,mods=~1,method="DL").

Weighted estimation (with inverse-variance weights) is the default and was used where

$\bar{\theta}_w = \sum_{i=1}^{k}(w_i\theta i)/\sum_{i=1}^{k} wi$

$\overline{\theta_w}$ is the weighted average of the true outcomes in the set of k studies, with weights equal to wi = 1/vi (the 'inverse-variance' method).

6.16. Appendix 16 Bayesian Sensitivity Analysis Details

This Appendix describes the Bayesian model used for the US-Specific Supportive Analysis 2 of the US-Specific Primary Estimand.

6.16.1. Adult Placebo Patient Level Data

Let Y_{AUij} be the primary outcome measure of patient i in study j, where r_{AUj} is response rate in the placebo group.

$$Y_{AUij} \sim Bernoulli\ (r_{AUj})$$

The response rate is modeled via a logit scale with baseline covariates from this study:

$$\theta_{Aij} = log\left(\frac{r_{AUij}}{1 - r_{AUij}}\right)$$

$$\theta_{Aij} = \beta_{0j} + \beta_{1j} X_{1Aij} + \cdots + \beta_{cj} X_{cAij}$$

$$\beta_{kj} \sim Norm(\mu_k, \tau_k) \qquad k = 0, 1, \ldots, c$$

where study specific parameters will be modeled at the population level, via

$$\mu_k \sim Norm(0, \tau) \qquad k = 0, 1, \ldots, c$$

$$\tau_k \sim Gamma(a, b) \qquad k = 0, 1, \ldots, c$$

where the hyperparameters are set to non-information priors, i.e. $\tau = 0.001, a = 0.001, b = 0.001$.

This model could be used to estimate the response rate given different covariate values based on various studies. It should be noted that only covariates that are statistically significantly associated with the outcome measure will be used for this purpose.

6.16.2. Covariate Adjusted Response Rate

Based on the model built from the adult placebo patient level data in Section 6.16.1, we can obtain a covariate adjusted response rate to match the population similar to the current CNTO1275CRD3004 study. More specifically, we use the average value for each covariate based on CNTO1275CRD3004 study, $\bar{X}_{cP}$, as input to the population level model described in Section 6.16.1, and calculate the covariate adjusted response rate r_{AUP}:

$$\theta_{AUP} = log\left(\frac{r_{AUP}}{1 - r_{AUP}}\right)$$

$$\theta_{AUP} = \mu_0 + \mu_1 \bar{X}_{1P} + \cdots + \mu_c \bar{X}_{cP}$$

6.16.3. Adult Placebo Study Level data

r_{AVj} is the proportion of patients on placebo in clinical remission from study *j* with study level data.

Then we have

$$Y_{AVij} \sim Bernoulli\ (r_{AV})\ and\ i = 1, \dots, n\ j = 1, \dots, m$$

$$\theta_{AVj} = log\left(\frac{r_{AVj}}{1 - r_{AVj}}\right)$$

$$\theta_{AVj} \sim Norm(\mu_{AV}, \tau_{AV})$$

The hyperparameters will be modeled with non-informative priors,

$$\mu_{AV} \sim Norm(0, \tau_A), \tau_{AV} \sim Gamma(a, b)$$

where the hyperparameters are set to non-information priors, i.e. $\tau_A = 0.001, a = 0.001, b = 0.001$. The overall proportion of patients on placebo from the studies with study level data, $r_{AV,}$ is given as

$$\mu_{AV} = log\left(\frac{r_{AV}}{1 - r_{AV}}\right)$$

6.16.4. Joint Adult Placebo Model

The joint adult model incorporates both r_{AUP} and r_{AV} with a weight of *w,* such that:

$$r_{AJ} = (1 - w) r_{AV} + w\, r_{AUP}$$

$$w \in [0, 1]$$

6.16.5. Pediatric Model

Let Y_{Pi} be the primary outcome measure of pediatric patient *i*, where r_P is response rate in the current CNTO1275CRD3004 study.

$$Y_{Pi} \sim Bernoulli\ (r_P)$$

6.16.6. Posterior Estimate

Based on the models described above, the posterior distribution of the difference in outcome measures between the treatment groups, i.e. $r_P - r_{AJ}$, and its corresponding 95% credible interval will be constructed.

6.17. Appendix 17 Exposure Optimization: An Exploratory Substudy

6.17.1. Hypothesis

The primary research hypothesis is that achieving exposures similar to those who responded to treatment in adult studies of ustekinumab in Crohn's disease will lead to response in pediatric participants, without a change to the safety profile.

6.17.2. Objectives

The primary objectives of this exploratory substudy are:

- To determine if a q4w dose regimen in participants who have induction nonresponse or LOR and low 8-week steady-state ustekinumab trough concentrations during maintenance will result in steady-state ustekinumab trough exposures ≥1.4 ug/mL.
- To evaluate the safety and immunogenicity of ustekinumab administered q4w in participants who have induction nonresponse or LOR and low ustekinumab exposure.

The secondary objective of this substudy is:

- To evaluate the efficacy of ustekinumab administered q4w in participants who have induction nonresponse or LOR and low ustekinumab exposure

6.17.3. Study Design

This is an exploratory sub-study within a Phase 3, multicenter, interventional study of ustekinumab in pediatric Crohn's disease (CNTO1275CRD3004). Participants who lose response during Study CNTO1275CRD3004 and have an 8 weeks post-dose serum ustekinumab concentration of <1.4 µg/mL during the maintenance period (at the Week M-8 or Week M-32 visit) will be eligible to enroll in this optional, open-label q4w substudy. Loss of response is defined in the main protocol. The Week M-8 and Week M-32 timepoints were selected to define participants with low exposure because ustekinumab trough concentration at these timepoints reflects an 8-week steady-state trough concentration for participants in both q8w and q12w dosing arms. Participants who fail to respond by Week M-8 (meeting Early Escape Criteria) and have low exposure (steady-state 8-week ustekinumab trough concentration <1.4 µg/mL drawn at the Week M-8 visit are also eligible to enroll in the substudy. In the case where a participant meets Early Escape criteria at Week M-8, but opts to await the Week M-8 trough concentration to determine substudy eligibility, the investigator may prescribe rescue medications if the investigator feels that this is in the participant's best interest.

All eligible participants must sign informed consent forms (based on requirements) prior to entry into the substudy. After enrolling in the substudy, participants, investigative sites, and study teams will remain blinded to the participant's initial dosing regimen (q8w or q12w).

During this substudy, ustekinumab will be administered subcutaneously q4w for a total duration of 16 weeks (5 doses) or through the Week M-40 visit, whichever is the longer duration of exposure. After entering the substudy, the frequency of study visits will be increased to q4w. Dose will be calculated the same way, only the dosing interval will change. Participants will continue to

follow the study protocol SoA. In addition to the main study schedule, participants in the substudy will have safety and PK visits added in between the main study visits, to ensure safety follow-upq4w. During these additional visits, weight and height will be obtained for BSA dosing, vital signs assessed, AEs and concomitant medications reviewed, and a serum ustekinumab trough concentration and safety labs obtained. A PCDAI/sPCDAI score will be recorded at each visit. If the final study visit occurs after Week M-44, a physical exam will be conducted, stool collected for fecal calprotectin/fecal lactoferrin, and serum obtained for antibodies to ustekinumab.

Any participant who is not in clinical response 16 weeks after entry into the substudy will be discontinued from the study intervention and complete a safety follow-up approximately 20 weeks after the last administration of study intervention. If a participant, <18 years of age and in the opinion of the investigator, would benefit from further treatment at the completion of the substudy, the participant may be enrolled in an LTE study; this study is described in a separate protocol and will require separate consent/assent. Dosing interval in the LTE will be based upon steady-state ustekinumab trough concentrations in the substudy. The ninety-fifth percentile of the average steady-state concentration for ustekinumab following q8w dosing ranges in the adult IM-UNITI and UNIFI studies was 7.2 µg/mL. After 3 doses at q4w dosing interval, if the steady-state ustekinumab trough concentration is > 7.2 µg/mL, the participant will not be permitted to continue q4w dosing in the LTE and must return to an q8w dosing interval if enrolling in the LTE.

A DBL for the Exposure Optimization Substudy will occur, when all participants have either completed their 16 week dosing administration or terminated study participation prior to completing 16 week dosing administration, or all participants who are not participating in the LTE have completed their final safety visit (20 weeks after the last administration of study intervention).

The same DMC as in the main study will be commissioned for this substudy and will be established to monitor safety data on an ongoing basis (Main Protocol Section 9.6) until all participants completed their 16 week dosing administration or terminated the study prior to the completion of their 16 week dosing administration. The DMC responsibilities, authorities, and procedures will be documented in the DMC charter.

6.17.4. Endpoints

- Adverse events, SAEs including serious infections, AEs leading to discontinuation of study intervention, and AEs of special interest (malignancy, active TB, or opportunistic infection).
- Proportion of participants with a serum steady-state ustekinumab trough concentration ≥1.4 µg/mL from initiation of the q4w dose regimen to Week M-44 (or 16 weeks of q4w exposure, whichever is longer).
- Median steady-state ustekinumab trough after 16 weeks of q4w dose regimen.
- Proportion of participants developing antibodies to ustekinumab at Week M-44 (or 16 weeks of q4w exposure, whichever is longer).
- Change in the PCDAI from initiation of the q4w dose regimen to Week M-44 (or 16 weeks of q4w exposure, whichever is longer).

- Proportion of participants in clinical response at Week M-44 (or 16 weeks of q4w exposure, whichever is longer).
- Proportion of participants in clinical remission over time
- Proportion of participants in clinical response over time
- Change in selected laboratory analytes (ie, hematology, chemistry, including serum CRP, fecal calprotectin/fecal lactoferrin) from the initiation of the q4w dose regimen to Week M-44 (or 16 weeks of q4w exposure, whichever is longer).

6.17.5. Sample Size Considerations

It is expected that approximately 30 of the participants will experience a LOR based on the adult data from Study CNTO1275UCO3001. Furthermore, the sponsor estimates that 1/3 of these participants will have an 8 weeks post-dose level of ustekinumab of <1.4 µg/mL (at Week M-8 or M-32). Therefore, based on a sample size of 90 participants, the sponsor expects approximately 9 participants will be eligible for the substudy, and approximately 5 additional participants who do not achieve induction response by Week M-8 may also be eligible.

6.17.6. Statistical Analyses

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, median, interquartile range (IQ), minimum and maximum, as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Graphical data displays (eg, line plots) may also be used to summarize the data.

6.17.6.1. Efficacy Analyses

Efficacy endpoints will be summarized for all participants who receive at least 1 dose of ustekinumab in the substudy. All data will be reported as observed analysis. Data will not be imputed for any missing values and no ICE rules will be applied.

6.17.6.2. Pharmacokinetic Analyses

PK will be summarized for all participants who receive at least 1 dose of ustekinumab in the substudy. Descriptive statistics of the serum ustekinumab concentrations will be calculated at each sampling time point. All concentrations below the lowest quantifiable concentration or missing.

6.17.6.3. Immunogenicity Analyses

The incidence of anti-ustekinumab antibodies will be summarized for all participants who receive at least 1 dose of ustekinumab in the substudy and have appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 sample obtained after their first dose of ustekinumab in the substudy).

6.17.6.4. Safety Analyses

Safety data will be summarized for all participants who receive at least 1 dose of ustekinumab in the substudy. For participants who entered the substudy, safety parameters will be summarized from Week I-0 through the end of follow-up, and from the initiation of the q4w dose regimen to the end of follow-up.

The following analyses will be used to assess the safety of participants in the substudy: frequency and type of AEs, serious adverse events, reasonably related AEs as assessed by the investigator, AEs leading to discontinuation of study intervention, infections (including serious infections, and infections requiring oral or parenteral antimicrobial treatment), and injection-site reactions.

Safety analyses will include descriptive summaries of AEs and laboratory parameters.

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