

Janssen Research & Development**Statistical Analysis Plan**

A Phase 3 Study of the Efficacy, Safety and Pharmacokinetics of Ustekinumab as Open-Label Intravenous Induction Treatment Followed by Randomized Double-Blind SC Ustekinumab Maintenance in Pediatric Participants with Moderately to Severely Active Ulcerative Colitis
UNIFI Jr

Protocol CNTO1275PUC3001; 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	04 April 2025	Sections 1 and 1.1: Minor clarification	Clarification
		Sections 1.1.1 and 1.1.2: Added additional endpoints	New analysis
		Section 1.2: Added PK interim analysis in study design, updated sample size, study enrollment strategy and timing of DBL, and minor clarification	Address FDA's comments and clarification
		Sections 1.2.1 and 1.2.2: Minor modifications	Modifications to align with protocol
		Section 1.2.3: Minor clarification	Clarification
		Section 1.2.5.2: Minor clarification	Clarification
		Section 3: Updated sample size, study enrollment strategy, and the precision calculation	Address FDA's comments
		Section 4: Added additional populations (analysis sets) for analysis	Clarification and new analysis
		Section 5: Added PK interim analysis	Clarification
		Section 5.1: Added statement for the statistical method used to construct the 95% CI of a proportion	Clarification of statistical method to address FDA's comments
		Section 5.1.1.: Added statement for assignment of visit number.	Clarification
		Section 5.2: Minor clarification	Clarification
		Section 5.3.1: Updated days used for calculation in the Mayo scores are done programmatically rather than the sites selecting the days used	Updated selection for days used in the Mayo score
		Section 5.3.2: Modified Global Primary Estimand 1 to 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 5.3.3: Updates to Supplementary Estimands Sections: - Section 5.3.3.1: Updated Global Supplementary Estimand 2 to use treatment policy strategy - Removed Global Supplementary Estimand using composite strategy	Address FDA's comments and minor modifications

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
		Section 5.3.3.2: Changed the prior Global Primary Estimand 1 to Global Supplementary Estimand 3	
		Section 5.3.4.1: Minor clarification	Clarification
		Section 5.3.4.2.1: Updated US-Specific Supplementary Estimand 2 to use treatment policy strategy	Address FDA's comments
		Removed composite strategy from original Section 5.3.4.2.1.	Address FDA's comments
		Section 5.3.4.2.2: Moved prior primary estimand analysis to this section	Address FDA's comments
		Section 5.3.4.3: Updated sections for global sensitivity analysis: - Section 5.3.4.3: Moved original wording for sensitivity analysis to Section 5.3.4.3.1. - Section 5.3.4.3.1: Added section for sensitivity analysis 1 - Sections 5.3.4.3.2: Added additional covariates	Address FDA's comments
		Section 5.3.6: Modified US-specific Primary Estimand to 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	To be consistent with the updated Primary Estimands
		Section 5.3.7: Updates made to the following Supplementary Estimands sections: - Section 5.3.7.1: Updated US-specific Supplementary Estimand 1 to use treatment policy strategy, and minor clarifications - Removed US-specific Supplementary Estimand using composite strategy - Section 5.3.7.2: Changed the original US-specific Primary Estimand 1 to US-specific Supplementary Estimand 2	To be consistent with the updated Primary Estimands and address FDA's comments
		Section 5.3.8.2.1: Updated estimand to use treatment policy strategy	Address FDA's comments
		Removed composite strategy from original Section 5.3.9.2.1.	Address FDA's comments

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
		Section 5.3.8.1: Added adjusted risk difference for US-specific Primary Estimand analysis	
		Section 5.3.8.2.3: Moved prior primary estimand analysis to this section	Address FDA's comments
		Section 5.3.8: Updated sections for US-specific sensitivity analysis: - Section 5.3.8.3: Moved original Sensitivity Analysis wording to its own section 5.3.8.3.1 - Sections 5.3.8.3.2: Added additional covariates - Section 5.3.8.3.3: Added Global Sensitivity Analysis 3: tipping point analysis	Address FDA's comments
		- Section 5.3.8.4: Added Supportive Analysis - Section 5.3.8.4.1: 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 5.3.8.4.2: 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	Address FDA's comments
		Section 5.4.1: Addition of global secondary endpoint, Histologic-endoscopic mucosal improvement at Weeks I-8	Global secondary endpoint added for induction and maintenance
		Section 5.4.2: - Addition of US-specific secondary endpoint, Histologic-endoscopic mucosal improvement at Weeks I-8. - Clinical remission at Week M-44 and not receiving corticosteroids for at least 90	US-specific secondary endpoint added for induction and maintenance, and change in the population for clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
		days prior to Week M-44 among participants who received corticosteroids at Week I-8 has changed to 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	
		Sections 5.4.4: Updated estimands for ICE handling strategy	To be consistent with the updated Primary Estimands
		Removed section on supplementary estimands for the secondary endpoints	Removed as results will be the same as the estimands for secondary endpoints
		Section 5.4.5.1.1: Minor clarification	Clarification
		Sections 5.5.2.1 and 5.5.2.2: Moved histologic-endoscopic mucosal improvement at Week I-8 to secondary endpoints and minor clarification, and changed histologic assessment analyses as exploratory to be reported in a separate report except Geboes	Moved an endpoint to secondary endpoints and minor clarification
		Section 5.5.2.3: Added shift tables for nutritional parameters	New analysis
		Section 5.5.4: Added additional analysis for IMPACT-III	New analysis
		Sections 5.5.6 and 5.5.7: Minor clarification	Clarification
		Section 5.5.9: Added analysis using Mayo diary data	New analysis
		Section 5.5.10: Analyses of Missing Endoscopy Score at Week M-44: removed summary by “reason why it was not done” and updated Sensitivity Analysis 2	Analyses as previously described included by mistake.
		Section 5.5.11: Supplementary Analyses Due to COVID-19: section removed (no data was missing due to COVID-19)	Removed since analyses will be redundant.
		Sections 5.5.12.1, 5.5.12.2, and 5.5.12.3: Moved from original Sections 5.11, 5.12, and 5.13	Moved section
		Section 5.5.13: Added new section Health Economics for UC-related hospitalizations and surgeries	Added health economic section for UC-related hospitalizations and surgeries
		Section 5.5.14: Moved from original section 5.5.13 and added additional definitions	Additional definitions were added

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
		Section 5.5.15: Updated estimands for ICE handling strategy and how missing data is handled for UC-related hospitalizations and surgeries	To be consistent with the updated Primary Estimands and clarification
		Section 5.6: Minor clarification	Clarification
		Section 5.6.1: Added new analysis for subjects who missed doses through Week M-44	Added new analysis for subjects who missed doses
		Section 5.6.2: Updated analysis sets, added one subgroup analysis and other minor clarification	Clarification and new analysis
		Section 5.6.3.1: Added change from baseline, shift tables and Hy's Law for clinical lab tests, changed categories for ALT and AST	Clarification, updates and new analysis
		Section 5.6.3.2: Added thresholds to identify abnormal postbaseline values.	Clarification
		Sections 5.7.1 and 5.7.2: Minor clarification	Clarification
		Section 5.7.7: Added one subgroup analysis	New analysis
		Section 5.8: Minor clarification	Clarification
		Section 5.8.1: Added PK interim analysis	New analysis
		Section 5.8.2: Moved from prior section 5.8.1	Added new section
		Section 6.1: Added to list of abbreviations	Added additional list of abbreviations
		Section 6.3: Added additional analysis, including weight z-score, changed to BMI from BSA	New analysis
		Section 6.5: Minor clarification and updated analysis set	Clarification
		Section 6.11: Minor clarification	Clarification
		Section 6.15: Added placebo meta-analysis details Section 6.15.1: Updated criteria for identification of studies Section 6.15.2: Title update	Added per FDA's request
		Section 6.17: Added Appendix 17 for Bayesian approach details	New analysis
		Section 6.18: Moved from Section 6.17	Moved original Section 6.17 to new section
		Section 7.0: Additional references were added	Added references

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 CNTO1275PUC3001, including 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. PK interim analyses will be described in Section 5.8.1. Analysis of data for the substudy will be described in Section 5.9.

1.1. Objectives and Endpoints

The primary objective and primary endpoint in this study is to assess clinical remission in moderately to severely active ulcerative colitis (UC) in pediatric participants. Please note the assessment timepoint for the primary objective and primary endpoint will be different for countries outside of the United States (global timepoint of Induction Week 8 [Week I-8]) and the United States (US-Specific timepoint 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 refers to the US-specific objectives and endpoints.

The objectives and endpoints for the Exposure Optimization Substudy are provided in Section 6.17.2 respectively.

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 UC.	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 UC.	- 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. - Reactions temporally associated with an intravenous (IV) infusion (induction period) and subcutaneous (SC) injection-site reactions (maintenance period).

Global Objectives	Global Endpoints
To evaluate ustekinumab exposure (pharmacokinetic [PK]).	Serum ustekinumab concentrations.
Secondary	
To evaluate the efficacy of IV ustekinumab during the induction period.	- Clinical response at Week I-8. - Symptomatic remission at Week I-8. - Clinical remission at Week I-8 as assessed by the Pediatric Ulcerative Colitis Activity Index (PUCAI) score. - Endoscopic improvement at Week I-8. - Histologic-endoscopic mucosal improvement at Week I-8.
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. - Symptomatic remission at Week M-44. - Clinical remission at Week M-44 as assessed by the PUCAI score. - Endoscopic improvement at Week M-44. - Corticosteroid-free clinical remission at Week M-44. - 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. - Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8. - Histologic-endoscopic mucosal improvement at Week M-44.
Other	
- To evaluate the effects of ustekinumab on the following factors: - Histological assessments - Serum and fecal biomarkers - Growth - Nutritional parameters	- Histologic improvement and remission based on the Geboes score, Robarts Histopathology Index (RHI) and Nancy Index (NI). Change from baseline in: - C-reactive protein (CRP) concentrations. - Fecal calprotectin and fecal lactoferrin levels.

Global Objectives	Global Endpoints
	- 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 UC-related quality of life (QoL)	Change from baseline in IMPACT-III scores at Week I-8 and 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 UC.	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 UC.	- AEs, SAEs, AEs leading to discontinuation of study intervention, and AEs of interest (eg, infections). - Clinical laboratory, hematology and chemistry. - Reactions temporally 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 response at Week I-8. - Symptomatic remission at Week I-8. - Clinical remission at Week I-8 as assessed by the PUCAI score. - Endoscopic improvement at Week I-8. - Histologic-endoscopic mucosal improvement at Week I-8.

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.	- Symptomatic remission at Week M-44. - Clinical remission at Week M-44 as assessed by the PUCAI score. - Endoscopic improvement at Week M-44. - Corticosteroid-free clinical remission at Week M-44. - 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. - Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8. - Histologic-endoscopic mucosal improvement at Week M-44.
Other	
- To evaluate the effects of ustekinumab on the following factors: - Histological assessments - Serum and fecal biomarkers - Growth - Nutritional parameters	- Histologic improvement and remission based on the Geboes score, Robarts Histopathology Index (RHI) and Nancy Index (NI). 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 UC-related QoL	Change from baseline in IMPACT-III scores at Week I-8 and Week M-44 for participants ≥ 10 years of age at Week I-0.

For participants with body weight <40 kg:

- 250 mg/m² 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 (Section 1.2.5) based on their response status (clinical response defined as a decrease from baseline in the Modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1). Thus, participants will be randomized in a blinded fashion in a 1:1 ratio stratified by response status at Week I-8 (induction responders and induction nonresponders) 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/m² 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/m² 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.

Beginning at Week M-8 for induction responders and beginning at Week M-16 for delayed responders (induction nonresponders who are in partial Mayo response [ie, a decrease from induction baseline of ≥2 in the partial Mayo score] 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 for an open-label Exposure Optimization Substudy with dosing interval adjustment to every 4 weeks (for details, see Section 6.16). 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

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 UC are allowed at the start of this study: oral 5-aminosalicylate (5-ASAs), oral corticosteroids, immunomodulators (ie, 6-MP, AZA, MTX), and single antibiotics for the treatment of UC. 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 UC should remain stable (without initiation or increase from baseline 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 UC 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 UC 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 or completed the 16-week dosing period (for subjects in the exposure substudy) and transitioned into the LTE study or completed their final safety visit (approximately 20 weeks after the administration of last study intervention), 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 (Protocol, Section 1.3).

Two DBLs are planned for this study:

1. **DBL1:** Occurs after all participants have either completed their Week M-44 visit or terminated study participation prior to Week M-44.
2. **DBL2:** Occurs after all participants including those in the Exposure Optimization Substudy have completed their study participation.

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 the CNTO1275CRD3004 and CNTO1275PUC3001 studies (combined) complete the Week M-8 visit (Section 5.8.1).

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 5.8.2) for both pediatric ustekinumab inflammatory bowel disease studies (CNTO1275PUC3001 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 the study) will review the results of the PK interim analysis (Section 5.8.1) to evaluate the ustekinumab dosage and safety for participants <40 kg (as measured at Week I-0). The DMC responsibilities, authorities, and procedures will be documented in the joint DMC charter for CNTO1275PUC3001 and CNTO1275CRD3004.

1.2.1. Early Escape Criteria (Induction Nonresponders)

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

- Induction nonresponders who do not achieve clinical response based on a partial Mayo response by Week M-8 (ie, a decrease from induction baseline of ≥ 2 in the partial Mayo score) 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 they have low exposure and would like to participate in the optional Exposure Optimization Substudy:
 - If a participant is documented to have low exposure (defined as a ustekinumab trough level < 1.4 $\mu\text{g/mL}$ 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 Section 6.17). If determined to be medically appropriate in the judgment of the investigator, participants who meet the Early Escape criteria may receive approved rescue therapies (Protocol Section 4.1.4) 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 $\mu\text{g/mL}$ 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 based on the partial Mayo score. 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:

- An increase in the partial Mayo score of at least 2 points above the reference partial Mayo score, and an absolute partial Mayo score ≥ 4 , at 2 consecutive visits at least 7 days apart. The reference partial Mayo score is Week M-0 for induction responders and Week M-8 for delayed induction responders.

OR

- An absolute partial Mayo score ≥ 7 points, at 2 consecutive visits at least 7 days apart, after Week M-0 for induction responders and Week M-8 for delayed induction responders.

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 (Section 6.18).

1.2.2.1. Exposure Optimization Substudy (Loss of Response and Low Exposure During the Maintenance Period)

Participants who have LOR during the maintenance period of the main study and have a trough serum ustekinumab concentration of $<1.4 \mu\text{g/mL}$ during the maintenance period (M-8 or M-32) will be eligible to enroll in this optional, open-label Exposure Optimization Substudy (for details, see Section 6.16). If the participant chooses not to enroll in the substudy, the participant can be withdrawn from study participation at the discretion of the investigator. All eligible participants must sign informed consent form/assent form (based on intuitional requirements) prior to entry into the substudy.

1.2.3. Dose Adjustment During the Maintenance Period

Beginning at Week M-8 for induction responders and beginning at Maintenance Week 16 (Week M-16) for delayed responders (induction nonresponders who are in partial Mayo response at Week M-8), participants who experience LOR (Section 1.2.2) may be eligible for a 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 a confirmed 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 partial Mayo response is achieved. The first LOR visit must be at the study site, and subsequent LOR visits may be conducted at the study site or remotely, at the investigator's clinical discretion.

Participants who have lost response will be assessed 16 weeks after dose adjustment. If the participant is not in partial Mayo response (ie, a decrease from induction baseline of ≥ 2 in the partial Mayo score) at that time, and does not have low exposure, the participant will be withdrawn from study intervention and return for the 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 or be withdrawn from study participation at the discretion of the investigator. Also, 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.

* Low exposure is defined as an 8-week, steady-state ustekinumab trough concentration <1.4 µg/mL at either Week M-8 or Week M-32, whichever occurs closer to the LOR.

1.2.4. Rescue Medication

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

Rescue therapies include:

- Oral and rectal corticosteroids
- Oral and rectal 5-ASA compounds
- Antibiotics for UC-specific therapy (more than one antibiotic for UC-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 UC 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 modified Mayo score with local read of the endoscopy subscore.

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 [$<1.4 \mu\text{g/mL}$] or normal).
- If a participant's ustekinumab trough concentration at the end of the Exposure Optimization Substudy (after at least 3 doses) is $>7.2 \mu\text{g/mL}$, the site will be informed and the participant will not be able to continue q4 week dosing, but may continue q8w dosing in the LTE (see Exposure Optimization Substudy [Section 6.17])

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.

The sponsor will be blinded to maintenance treatment assignment until after the 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 5.8.1 for further details).

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 serious unexpected associated adverse reactions (SUARs). 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).

Induction responders and delayed responders who lose response during maintenance and have a low steady state, 8-week trough ustekinumab concentration will receive open-label q4w dosing under close surveillance.

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 UC. A determination of the efficacy of ustekinumab for the treatment of pediatric UC will be made based on the totality of evidence from an assessment of the global primary and secondary endpoints. This totality of evidence will be presented descriptively.

The **US-Specific** primary hypothesis, used for the United States, is:

The primary hypothesis is that ustekinumab is an effective therapy in pediatric participants with moderately to severely active UC. A determination of the efficacy of ustekinumab for

the treatment of pediatric UC will be made based on the totality of evidence from an assessment of the US-specific 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 100 participants will be enrolled in this study. All participants entering maintenance will be randomized to one of two maintenance doses. The study will continue enrolling until at least 80 responders (ie, induction responders at Week I-8) have been attained. Main analysis will be conducted by induction responders at Week I-8, and for selected endpoints, analysis will be conducted for the responder population (see Section 5.5.6). 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 **global** primary endpoint is provided in Section 3.1.

The sample size determination for the **US-Specific** primary endpoint is provided in Section 3.2.

3.1. Sample Size Determination for the Global Primary Endpoint

With a sample size of approximately 100 participants enrolled (ie, 80 responders [induction responders at Week I-8] 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 7.1% (assuming the proportion of participants in clinical remission is 15.5% at Week I-8 [based on a weighted average from the biologic-failure population (14.5%; ~6 mg/kg treatment group) and from the non-biologic-failure population (24.4%; ~6 mg/kg treatment group)] from the ustekinumab adult study CNTO1275UCO3001). Table 2 provides the precision based on different assumptions for the proportion of participants who are biologic failures.

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

Proportion of biologic failure	Weighted Average of Participants in Clinical Remission	Precision
90%	15.5%	7.1%
75%	17.0%	7.4%
50%	19.5%	7.8%

3.2. 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 80 participants will be responders (ie, induction responders at Week I-8). Assuming 90% of the participants in this study are biologic failures, the precision in estimating the true proportion of pediatric participants in clinical remission at Week M-44 among all responders is 10.8% and among clinical responders at Week I-8 is 11.2% (assuming the proportion of participants in clinical remission is 41.6% at Week M-44 [based on a weighted average from the biologic-failure population (40.7%; 90 mg q8w treatment group) and from the non-biologic-failure population (49.4%; 90 mg q8w treatment group)] from the adult study CNTO1275UCO3001). [Table 3](#) provides the precision based on different assumptions for the proportion of participants who are biologic failures.

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

Proportion of biologic failure	Weighted Average of Participants in Clinical Remission	Precision based on induction responders at Week I-8	Precision based on all responder
90%	41.6%	11.2%	10.8%
75%	42.9%	11.2%	10.9%
50%	45.1%	11.3%	10.9%

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 Clinical Responder Analysis Set (FASCR)	All participants who were randomized into the maintenance period (Week M-0) of the study and were in clinical response as determined by the IWRS 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 as determined by the IWRS 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 (SAF)	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 (Week M-0) 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 (Week M-0) of the study and were in clinical response as determined by the IWRS to ustekinumab induction therapy

Analysis Sets	Description
	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 Clinical Responder Analysis Set (PKASCR)	All participants who were randomized into the maintenance period of the study (Week M-0) and were in clinical response as determined by the IWRS 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 as determined by the IWRS 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 sample collection in maintenance.
Immunogenicity Analysis Set (IAR)	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 (Week M-0) of the study and were in clinical response as determined by the IWRS to ustekinumab induction therapy at Week I-8, received at least 1 administration of study intervention 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 as determined by the IWRS to ustekinumab therapy at Week I-8 or at Week M-8, and have received at least 1 administration of study intervention 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	All participants who entered the exposure optimization substudy and received at least 1 administration of study intervention during the substudy

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.

Sections 5.1 through Section 5.8 summarize the planned statistical analyses at DBL1, including the primary, secondary and tertiary efficacy endpoint analyses (Sections 5.3, 5.4 and 5.5), safety analyses (Section 5.6: ie, extent of exposure, AE, Laboratory, Vital Signs and Physical Examination Findings), other analyses (Section 5.7: ie, PK, immunogenicity, biomarker), and interim analysis (Section 5.8: ie, PK interim analysis, DMC).

Section 5.9 provides the analyses for the 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 Mayo endoscopy subscore as obtained during the central review of the video of the endoscopy (Section 5.3.1) will be used for all efficacy analyses involving the Mayo endoscopy subscore. Additionally, for all endpoints that require achievement of a Mayo endoscopy subscore of 0 or 1, the endpoints will be considered to not have been met if friability is present on endoscopy.

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

5.1.1. Visit Windows

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

A visit number will be assigned to scheduled visits except for the early termination visit. If the early termination visit falls in the protocol-specified window of a scheduled visit and there are not already data for the scheduled visit, the scheduled visit number will be assigned to the early termination visit. If there are already data for the same scheduled visit, those data will be used in lieu of the early termination visit data.

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 administration. If the date of the first study intervention administration is missing or the first study intervention administration 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 due to COVID-19 related reasons)
- Participants who dose adjusted
- 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.

The number (%) of participants with a dose adjustment during the maintenance period and the number of participants who enter the substudy will be summarized for the Safety Randomized Analysis Set (SASR).

A listing of participants will be provided through the end of the study 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 due to COVID-19 related reasons)
- Participants who were unblinded during the maintenance study period (other than substudy unblinding)

5.3. Primary Endpoint Analysis

Please 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 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 as determined by the IWRS.

5.3.1. Definition of Endpoint

Clinical remission is defined by Mayo subscores as: A stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.

Mayo Score

The Mayo score ([Schroeder, 1987](#)) was developed from the criteria of Truelove and Witts ([Truelove and Witts, 1955](#)) for mild, moderate, and severe UC; and from the criteria of Baron ([Baron, 1964](#)) for grading the mucosal appearance.

The Mayo score consists of 4 subscores (Section [6.13](#)):

- Stool frequency
- Rectal bleeding
- Findings of endoscopy
- Physician's global assessment (PGA)

Each subscore is rated on a scale from 0 to 3, indicating normal to severe activity.

The full **Mayo score** is calculated as the sum of the 4 subscores (stool frequency, rectal bleeding, PGA, and endoscopy findings). Thus, the Mayo score may take on values in the range of 0 to 12. A Mayo score of 3 to 5 points indicates mildly active disease; a score of 6 to 10 indicates moderately active disease; and a score of 11 to 12 indicates severe disease.

The **partial Mayo score**, which is the Mayo score without taking into account the findings of endoscopy, is calculated as the sum of the stool frequency, rectal bleeding, and PGA subscores, and may take on values from 0 to 9.

The **modified Mayo score**, which is the Mayo score without the PGA subscore, is calculated as the sum of the stool frequency, rectal bleeding, and endoscopy subscores, and may take on values from 0 to 9.

Due to the requirement for endoscopy findings for the evaluation of the Mayo score, it is not feasible to evaluate the Mayo score at each scheduled visit in the study. Therefore, the Mayo and modified Mayo score will be evaluated at Week I-0, Week I-8 and Week M-44, and the partial Mayo score will be evaluated at the other study visits. Note that the modified Mayo score is not a separate evaluation from the Mayo score as the latter contains all the components that are needed for the calculation of the modified Mayo score.

The following rules will be applied to calculate the Mayo score and partial Mayo score in case of partially missing data (ie, 1-3 of the subscores is missing, but not all 4 subscores) during the induction Phase. For missing subscores, for the Mayo score, the last available subscore values will be carried forward to calculate the Mayo score. For missing subscores for the partial Mayo score, the last available subscore values will be carried forward to calculate the score. If the Mayo score or partial Mayo score cannot be calculated, it will be considered missing (insufficient data) for that visit.

In addition, due to the potential for a substantial number of missing endoscopies at Week M-44 in this pediatric study, the following rules will be applied to calculate the Mayo score in case of partially missing data (ie, 1-3 of the subscores is missing, but not all 4 subscores) during the maintenance period. If the endoscopy subscore is not missing at Week M-44, then for missing subscores for the other Mayo subscores, the last available subscore value will be carried forward to calculate the Mayo score. **If the endoscopy subscore is missing at Week M-44, then the Mayo score cannot be calculated and will be considered missing (insufficient data) for the Week M-44 visit.** Thus, participants with missing endoscopy at Week M-44 will be considered not to be in clinical response or clinical remission, and not to have endoscopic improvement at Week M-44. The modified Mayo score will be calculated in a similar fashion.

Stool Frequency and Rectal Bleeding Subscores

The tablet captures seven days of rectal bleeding data and the number of stools per day prior to each visit at which the partial Mayo score or Mayo score is collected. Three days which are used to calculate stool frequency and rectal bleeding subscores (see below for information on what days the sites are instructed to use) will be programmatically assessed. **Absolute stool number** is the average of the daily stool number over the three days, and the rectal bleeding subscore is calculated using the average rectal bleeding number for the three days based on the criteria in Section 6.13. At the screening visit, each person indicates the number of stools he/she passed in a 24-hour period when in remission or before his/her UC diagnosis. The stool frequency subscore will be calculated based on the criteria in Section 6.13 by subtracting the number of stools when in remission or prior to UC from the absolute stool number.

Programmatical algorithm on which 3 days to use in the calculation of the Mayo rectal bleeding and stool frequency subscores: The most recent 3 consecutive days within the 7 days prior to the visit excluding the following:

- The day medications were taken for constipation, diarrhea or irregularity
- The day of a procedure or preparation for procedure (eg, enema, other laxatives, or clear liquid diet) that would affect stool frequency and/or blood content of the stool
- The 48 hours after the use of antimotility agents (ie, diphenoxylate hydrochloride with atropine sulfate or loperamide)

Note: For participants maintained on a chronic stable dose of antimotility agents throughout the study, the days on which these agents are taken will not be excluded from consideration in calculating the Mayo score

- The 48 hours immediately following a colonoscopy*

If three consecutive days are not available, two consecutive days and the closest nonconsecutive day will be programmatically selected. If two consecutive days are not available, then three nonconsecutive days closest to the visit will be chosen. If 3 days (within the week prior to the indicated visit) that meet the criteria defined above are not available, then the absolute stool number, stool frequency subscore and rectal bleeding subscore cannot be calculated and will be missing in the tablet.

*Note: In case a sigmoidoscopy was done instead of a full colonoscopy, the 48 hours immediately following the sigmoidoscopy will not be excluded.

Endoscopy Subscore

The endoscopic findings will be assessed by the investigator (ie, local endoscopist) during the endoscopy procedure and by the central reader reviewing a video of the endoscopy. The endoscopy may be either a colonoscopy or sigmoidoscopy.

Participant eligibility at baseline will be based on the final reported endoscopic subscore as determined by the following process:

- If the local endoscopist and the central reader agree on the endoscopic subscore, the agreed score will be the final reported endoscopic subscore.
- If there is a discrepancy between the local endoscopist and the central reader subscores, the video endoscopy will be submitted to a second central reader (designated for adjudication). The adjudicator will be blinded to the scores of the local and first central reader. From the 3 Mayo endoscopic subscores, the score with which 2 readers agree will be reported as the final Mayo endoscopic subscore. In the unlikely event that no 2 readers agree on the Mayo endoscopic subscore, the median score of the 3 completed reads (ie, local read, central read #1 and central read #2 designated for adjudication) will be chosen as the final reported endoscopic subscore.

Unless otherwise specified, the analysis of endpoints that include the Mayo endoscopy subscore will be based on the final reported endoscopic subscore. If the final reported endoscopic subscore is not available, the corresponding central endoscopy score (central read #1) will be used, if available. If the central endoscopy score (central read #1) is also missing, then the local endoscopy score will be used, if available. If both the local and the central endoscopic score are not available, then the endoscopy subscore for the analysis will be left missing.

Specific details of the central review will be provided in the imaging charter, including details regarding video acquisition, standardization, reading, and data transfer.

The central reader will perform a friability assessment for each endoscopy (sigmoidoscopy or colonoscopy) received by providing a response to the following question: “Is hemorrhage detected with incidental trauma caused by the endoscopic procedure?” If friability is present, the central reader will also provide a confidence level (High or Low) when evaluating friability. Please note that the friability assessment should not be performed for those with an assessed endoscopy subscore of 0, which requires that no friability is present. Further details are provided in the Imaging Charter.

A participant’s clinical response status at Week I-8 of the induction study period to determine stratification will be based on the endoscopy subscore assigned by the local endoscopist.

Sensitivity analyses of endpoints based on the local read of the endoscopy will also be performed.

Physician's Global Assessment Subscore

The physician's global assessment acknowledges the 3 other Mayo subscores, the patient's recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

5.3.2. Global Primary Estimand

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

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?

Global Primary Estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. The estimand is defined by the following 5 attributes: **study intervention**, **population**, **variable**, **population-level summary**, and **intercurrent events (ICE)** and their corresponding strategies.

The 5 attributes of the estimand are as follows:

- a. **Study intervention:**
 - Ustekinumab (experimental treatment/intervention)
- b. **Population:** Participants who are 2 to <18 years of age with moderately to severely active UC.
- c. **Variable:** Clinical remission at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not 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. **Intercurrent events and their corresponding strategies:**
 1. Had a colectomy (partial or full) or ostomy
 2. Discontinued study intervention due to lack of efficacy or an AE of worsening of UC
 3. Had prohibited changes in UC medications (for details, see Section 6.11)
 4. Discontinued study intervention due to COVID-19 reasons (excluding COVID-19 infections)
 5. Discontinued study intervention for reasons other than those in ICE 2 and 4.

ICEs in attribute e, categories 1-3, and 5 will be handled by the composite strategy, ICE category 4 will be handled by the hypothetical strategy (as if participants would not have experienced this ICE). The composite strategy assesses the treatment effects not only based on the variable measurements but also based on ICEs. This estimand acknowledges that having an ICE in

categories 1-3, and 5 is an unfavorable outcome. For participants experiencing ICE 4, data at all visits after the ICE will be set to missing.

5.3.3. Global Supplementary Estimands

5.3.3.1. Global Supplementary Estimand 1

A supplementary estimand will be used to complement Estimand 1. In this estimand, all ICEs are addressed by the **treatment policy estimand**: the data collected at and after the event will be used for analysis, if available.

The attributes of this supplementary estimand are the same as those for the global primary estimand with the exception of Variable (Endpoint), which is described as follows:

Variable (Endpoint)

Clinical remission at Week I-8.

5.3.3.2. Global Supplementary Estimand 2

In this supplementary estimand, ICEs in categories 1-3 will be handled by the composite strategy. This estimand acknowledges that having an ICE in categories 1-3 is an unfavorable outcome and will be considered not to be in clinical remission at Week I-8.

ICE category 4 will be handled by the hypothetical strategy (as if participants would not have experienced this ICE) and ICE 5 will be handled by the 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).

The attributes of this supplementary estimand are the same as those for the global primary estimand with the exception of the Variable (Endpoint), which is described as follows:

Variable (Endpoint):

Clinical remission at Week I-8. Participants with ICEs in categories 1-3 will be considered to not be in clinical remission at Week I-8.

5.3.4. Analysis Methods for the Global Primary Estimand

5.3.4.1. Main Estimator (Analysis) for the Global Primary Estimand

Global primary estimand analysis will be based on all participants in the FAS.

The main estimator for the global primary estimand is based on the proportion of participants in clinical remission at Week I-8. Participants with ICEs in categories 1-3, and 5 by Week I-8 will be considered to not be in clinical remission at Week I-8. For participants experiencing ICE 4, data at all visits after the ICE 4 will be set to missing. After accounting for the ICEs, participants who are missing any of the 3 Mayo subscores that comprise the clinical remission definition will be considered not to have achieved clinical remission at Week I-8.

The proportion of participants who are in clinical remission at Week I-8, will be provided, as well as its respective 95% CI. The 95% CI for the proportion of pediatric participants in clinical remission at Week I-8 will be descriptively compared with the 95% CI among adult participants with UC who received ustekinumab induction therapy (~6 mg/kg) as well as participants who received placebo in the Phase 3 adult study CNTO1275UCO3001. For this comparison, the analysis from the adult study CNTO1275UCO3001 which uses the same definition for clinical remission as this study (see Section 5.3.1 for more details) will be used.

5.3.4.2. Estimator (Analysis) for the Global Supplementary Estimands

The following describes the estimators for the supplementary estimands of the global primary endpoint.

5.3.4.2.1. Estimator for Global Supplementary Estimand 1

The global primary estimand will be analyzed using Global Supplementary Estimand 1, which uses the treatment policy estimand. A similar analysis, including the handling of missing Mayo scores (ie, non-responder imputation), will be conducted as described for the Global Primary Estimand (Section 5.3.4.1).

5.3.4.2.2. Estimator for Global Supplementary Estimand 2

The global primary estimand will be analyzed using Global Supplementary Estimand 2. The same analysis will be conducted as described for the Global Primary Estimand (Section 5.3.4.1, including the handling of missing Mayo scores).

5.3.4.3. Global Sensitivity Analyses

To examine the robustness of the primary endpoint analysis, the following sensitivity analyses will be evaluated using the Global Primary Estimand (Section 5.3.2):

5.3.4.3.1. Global Sensitivity Analysis 1

Global Sensitivity Analysis 1 (Observed case): excludes participants who have missing Mayo scores at Week I-8 after accounting for ICE prior to Week I-8.

5.3.4.3.2. Global Sensitivity Analysis 2

Global Sensitivity Analysis 2 (Multiple Imputation): after accounting for the ICEs, missing Mayo subscores for stool frequency, rectal bleeding, endoscopy, as well as friability assessments will be imputed using multiple imputation methods. The imputation model will include Mayo subscores at Week I-0 and Week I-8 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.

5.3.5. Subgroup Group Analysis for Global Primary Endpoint

The consistency of treatment effect for the global primary endpoint will be evaluated for the subgroups defined in Section 5.7.7, using the Global Primary Estimand.

5.3.6. US-Specific Primary Estimand

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

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?

US-Specific Primary Estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. The estimand is defined by the following 5 attributes: **study intervention, population, variable, population-level summary, and ICE** and their corresponding strategies.

The 5 attributes of the estimand are as follows:

a. Study intervention:

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

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

c. Variable: Clinical remission at Week M-44. Participants with ICE in categories 1-5, and 7 (see below) will be considered to not be in clinical remission at Week M-44

d. Summary measure (Population-level summary): Proportion of participants in clinical remission at Week M-44

e. Intercurrent events and their corresponding strategies:

1. Had a colectomy (partial or full) or ostomy
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of UC
3. Had prohibited changes in UC medications (for details, see Section 6.11)
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)
5. Dose adjusted after Week M-8
6. Discontinued study intervention due to COVID-19 reasons (excluding COVID-19 infections)
7. Discontinued study intervention for reasons other than those in ICE 2 and 6.

ICEs in attribute e, categories 1-5, and 7 will be handled by the composite strategy, and ICE category 6 will be handled by the hypothetical strategy. The composite strategy assesses the treatment effects not only based on the variable measurements but also based on ICEs. This estimand acknowledges that having an ICE in categories 1-5, and 7 is an unfavorable outcome. For participants experiencing ICE 6, data at all visits after the ICE will be set to missing.

5.3.7. US-Specific Supplementary Estimands

5.3.7.1. US-Specific Supplementary Estimand 1

A supplementary estimand will be used to complement the primary estimand. In this estimand, all ICEs are addressed by the **treatment policy estimand** (the data collected at and after the event will be used for analysis, if available).

The attributes of this supplementary estimand are the same as those for the US-Specific primary estimand (US-Specific Primary Estimand) except for Variable (Endpoint), which is described as follows:

Variable (Endpoint)

Clinical remission at Week M-44.

5.3.7.2. US-Specific Supplementary Estimand 2

In this supplementary estimand, ICEs in categories 1-5, will be handled by the composite strategy. The composite strategy assesses the treatment effects not only based on the variable measurements but also based on ICEs. This estimand acknowledges that having an ICE in categories 1-5 is an unfavorable outcome. ICE category 6 will be handled by the hypothetical strategy, and ICE 7 will be handled by the treatment policy strategy.

The attributes of this supplementary estimand are the same as those for US-Specific Primary Estimand except for the Variable (Endpoint), which is described as follows:

Variable (Endpoint):

Clinical remission at Week M-44. Participants with ICEs categories 1-5 will be considered to not be in clinical remission at Week M-44.

5.3.7.3. US-Specific Supplementary Estimand 3

In this supplementary estimand, ICEs in categories 1-5, and 7 will be handled by the composite strategy, and ICE category 6 will be handled by the hypothetical strategy.

The attributes of this supplementary estimand are the same as those for US-Specific Primary Estimand with the exception of the Population, which is described as follows:

Population:

Participants who are 2 to <18 years of age with moderately to severely active UC who are in clinical response at Week I-8. The clinical response is determined by the modified Mayo score with central read at Week I-0 and local read at Week I-8 of the endoscopy subscore (i.e., response is derived manually and not determined by the IWRS).

5.3.8. Analysis Methods for the US-Specific Primary Estimand**5.3.8.1. Main Estimator (Analysis) for the US-Specific Primary Estimand**

Data used in the US-Specific primary estimand analysis include all values for estimating the clinical remission status at Week M-44 for all participants in the FASCR. After accounting for the ICEs, participants who are missing any or all of the 3 Mayo subscores (rectal bleeding, stool frequency, and endoscopy) that comprise the clinical remission definition will be considered not to have achieved clinical remission at Week M-44.

The efficacy data for each participant will be analyzed according to the assigned treatment regardless of the actual treatment received. The primary endpoint will be analyzed based on the primary estimand (US-Specific Primary Estimand).

The main estimator for the primary estimand is based on the proportion of participants in 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 Week M-0 (<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 treatment group who are in clinical remission at Week M-44 will be descriptively compared with a 95% CI among adult participants with UC who received ustekinumab maintenance therapy (90 mg q8w and 90 mg q12w) in the CNTO1275UCO3001 study. For this comparison, the analysis from the adult study CNTO1275UCO3001 which uses the same definition for clinical remission as this study (see Section 5.3.1, for more details) will be used.

In addition, the 95% CI for the proportion of pediatric participants in the combined treatment group 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 at Week M-44, which will be based on a meta-analysis of placebo clinical remission rates using historical adult UC randomized withdrawal studies (ie, similar design and study populations, see Section 6.15, for more details).

5.3.8.2. Estimator (Analysis) for the US-Specific Supplementary Estimands

The following describes the estimators for the supplementary estimands of the US-Specific primary estimand.

5.3.8.2.1. Estimator for US-Specific Supplementary Estimand 1

The US-specific primary endpoint will be analyzed using US-Specific Supplementary Estimand 1, where all ICEs are addressed by the treatment policy strategy. Similar analysis, including the handling of missing Mayo scores, will be conducted as described for the US-specific Primary Estimand (Section 5.3.8.1).

5.3.8.2.2. Estimator for US-Specific Supplementary Estimand 2

The US-specific primary endpoint will be analyzed using US-Specific Supplementary Estimand 2. Similar analyses, including the handling of missing Mayo scores, will be conducted as described for the US-specific Primary Estimand (Section 5.3.8.1).

5.3.8.2.3. Estimator for US-Specific Supplementary Estimand 3

The US-specific primary endpoint will be analyzed using US-Specific Supplementary Estimand 3. Similar analyses, including the handling of missing Mayo scores, will be conducted as described for the US-specific Primary Estimand (Section 5.3.8.1).

5.3.8.3. US- Specific Sensitivity Analyses

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 (Section 5.3.6).

5.3.8.3.1. US-Specific Sensitivity Analysis 1

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

5.3.8.3.2. US-Specific Sensitivity Analysis 2

US-Specific Sensitivity Analysis 2 (Multiple imputation): after accounting for ICEs, missing Mayo subscores for stool frequency, rectal bleeding and endoscopy, as well as friability assessments will be imputed using multiple imputation methods. The imputation model will include Mayo subscores at Week I-0, Week I-8 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.

5.3.8.3.3. US-Specific Sensitivity Analysis 3

US-Specific Sensitivity Analysis 3 (Tipping point analysis): to comprehensively evaluate the robustness of departures from the missing data assumption (MAR) used in the US-Specific Primary Estimand 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% CI will be descriptively compared with the upper bound of the 95% CI for the historical adult placebo control for clinical remission (defined using the Mayo) at Week M-44 (see Section 5.3.6).

5.3.8.4. Supportive Analysis for US-Specific Primary Estimand

5.3.8.4.1. US-Specific Supportive Analysis 1

US-Specific Supportive Analysis 1: The data from participants who were in clinical response to ustekinumab induction therapy and randomized to placebo in the adult UC study CNTO1275UCO3001 will be used in this 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: baseline Mayo score, biologic failure (biologic-failure, non-biologic-failure), CRP (≤ 3 mg/L, > 3 mg/L), and baseline 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 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.

5.3.8.4.2. US-Specific Supportive Analysis 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. The adult placebo proportion in clinical remission will be estimated using the weighted average of the covariate-adjusted remission rate based on studies with the participant-level data and the studies with the study-level data. A Bayesian logistic model will be used to obtain the covariate adjusted remission rate to account for the potential difference in the current pediatric study and in the participants of the adult studies. The following covariates will be used if they are significantly associated with the outcome measure in the adult studies: baseline Mayo score, biologic failure (biologic-failure, non-biologic-failure), CRP (≤ 3 mg/L, > 3 mg/L), and baseline oral corticosteroids (receiving, not receiving). The posterior distribution of the difference

in outcome measures between the treatment groups and its corresponding 95% credible interval (CrI) will be constructed for 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. Details are in Section 6.17.

5.3.9. Subgroup Analysis for US-Specific Primary Endpoint

The consistency of treatment effect for the US-Specific primary endpoint will be evaluated for the subgroups defined in Section 5.7.7, using the US-Specific Primary Estimand.

5.4. Secondary Endpoints Analysis

Objective: To evaluate the efficacy of ustekinumab in participants who are 2 to <18 years of age with moderately to severely active UC

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 similar. The only difference is:

- clinical remission at Week M-44 is a secondary endpoint for Global, but primary for US-Specific
- clinical remission at Week I-8 is a secondary endpoint for US-Specific, but primary for Global

5.4.1. Global Secondary Endpoints

The following secondary endpoints will be evaluated at Week I-8:

1. Clinical response
2. Symptomatic remission
3. Clinical remission as assessed by the PUCAI score
4. Endoscopic improvement
5. Histologic-endoscopic mucosal improvement at Week I-8 (for Geboes Score and Robarts Histopathology Index)

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

1. Clinical remission
2. Symptomatic remission
3. Clinical remission as assessed by the PUCAI score
4. Endoscopic improvement
5. Corticosteroid-free clinical remission at Week M-44
6. 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

7. Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8
8. Histologic-endoscopic mucosal improvement at Week M-44 (for Geboes Score and Robarts Histopathy Index)

5.4.2. US-Specific Secondary Endpoints

The following secondary endpoints will be evaluated at Week I-8:

1. Clinical remission
2. Clinical response
3. Symptomatic remission
4. Clinical remission as assessed by the PUCAI score
5. Endoscopic improvement
6. Histologic-endoscopic mucosal improvement at Week I-8

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. Symptomatic remission
2. Clinical remission as assessed by the PUCAI score
3. Endoscopic improvement
4. Corticosteroid-free clinical remission at Week M-44
5. 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
6. Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8
7. Histologic-endoscopic mucosal improvement at Week M-44.

5.4.3. Definition of Endpoints

Clinical remission as measured by the PUCAI Score:

- A PUCAI score <10.

Symptomatic remission:

- A Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline.

90-day Corticosteroid-free clinical remission:

- A Mayo stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline; and not receiving corticosteroids for at least 90 days prior to Week M-44.

Clinical response:

- A decrease from baseline in the Modified Mayo score by $\geq 30\%$ and ≥ 2 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

Endoscopic improvement:

A Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

Histologic-endoscopic mucosal improvement:

- Achieving a combination of histologic and endoscopic improvement (endoscopy subscore of 0 or 1 with no friability present on the endoscopy). More details on the definition of histology-related endpoints will be provided in the Histology SAP.

Note that endpoints that are based on the Mayo score will utilize the Mayo endoscopy subscore as assessed during central review of the video of the endoscopy.

5.4.4. Estimands For Secondary Endpoints**5.4.4.1. Global****5.4.4.1.1. Endpoints at Week I-8**

[Table 4](#), describes the attributes of the estimands for the secondary endpoints at Week I-8 (referred to as Estimands 7-11):

Study intervention:

Ustekinumab (experimental treatment/intervention)

Population (for Estimands 7-11): Participants who are 2 to <18 years of age with moderately to severely active UC disease

Variables and Population-level Summary (for Estimands 7-11):**Table 4: Variables and Population-level Summary for the Estimand for Each Global Secondary Endpoint at Week I-8**

Estimand	Variable (Endpoint)	Population-level summary
7	Clinical response at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in clinical response at Week I-8.	Proportion of participants in clinical response at Week I-8
8	Symptomatic remission at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in symptomatic remission at Week I-8.	Proportion of participants in symptomatic remission at Week I-8
9	Clinical remission as assessed by the PUCAI score at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in clinical remission as assessed by the PUCAI score at Week I-8.	Proportion of participants in clinical remission as assessed by the PUCAI score at Week I-8
10	Endoscopic improvement at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in endoscopic improvement at Week I-8.	Proportion of participants with endoscopic improvement at Week I-8
11	Histologic-endoscopic mucosal improvement at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in histologic-endoscopic mucosal improvement at Week I-8.	Proportion of participants with histologic endoscopic mucosal improvement at Week I-8

Intercurrent Events and Corresponding Strategies:

The ICEs for all secondary endpoints at Week I-8 are the same as those used in the Global Primary Estimand, and are as follows:

1. Had a colectomy (partial or full) or ostomy
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of UC
3. Had prohibited changes in UC medications (for details, see Section 6.11)
4. Discontinued study intervention due to COVID-19 reasons (excluding COVID-19 infections)
5. Discontinued study intervention for reasons other than those in ICE 2 and 4.

ICEs 1-3, and 5 are handled by the composite strategy and ICE 4 is handled by the hypothetical strategy. The estimands for the secondary endpoints acknowledge that having an ICE in categories 1-3, and 5 is an unfavorable outcome. If a participant had any of the ICE categories 1-3, and 5 prior to Week I-8, the participant will be considered not to be in **clinical response**, **symptomatic remission**, **clinical remission as assessed by the PUCAI score**, **endoscopic improvement**, or **histologic-endoscopic mucosal improvement**, at Week I-8. For participants experiencing ICE 4, data at all visits after the ICE 4 will be set to missing.

5.4.4.1.2. Endpoints at Week M-44

Table 5 describes the attributes of the estimands for the secondary endpoints at Week M-44 (referred to as Estimands 12-19):

Study intervention:

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

Population (for Estimands 12-19): Participants who are 2 to <18 years of age with moderately to severely active UC disease and are in clinical response at Week I-8

Variables and Population-level Summary (for Estimands 12-19):

Table 5: Variables and Population-level Summary for the Estimand for Each Global Secondary Endpoint at Week M-44

Estimand	Variable (Endpoint)	Population-level summary
12	Clinical remission at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in clinical remission at Week M-44.	Proportion of participants in clinical remission at Week M-44
13	Symptomatic remission at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in symptomatic remission at Week M-44.	Proportion of participants in symptomatic remission at Week M-44
14	Clinical remission as assessed by the PUCAI score at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in clinical remission as assessed by the PUCAI score at Week M-44.	Proportion of participants in clinical remission as assessed by the PUCAI score at Week M-44
15	Endoscopic improvement at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in endoscopic improvement at Week M-44.	Proportion of participants in endoscopic improvement at Week M-44
16	Corticosteroid-free clinical remission at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in corticosteroid-free clinical remission at Week M-44.	Proportion of participants in corticosteroid-free clinical remission at Week M-44
17	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. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in corticosteroid-free clinical remission at Week M-44.	Proportion of participants in 90-day corticosteroid-free remission at Week M-44 among subjects who were receiving corticosteroids at Week I-0
18	Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8. Participants with ICEs in categories	Proportion of participants who maintained clinical remission at Week M-44

Table 5: Variables and Population-level Summary for the Estimand for Each Global Secondary Endpoint at Week M-44

Estimand	Variable (Endpoint)	Population-level summary
	1-5, and 7 (see below) by Week M-44 will be considered to not be in clinical remission at Week M-44.	
19	Histologic-endoscopic mucosal improvement at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in histologic-endoscopic mucosal improvement at Week M-44.	Proportion of participants with histologic endoscopic mucosal improvement at Week M-44

Intercurrent Events and Corresponding Strategies:

The ICEs and associated strategies for all secondary endpoints at Week M-44 are the same as those used in the US-Specific Primary Estimand, and are as follows:

1. Had a colectomy (partial or full) or ostomy
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of UC
3. Had prohibited changes in UC medications (for details, see Section 6.11)
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)
5. Dose adjusted after Week M-8
6. Discontinued study intervention due to COVID-19 reasons (excluding COVID-19 infections)
7. Discontinued study intervention for reasons other than those in ICE 2 and 6.

ICEs 1-5, and 7 are handled by the composite strategy and ICE 6 is handled by the hypothetical strategy. The estimands for the secondary endpoints acknowledge that having an ICE in categories 1-5, and 7 is an unfavorable outcome. If a participant had any of the ICE categories 1-5, and 7 prior to Week M-44, the participant will be considered not to be in **clinical remission, symptomatic remission, clinical remission as assessed by the PUCAI score, endoscopic improvement, steroid free remission, maintenance of clinical remission, or histologic-endoscopic mucosal improvement** at Week M-44. For participants experiencing ICE 6, data at all visits after the ICE 6 will be set to missing.

5.4.4.2. US-Specific

5.4.4.2.1. Endpoints at Week I-8

Table 6 describes the attributes of the estimands for the secondary endpoints at Week I-8 (referred to as Estimands 20-25):

Study intervention:

Ustekinumab (experimental treatment/intervention)

Population (for Estimands 20-25): Participants who are 2 to <18 years of age with moderately to severely active UC disease

Variables and Population-level Summary (for Estimands 20-25):

Table 6: Variables and Population-level Summary for the Estimand for Each US-Specific Secondary Endpoint At Week I-8

Estimand	Variable (Endpoint)	Population-level summary
20	Clinical remission at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in clinical remission at Week I-8.	Proportion of participants in clinical remission at Week I-8
21	Clinical response at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in clinical response at Week I-8.	Proportion of participants in clinical response at Week I-8
22	Symptomatic remission at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in symptomatic remission at Week I-8.	Proportion of participants in symptomatic remission at Week I-8
23	Clinical remission as assessed by the PUCAI score at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in clinical remission as assessed by the PUCAI score at Week I-8.	Proportion of participants in clinical remission as assessed by the PUCAI score at Week I-8
24	Endoscopic improvement at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in endoscopic improvement at Week I-8.	Proportion of participants with endoscopic improvement at Week I-8
25	Histologic-endoscopic mucosal improvement at Week I-8. Participants with ICEs in categories 1-3, and 5 (see below) by Week I-8 will be considered to not be in histologic-endoscopic mucosal improvement at Week I-8.	Proportion of participants with histologic-endoscopic mucosal improvement at Week I-8

Intercurrent Events and Corresponding Strategies:

The ICEs for all secondary endpoints at Week I-8 are the same as those used in the Global Primary Estimand, and are as follows:

1. Had a colectomy (partial or full) or ostomy
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of UC
3. Had prohibited changes in UC medications (for details, see Section 6.11)

4. Discontinued study intervention due to COVID-19 reasons (excluding COVID-19 infections)
5. Discontinued study intervention for reasons other than those in ICE 2 and 4.

ICEs 1-3, and 5 are handled by the composite strategy and ICE 4 is handled by the hypothetical strategy. The estimands for the secondary endpoints acknowledge that having an ICE in categories 1-3, and 5 is an unfavorable outcome. If a participant had any of the ICE categories 1-3, and 5 prior to Week I-8, the participant will be considered not to be in **clinical remission, clinical response, symptomatic remission, clinical remission as assessed by the PUCAI score, endoscopic improvement, or histologic-endoscopic mucosal improvement** at Week I-8. For participants experiencing ICE 4, data at all visits after the ICE 4 will be set to missing.

5.4.4.2.2. Endpoints at Week M-44

Table 7 describes the attributes of the estimands for the secondary endpoints at Week M-44 (referred to as Estimands 26-32):

Study intervention:

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

Population (for Estimands 26-32): Participants who are 2 to <18 years of age with moderately to severely active UC disease at enrollment and are in clinical response at Week I-8

Variables and Population-level Summary (for Estimands 26-32):

Table 7: Variables and Population-level Summary for the Estimand for Each US-Specific Secondary Endpoint at Week M-44

Estimand	Variable (Endpoint)	Population-level summary
26	Symptomatic remission at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in symptomatic remission at Week M-44.	Proportion of participants in symptomatic remission at Week M-44
27	Clinical remission as assessed by the PUCAI score at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in clinical remission as assessed by the PUCAI score at Week M-44.	Proportion of participants in clinical remission as assessed by the PUCAI score at Week M-44
28	Endoscopic improvement at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in endoscopic improvement at Week M-44.	Proportion of participants in endoscopic improvement at Week M-44
29	Corticosteroid-free clinical remission at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in histologic- corticosteroid-free clinical remission at Week M-44.	Proportion of participants with corticosteroid-free clinical remission at Week M-44

Table 7: Variables and Population-level Summary for the Estimand for Each US-Specific Secondary Endpoint at Week M-44

Estimand	Variable (Endpoint)	Population-level summary
30	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. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in corticosteroid-free clinical remission at Week M-44.	Proportion of participants in 90-day corticosteroid free remission at Week M-44 among participants who were receiving corticosteroids at Week I-0
31	Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in clinical remission at Week M-44.	Proportion of participants who maintained clinical remission at Week M-44
32	Histologic-endoscopic mucosal improvement at Week M-44. Participants with ICEs in categories 1-5, and 7 (see below) by Week M-44 will be considered to not be in histologic-endoscopic mucosal improvement at Week M-44.	Proportion of participants with histologic-endoscopic mucosal improvement at Week M-44

Intercurrent Events and Corresponding Strategies:

The ICEs for all secondary endpoints are the same as those used in US-Specific Primary Estimand, and are as follows:

1. Had a colectomy (partial or full) or ostomy
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of UC
3. Had prohibited changes in UC medications (for details, see Section 6.11)
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)
5. Dose adjusted after Week M-8
6. Discontinued study intervention due to COVID-19 reasons (excluding COVID-19 infections)
7. Discontinued study intervention for reasons other than those in ICE 2 and 6.

ICEs 1-5, and 7 are handled by the composite strategy and ICE 6 is handled by the hypothetical strategy. The estimands for the secondary endpoints acknowledge that having an ICE in categories 1-5, and 7 is an unfavorable outcome. If a participant had any of the ICE categories 1-5, and 7 prior to Week M-44, the participant will be considered not to be in **symptomatic remission**,

clinical remission as assessed by the PUCAI score, endoscopic improvement, steroid free remission, maintenance of clinical remission, or histologic-endoscopic mucosal improvement at Week M-44. For participants experiencing ICE 6, data at all visits after the ICE 6 will be set to missing.

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. Week I-8 Endpoints

The analysis population for secondary endpoints at Week I-8 includes all participants who received one administration of study administration at Week I-0 (FAS).

After accounting for the ICEs, participants who have missing data for the endpoint at Week I-8 will be considered not to have achieved their respective endpoints.

For the secondary endpoints at Week I-8, the proportion of participants who meet the endpoint at Week I-8 will be summarized overall, and a 95% CI will be provided.

The 95% CI for the proportion of pediatric participants who are in clinical remission, symptomatic remission, clinical response, endoscopic improvement at Week I-8 will be descriptively compared with a 95% CI among adult participants with UC who received ustekinumab induction therapy (~6 mg/kg) in the CNTO1275UCO3001 study. For this comparison, the analyses from the adult study CNTO1275UCO3001 which use the same definitions as this study for secondary endpoints (symptomatic remission, clinical response and endoscopic improvement; see Section 5.4.3 for more details) will be used.

5.4.5.1.2. Week M-44 Endpoints

The analysis population for 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 in the maintenance period (FASCR).

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

For the secondary endpoints in maintenance, the proportion of participants who meet the endpoint at Week M-44 will be summarized overall and by maintenance treatment group, and 95% CIs will be provided. In addition, an estimate of the difference between maintenance treatment arms will be provided using the Cochran-Mantel-Haenszel (CMH) method adjusting for weight at week M-0 (<40 kg, ≥40 kg). The corresponding 95% CI for the difference will be provided based on the Wald statistics (CMH weights).

For all randomized participants who were clinical responders at Week I-8 and who were treated with ustekinumab (combined treatment group) in maintenance, the secondary endpoints at Week

M-44 will be descriptively compared with the proportion (and 95% CI) of adult participants who meet the endpoint at Week M-44 in the CNTO1275UCO3001 study among participants who are clinical responders at Week I-8 (90 mg q8w and 90 mg q12w treatment groups). In addition, a 95% CI for the adult placebo rate from CNTO1275UCO3001 will be provided to assess the effect of ustekinumab compared with a historical placebo. For this comparison, the analyses from the adult study CNTO1275UCO3001 which use the same definitions as this study for secondary endpoints (symptomatic remission, clinical response and endoscopic improvement; see Section 5.4.3 for more details) will be used.

5.4.5.1.2.1. US-Specific Secondary Endpoint Analyses

The planned analyses for symptomatic remission are identical to those planned for clinical remission at Week M-44 (US-Specific primary estimand). In addition, the 95% CI for the proportion of pediatric participants in symptomatic remission in the combined treatment group at Week M-44 will be descriptively compared with a 95% CI for a historical adult placebo control for symptomatic remission at Week M-44 (see Section 6.15, for more details).

5.5. Tertiary Endpoints Analysis

The following are tertiary endpoints.

5.5.1. Remission Endpoints

For the listed remission endpoints below, an endoscopy subscore of 0 or 1 will exclude friability.

5.5.1.1. Through Week I-8

The following endpoints will be summarized for FAS.

1. Clinical Remission at Week I-8, alternative definition 1: defined as a stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1
2. Clinical Remission at Week I-8, alternative definition 2: defined as an absolute stool number ≤ 3 , a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1
3. Clinical Remission at Week I-8, alternative definition 3: defined as Mayo score ≤ 2 points, with no individual subscore > 1
4. Symptomatic remission through Week I-8

5.5.1.2. Through Week M-44

The following endpoints will be summarized for FASCR.

1. Clinical Remission at Week M-44, alternative definition 1: defined as a stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1
2. Clinical Remission at Week M-44, alternative definition 2: defined as an absolute stool number ≤ 3 , a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1
3. Clinical Remission at Week M-44, alternative definition 3: defined as Mayo score ≤ 2 points, with no individual subscore > 1

4. Symptomatic remission through Week M-44
5. Clinical remission as assessed by PUCAI through Week M-44
6. Symptomatic remission through Week M-44 for participants who are in symptomatic remission at Week I-8
7. Clinical remission through Week M-44, as assessed by the PUCAI score, for participants who are in clinical remission (by PUCAI score) at Week I-8
8. Participants who are on corticosteroids at baseline and who were not receiving corticosteroids for at least 90 days prior to Week M-44 and in symptomatic remission at Week M-44
9. Participants who are on corticosteroids at baseline and who were not receiving corticosteroids for at least 90 days prior to Week M-44 and in clinical remission at Week M-44, as assessed by the PUCAI score
10. Durable symptomatic remission: Achieving symptomatic remission at $\geq 75\%$ of all visits (at least 6 out of 8 visits) prior to Week M-44 and in symptomatic remission at last visit (Week M-44)
11. Durable PUCAI remission: Achieving PUCAI remission at $\geq 75\%$ of all visits (at least 6 out of 8 visits) prior to Week M-44 and in PUCAI remission at last visit (Week M-44)
12. Clinical remission at both Week I-8 and Week M-44
13. Symptomatic remission at both Week I-8 and Week M-44

5.5.2. Other Clinical Efficacy Endpoints

5.5.2.1. Through Week I-8

1. Clinical response as assessed by the Mayo score at Week I-8
2. Clinically important change as assessed by the PUCAI score through Week I-8
3. Baseline and postbaseline values and the change from baseline in the Mayo score at Week I-8
4. Baseline and postbaseline values and the change from baseline in the Modified Mayo score at Week I-8
5. Baseline and postbaseline values and the change from baseline in the Partial Mayo score over time through Week I-8
6. Baseline and postbaseline values and the change from baseline in the PUCAI score through Week I-8
7. Baseline and postbaseline values in the Mayo subscores at Week I-8
8. Change from baseline in the stool frequency and rectal bleeding subscores through Week I-8
9. Histologic improvement at Week I-8
10. Histologic remission at Week I-8
11. Endoscopic normalization at Week I-8
12. Baseline and postbaseline values in the average daily corticosteroid use through Weeks I-8

13. Summary of ICEs from Week I-0 through Week I-8
14. Summary of missing data for the Mayo score from Week I-0 through Week I-8 after accounting for the ICEs
15. Clinical response at Week I-8 determined by the modified Mayo score with central read at Week I-0 and local read at Week I-8 of the endoscopy subscore.

Histologic assessment analyses made by other indexes (e.g. RHI and NI) are considered exploratory and will be summarized in separate technical reports.

5.5.2.2. Through Week M-44

1. Clinical response at Week M-44
2. Clinical response as assessed by the Mayo score at Week M-44
3. Clinically important change as assessed by the PUCAI score through Week M-44
4. Baseline (Week I-0) and postbaseline values and the change from baseline in the Mayo score at Week M-44
5. Baseline (Week I-0) and postbaseline values and the change from baseline in the Modified Mayo score at Week M-44
6. Baseline (Week I-0) and postbaseline values and the change from baseline in the Partial Mayo score over time through Week M-44
7. Baseline (Week I-0) and postbaseline values and the change from baseline in the PUCAI score over time through Week M-44
8. Baseline (Week I-0) and postbaseline values in the Mayo subscores at Week M-44
9. Histologic improvement at Week M-44
10. Histologic remission at Week M-44
11. Endoscopic normalization at Week M-44
12. Baseline (Week I-0) and postbaseline values in the average daily corticosteroid use through Weeks M-8, M-30, and M-44
13. Summary of ICEs from Week M-0 through Week M-44
14. Summary of missing data for the Mayo score from Week M-0 through Week M-44 after accounting for the ICEs

Histologic assessment analyses made by other indexes (e.g., RHI and NI) are considered exploratory and will be summarized in separate technical reports.

5.5.2.3. Growth and Nutritional Parameters At Weeks I-8, M-4 and M-44

1. Baseline, post baseline values and change from baseline (Week I-0) in parameters of growth (age and gender-specific z-scores for height, weight and BMI) at Weeks I-8 and M-44

2. Baseline, post baseline values and change from baseline in 25-hydroxyvitamin D, Methyl Malonic Acid (MMA), and iron at Weeks M-4 and M-44
3. 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).

5.5.3. CRP and Fecal Marker Endpoints

Baseline and postbaseline values and the change from baseline in CRP through Week I-8 and during the maintenance period through Week M-44

Baseline and postbaseline values and the change from baseline in fecal calprotectin and lactoferrin concentrations through Week I-8 and during the maintenance period through Week M-44

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

Normalization of fecal calprotectin (≤ 250 mg/kg) and lactoferrin (≤ 7.24 μ g/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 μ g/g) at Week I-0

5.5.4. Quality of Life

Baseline and postbaseline values and the change from baseline in IMPACT-III through Week I-8 and during the maintenance period through 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.

5.5.5. Key Efficacy Endpoints by Baseline Subgroups

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

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

Subgroup efficacy endpoints analyses through Week I-8 will be based on the FAS. Subgroup efficacy endpoint analyses during the maintenance period through Week M-44 will be summarized based on the FASCR by treatment intervention. In addition, analyses during the maintenance period through Week M-44 will also be summarized overall based on the FASRES.

5.5.6. Efficacy Analyses 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 FASRES:

1. Clinical remission at Week M-44, as assessed by the Mayo score

2. Clinical remission at Week M-44, as assessed by the PUCAI score
3. Symptomatic remission at Week M-44
4. Endoscopic improvement at Week M-44
5. 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
6. Clinical response at Week M-44 as assessed by the Modified Mayo score (based on Mayo endoscopy subscore assigned by the central endoscopist)
7. Clinical response at Week M-44 as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the central endoscopist)
8. Clinical remission at Week M-44, as assessed by the Mayo score, for participants who are in clinical remission (by Mayo score) at Week I-8
9. Baseline and postbaseline values and the change from baseline in the Mayo score from Week I-0 through Week M-44
10. Baseline and postbaseline values and the change from baseline in the Modified Mayo score at Week M-44
11. Baseline and postbaseline values and the change from baseline in the Partial Mayo score over time from Week I-0 through Week M-44
12. Baseline and postbaseline values and the change from baseline in the PUCAI score over time from Week I-0 through Week M-44
13. Baseline and postbaseline values in the Mayo stool frequency and rectal bleeding subscores from Week I-0 through Week M-44

5.5.7. Efficacy Analyses for Participants Who Had a Dose Adjustment

The following efficacy analyses will also be summarized overall for participants who dose adjust from q8w → q8w (sham adjustment) 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 Mayo score
2. Clinical remission at Week M-44, as assessed by the PUCAI score
3. Symptomatic remission at Week M-44
4. Endoscopic improvement at Week M-44
5. 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
6. Clinical response at Week M-44
7. Clinical response at Week M-44, as assessed by the Mayo score
8. Change in PUCAI score at 16 weeks after dose adjustment from before dose adjustment
9. Change from before dose adjustment to values after dose adjustment in the Partial Mayo score
10. Change from before dose adjustment to values after dose adjustment in the PUCAI score

5.5.8. Efficacy Analyses by Local Endoscopist

The following endpoints will be based on the endoscopy subscore assigned by the local endoscopist by FAS for endpoints through Week I-8 and by FASCR from endpoints at Week M-44:

1. Clinical response at Week I-8
2. Clinical response as assessed by the Mayo score at Week I-8
3. Clinical remission at Week I-8
4. Clinical remission at Week I-8 defined as Mayo score ≤ 2 points, with no individual subscore > 1
5. Endoscopic improvement at Week I-8
6. Endoscopic normalization at Week I-8
7. Histo-endoscopic mucosal improvement at Week I-8 (for Geboes Score and Robarts Histopathy Index)
8. Clinical response as assessed by the Modified Mayo score at Week M-44
9. Clinical response as assessed by the Mayo score at Week M-44
10. Clinical remission at Week M-44
11. Clinical remission at Week M-44 defined as Mayo score ≤ 2 points, with no individual subscore > 1
12. Endoscopic improvement at Week M-44
13. Endoscopic normalization at Week M-44
14. Histo-endoscopic mucosal improvement at Week M-44

5.5.9. Efficacy Endpoints Based on 7-Day Average of Daily Rectal Bleeding and Stool Frequency Subscores

The following endpoints will be evaluated by averaging all available daily rectal bleeding and stool frequency subscores from within the 7-day period prior to the visit, excluding days meeting criteria as specified in Section 5.3.1. A minimum of 3 days should be used in the calculation of the Mayo subscores, if 3 days are not available then the stool frequency subscore and rectal bleeding subscore cannot be calculated and will be set to missing. Endpoints through Week I-8 will be evaluated by FAS and by FASCR for endpoints at Week M-44:

1. Clinical remission at Week I-8
2. Clinical response at Week I-8
3. Symptomatic remission at Week I-8
4. Symptomatic remission at Week M-44
5. Clinical remission at Week M-44

6. 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
7. Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8

5.5.10. Analyses of Missing Endoscopy Score at Week M-44

Even though the endoscopy score at Week M-44 is mandatory, there still may be a high risk of missing endoscopy scores at Week M-44 as participants may drop out of the study; therefore sensitivity analysis with different approaches to the missing data are proposed. In case of missing data, caution should be exercised for interpreting endpoints beyond Week I-8 that involve endoscopy at Week M-44, particularly if a large number of participants did not have a Week M-44 endoscopy performed.

Sensitivity analyses, with differing approaches to handling missing endoscopies at Week M-44, will be performed for the following endpoints:

1. Endoscopic improvement at Week M-44
 2. Clinical remission at Week M-44
 3. Clinical response at Week M-44
- **Sensitivity Analysis 1 (Observed case):** Excludes participants who have missing endoscopy data at Week M-44 after accounting for ICEs prior to Week M-44.
 - **Sensitivity Analysis 2:** For participants with missing endoscopy data at Week M-44 after accounting for ICEs prior to Week M-44, Week I-8 endoscopy scores will be carried forward.

5.5.11. Exploratory Endpoints

5.5.11.1. 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 CNTO1275UCO3001
2. Ratio of the proportion of pediatric participants in symptomatic remission at Week I-8 over proportion of the adult participants in symptomatic remission at Week I-8 in the ustekinumab ~6 mg/kg intervention group from study CNTO1275UCO3001
3. Ratio of the proportion of pediatric participants in clinical remission at Week M-44 over the proportion of adult participants in clinical remission at Week M-44 in the ustekinumab 90 mg SC q8w and 90 mg SC q12w intervention groups from study CNTO1275UCO3001
4. Ratio of the proportion of pediatric participants in symptomatic remission at Week M-44 over proportion of the adult participants in symptomatic remission at Week M-44 in the ustekinumab 90 mg SC q8w and 90 mg SC q12w intervention groups from study CNTO1275UCO3001

5.5.11.2. TUMMY-UC and Observer TUMMY-UC

Baseline and postbaseline values and the change from baseline in TUMMY-UC and Observer TUMMY-UC, for participants 8 to 18 years and participants <8 years, respectively, at Week I-0 through Week I-8 and during the maintenance period through Week M-44 for FASCR.

5.5.12. UC-related Hospitalization and Surgery

1. UC-related hospitalization through Week 44
2. UC-related surgery through Week 44

5.5.13. Definitions

5.5.13.1. 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 UC, elevated CRP has been associated with more severe clinical activity, an elevated sedimentation rate, and active disease as detected by colonoscopy. Blood samples for the measurement of CRP will be collected from all participants at visits indicated in the Schedule of Activities (Protocol Section 1.3). C-reactive protein will be assayed using a validated, high sensitivity assay. Results of CRP measurement will be released to the investigators by the central laboratory.

5.5.13.2. 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. Results of fecal calprotectin and fecal lactoferrin measurement will be released to the investigators by the central laboratory.

5.5.13.3. 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. A fixed z-score interval implies a fixed height, weight, or BMI difference for children of a given age. 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/m², 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.

5.5.13.4. 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. Participants who become age 10 after Week I-0 do not complete any questionnaires during the study. 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 questionnaire's 35 questions cover the following 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). The recall period is 2 weeks and the questionnaire takes approximately 10 minutes. The score 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 2007, 2007; Ogden 2008; Otley 2002, 2006). The IMPACT-III data will be collected on an electronic device.

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 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.

5.5.13.5. PUCAI

The PUCAI ([Turner 2007](#)), a noninvasive measure of UC disease activity, consists of the following 6 subscores:

- Abdominal Pain
- Rectal Bleeding
- Stool consistency of most stools
- Number of stools per 24 hours
- Nocturnal bowel movement (any diarrhea episode causing waking)
- Activity level

The PUCAI score is calculated as the sum of the 6 subscores of abdominal pain, rectal bleeding, stool consistency, number of stools, nocturnal bowel movement, and activity level. The PUCAI score may take on values in the range of 0 to 85.

The PUCAI score will be calculated if at least 3 of the 6 subscores are available from the visit at which the PUCAI score is measured. For missing PUCAI subscores, the last available subscore value will be carried forward to calculate the score. If the PUCAI score cannot be calculated, it will be considered missing (insufficient data) for that visit.

The baseline PUCAI score is defined as the PUCAI score calculated just prior to the first administration of study agent at Week 0.

5.5.13.6. TUMMY-UC and Observer TUMMY-UC

The TUMMY-UC is an exploratory noninvasive PRO for the measurement of signs and symptoms for pediatric UC that will be completed by participants of ages 8 to <18 years and is undergoing validation ([Marcovitch, 2017](#)). It is calculated using variables listed in Protocol Section 10.10 (Appendix 10). It includes 8 components similar to the PUCAI index and score ranges from 0 to 114. The Observer TUMMY-UC is for participants under age 8 and is completed by caregivers. The version used at the Week I-0 assessment will be used at all subsequent assessments even if the participant's age changes. The evaluation is conducted using electronic questionnaires.

5.5.13.7. Histological Assessment

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.

More details on the definition of histology-related endpoints will be provided in the Histology SAP.

5.5.13.8. Other Endpoint Definitions

Clinical response as assessed by the Mayo score: A decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

Clinically important change in the PUCAI score: a decrease of ≥ 20 from Week I-0.

Histologic improvement:

- Based on Geboes grading system (GS; [Geboes, 2000](#)): Neutrophil infiltration in $<5\%$ of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue.
- Based on Robarts Histopathy Index (RHI; [Mosli 2017](#)): $RHI \leq 9$ with sub-scores of 0 for neutrophils in the epithelium and without erosions or ulcers.

Histologic remission:

- Based on GS: No increase in neutrophils in lamina propria, no neutrophils in epithelium, no crypt destruction, and no erosions, ulcerations or granulation tissue.
- Based on RHI: $RHI \leq 3$, with sub-scores of 0 for lamina propria neutrophils and neutrophils in the epithelium and without ulcers or erosions.
- Based on Nancy Index (NI; [Marchal-Bressenot 2017](#)): $NI \leq 1$

Endoscopic normalization: An endoscopy subscore of 0.

Average daily prednisone-equivalent corticosteroid dose: For corticosteroid medication (excluding budesonide and beclomethasone dipropionate) use at a specific time point, the average daily prednisone-equivalent corticosteroid dose is calculated using the corticosteroid dosage levels from the 6 days prior to the day before the visit.

5.5.14. Analysis Methods

No statistical comparisons will be made. Data will be summarized through Week I-8 for FAS. Data will also be summarized overall and by intervention group from Week M-0 through Week M-44 for FASCR.

The global primary estimand approach and analysis methods specified in Section 5.3.4 for dichotomous endpoints at Week I-8 will be used. Participants with an ICE in category 1-3, and 5 before Week I-8 visit will be considered not to have met the endpoint at that visit and all subsequent

visits. This estimand acknowledges that having an ICE in categories 1-3, and 5 is an unfavorable outcome. For participants experiencing ICE 4, data at all visits after the ICE will be set to missing. No imputation will be performed for missing UC disease-related hospitalizations and surgeries, the missing values will remain as missing.

For continuous endpoints through Week I-8, participants with an ICE in category 1-3, and 5 prior to a visit will be considered to have no change from baseline for that endpoint at that visit and all subsequent visits. For participants experiencing ICE 4, data at all visits after the ICE will be set to missing.

Similarly, the US-specific primary estimand approach and analysis methods specified in Section 5.3.9 for dichotomous endpoints at Week M-44, respectively, will be applied. Participants with an ICE in category 1-5, and 7 before the Week M-44 visit will be considered not to have met the endpoint at that visit and all subsequent visits. This estimand acknowledges that having an ICE in categories 1-5, and 7 is an unfavorable outcome. For participants experiencing ICE 6, data at all visits after the ICE will be set to missing.

For continuous endpoints, participants with an ICE in category 1-5, and 7 prior to a visit will be considered to have no change from baseline for that endpoint at that visit and all subsequent visits, and the value at the visit will be baseline carried forward (BOCF). This estimand acknowledges that having an ICE in categories 1-5, and 7 is an unfavorable outcome. For participants experiencing ICE 6, data at all visits after the ICE will be set to missing.

These rules will override the response status based on the Mayo, PUCAI, and endoscopy subscores.

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

5.6. Safety Analyses

Safety through the induction period will be summarized from Week I-0 through Week I-8 for the Safety Analysis Set (SAF). Safety during the maintenance period will be summarized for the Safety Randomized Analysis Set (SASR) from Week M-0 through Week M-44, and will be based on the randomized treatment group. Additionally, safety during the entire study will also be summarized (only for selected safety analyses as specified below) from Week I-0 through the end of study for the SAF. 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.

5.6.1. 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 adverse event (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 for the SASR will be provided for the following:

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

5.6.2. 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 a 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 SAF, from Week M-0 through Week M-44 for the SASR, and from Week I-0 through the end of the study overall and by intervention group for the SAF. 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 an infusion reaction during the induction period (Week I-0 through Week I-8) or 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 (i.e., from Week M-0 through Week M-44) 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 the end of the study for the SASCR.

A summary of key safety events (death, discontinued 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) will be provided overall and by treatment intervention. Injection site reactions will be summarized during maintenance.

Key safety events during the induction Phase from Week I-0 through Week I-8 will be summarized for the SAF by:

1. baseline age (2 to 11 years, including 2 to 5 years, 6 to 11 years, 12 to 17 years)
2. baseline weight (<40 kg, including <30 kg and 30 to 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 Phase from Week M-0 through Week M-44 will be summarized for the SASR by:

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

3. responders status (clinical responders at Week M-0, delayed responders at Week M-8, and non-responders at Week M-0 and Week M-8) as determined by the IWRS
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)

Additionally, key safety events during the entire study from Week I-0 through the end of study will also be summarized for the SAF and the SASCR.

In addition to the summary tables, listings will be provided from Week I-0 through the end of the study, using the SAF, 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.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the Safety Analysis Set and 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 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 (Grade 0-4). 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:

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

In addition, the following summaries will be done:

1. Summary of maximum postbaseline total bilirubin relative to ULN
2. Summary of maximum postbaseline ALT and AST measurements
3. Number and percentage of participants who met the criteria of possible Hy's law (i.e., ALT or AST ≥ 3 xULN and total bilirubin ≥ 2 xULN)

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.

5.6.3.2. 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 SAF from Week I-0 through Week I-8, and for the entire study from Week I-0 through the end of study. In addition, vital sign parameters during the maintenance period from Week M-0 through M-44 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.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Pharmacokinetic analyses will be performed on the PK analysis set, 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 $\pm$ SD PK ustekinumab concentrations over time by intervention group.

Serum ustekinumab concentrations will be summarized through Week I-8 for the **PK Analysis Set (PKAS)**. Serum ustekinumab concentrations during the maintenance period from Week M-0 through Week M-44 will be summarized overall and by treatment intervention for the **PK Clinical Responder Analysis Set (PKASCR)**. In addition, serum ustekinumab concentrations from Week I-0 through Week M-44 will be summarized by intervention group (q8w and q12w) for **PK All Responder Analysis Set (PKASRES)** (responder, delayed responder). Serum ustekinumab concentrations from Week M-0 through Week M-44 will also be summarized by PK Randomized Analysis Set for Participants Who Had a Dose Adjustment (from the time of dose adjustment).

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 PK Analysis Set and during maintenance from Week M-0 through Week M-44 for the PK Clinical Responder Analysis Set.

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 Dosing).

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 to 5 years, 6 to 11 years, 12 to 17 years)
2. Baseline weight (<40 kg, including <30 kg and 30 to 40 kg, ≥ 40 kg)
3. Clinical response status as determined by the IWRS
4. Baseline immunomodulator status

There will be a descriptive comparison of the adult PK data (CNTO1275UCO3001) with the pediatric PK data (CNTO1275PUC3001) for the PK evaluable analysis set 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. Plot of serum ustekinumab concentrations over time by study (CNTO1275UCO3001, CNTO1275PUC3001).

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

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

Additional PK data from other studies may be used to support the population PK analysis in pediatric participants with UC. The results of the population PK analysis will be provided in a separate report from the CSR.

5.7.1.1. Pharmacokinetics and Efficacy

To determine the influence of ustekinumab concentrations 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 study (CNTO1275UCO3001) with the pediatric study (CNTO1275PUC3001) 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 Mayo 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 Mayo scores at Week M-44 will be summarized by ustekinumab concentration quartiles (micrograms/mL) at Week M-44 for the PKASCR population.

5.7.2. Immunogenicity

Sample anti-drug antibody (ADA) status and sample titer data as well as the cumulative “participant ADA status” and peak titer data 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 antibodies negative sample prior to ustekinumab administration and at least one anti-ustekinumab antibodies positive sample after ustekinumab administration.

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

In participants who have a positive sample 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 (NAb) to ustekinumab will be summarized overall through Week I-8 by **Immunogenicity Analysis Set**. Summaries for Week M-0 through Week M-44 will be provided by intervention group, irrespective of dose adjustment for **Immunogenicity Clinical Responder Analysis Set** (q8w, q12w, overall) and by **Immunogenicity All Responder (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 (CNTO1275PUC3001, CNTO1275UCO3001) for Immunogenicity Analysis Set.

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. Example: $\leq 1:10$, 10 to 100, 100 to 1000, >1000 , if needed.

Incidence of treatment-emergent positive antibody across Peak Titer categories may 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 status.

5.7.3. Pharmacodynamics

Blood, fecal and mucosal biopsy samples will be collected at visits indicated in the Schedule of Activities 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 and mucosal biopsies and microbiome analysis will be performed. Biomarker analyses are considered exploratory and will be summarized in separate technical reports.

5.7.4. 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.

5.7.5. 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.

5.7.6. Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

5.7.7. Definition of Subgroups

The consistency of treatment effect for the primary endpoint will be evaluated for subgroups based on demographic, UC disease characteristics, UC-related concomitant medication usage and UC-related medication history ([Table 8](#), [Table 89](#), [Table 10](#) and [Table 11](#)) using the Primary Estimand (Global Primary Estimand or US-Specific Primary Estimand).

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

The subgroups for subgroup analysis include the following:

Table 8: Demographic subgroups

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

Table 8: Demographic subgroups

Subgroup	Definition
Gender	- Male - Female

Table 9: Clinical Disease Characteristics at Baseline Subgroups

Subgroup	Definition
<i>Clinical Disease Characteristics at Baseline</i>	
UC disease duration	≤1 year > 1 year
Extent of disease	- Limited to left side of colon - Extensive
Severity of UC disease by Mayo Score	- Moderate: 6 ≤ Mayo score ≤ 10 - Severe: Mayo score > 10
Endoscopy score	- Moderate: subscore of 2 - Severe: subscore of 3
Severity of UC disease by PUCAI score	- No or mild disease: ≤ 34 - Moderate or Severe: > 34
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 10: Concomitant Medication Use at Week I-0

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

Table 11: UC-related medication History

Subgroup	Definition
<i>UC-related Medication History</i>	
Biologic vs Non-biologic failures	- Yes - No
Biologic washout period duration	≥ 5 half-lives < 5 half-lives

5.8. Interim Analyses/DMC

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

5.8.1. PK Interim Analysis

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

5.8.2. DMC or Other Review Board

The independent external 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 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.

None of the DMC members will be involved in the study; they will be independent of the sponsor. The independent DMC consists of 2 medical experts in the 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.

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 within 3 months of the Week M-44 DBL or for subjects participating 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 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 DMC Charter prior to the first DMC review.

5.9. Exposure Optimization Substudy Analysis

For participants in the Exposure Optimization Substudy, all collected data will be included in Database Lock 1 (see Section 1.2, for more details).

Refer to Section 6.18, for an overview of the Exposure Optimization Substudy. Participants will be summarized overall and by treatment group (q12w→q4w, q8w→q4w).

5.9.1. 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

5.9.2. Protocol Deviations

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

- List of participants with major protocol deviations

5.9.3. Efficacy

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

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

Proportion of participants in partial Mayo response from initiation of q4w dose regimen to Week M-44 (or 16 weeks of q4w exposure, whichever is longer).

Proportion of participants in PUCAI remission from initiation of q4w dose regimen to Week M-44 (or 16 weeks of q4w exposure, whichever is longer).

5.9.4. Adverse Events

Summary tables during the substudy will be provided for TEAEs:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study participation
- 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.

5.9.5. Laboratory

Change from initiation of the q4w dose regimen in selected laboratory analytes (ie, hematology, chemistry, including serum CRP, fecal calprotectin/fecal lactoferrin) from initiation of the q4w dose regimen through 16 weeks of administration will be summarized by treatment group (q12w → q4w, q8w → q4w, and combined ustekinumab).

5.9.6. PK

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

5.9.7. 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
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRP	C-reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CrI	Credible Interval
DBL	Data Base Lock
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
FAS	Full Analysis Set
FASCR	Full Clinical Responder Analysis Set
FASR	Full randomized analysis set
FASRES	All Responder Analysis Set
GGT	Gamma-Glutamyl Transferase
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 Event
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMPACT-III	A Quality of Life Questionnaire for Children with Inflammatory Bowel Disease
IRB	Institutional Review Board
IQ	Interquartile
IV	Intravenous
IWRS	Interactive Web Response System
Kg	Kilogram
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
LOR	Loss of Response
LTE	Long Term Extension
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methyl Malonic Acid
MMF	Mycophenolate Mofetil
MTX	Methotrexate
Nab	Neutralizing Antibodies
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
PD	Pharmacodynamic
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PKAS	PK Analysis Set
PKASCR	PK Clinical Responder Analysis Set
PKASR	PK Randomized Analysis Set

PKASRES	PK All Responder Analysis Set
PUCAI	Pediatric Ulcerative Colitis Activity Index
q12w	Every 12 Weeks
q4w	Every 4 Weeks
q8w	Every 8 Weeks
SASCR	Safety Clinical Responder Analysis Set
SASR	Safety Randomized Analysis Set
QoL	Quality of Life
RHI	Robarts Histopathology Index
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
SSAS	Substudy Analysis Set
SUARS	Serious Unexpected Associated Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
TNF α	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

6.2. Appendix 2: Changes to Protocol-Planned Analyses

Protocol Section 3.1 states that histologic assessments include GHAS, Geboes score, RHI and Nancy histological index. The definition of histologic improvement and remission will be based on the Geboes grading system, and histologic assessment analyses made by other indexes are considered exploratory. Thus, since the GHAS index is commonly used to assess histologic improvement and remission in Crohn's disease and has not been validated in UC, it was incorporated by error into the CNTO1275PUC3001 Protocol Amendment 4 and the study team decided to remove this index as part of the list of assessments.

Protocol Section 4.1. states that three database locks will occur during the study. However, during the conduct of the study and after receiving feedback from regulatory agencies regarding submission timelines, the study team modified this plan to two database locks only (for further details see SAP Section [1.2](#)).

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.

Table 12 presents a list of the demographic variables that will be summarized overall for the FAS analysis set.

Table 12: 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	
BMI z-score	
Body Mass Index (BMI) (kg/m ²)	
Categorical Variables	
Age (2-11 years [2 to 5 years, 6 to 11 years], 12 to 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 [Russia, Poland, Hungary]; Rest of World [United States, Germany, UK and Belgium])	
BMI (Underweight: <18.5, Normal: 18.5-<25, Overweight: 25-<30, Obese: ≥30)	

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

Table 13 presents a list of the baseline disease characteristics variables that will be summarized overall for the FAS analysis set.

Table 13: Baseline Disease Characteristics

Continuous Variables:	Summary Type
Age at diagnosis (years)	Descriptive statistics (N, mean, SD, median and range [minimum and maximum], and IQ range).
UC disease duration (years)	
Mayo Score	
Modified Mayo Score	
Pediatric ulcerative colitis activity index (PUCAI) Score	
C-reactive protein (CRP)	
IMPACT-III	
Fecal calprotectin concentrations	
Fecal lactoferrin concentrations	
Categorical Variables	
Extent of disease (Limited to left side of colon, Extensive)	Frequency distribution with the number and percentage of participants in each category.
Severity of disease by Mayo Score (No: Mayo Score ≤ 2; Mild: 3 ≤ Mayo Score < 6; Moderate: 6 ≤ Mayo Score ≤ 10; Severe: >10)	

Severity of disease by PUCAI Score (No: <10; Mild: 10 - ≤34; Moderate: 34 - <65; Severe: ≥65)	
Severity of endoscopy subscore (Moderate: endoscopy subscore=2; Severe: endoscopy subscore=3)	
Abnormal CRP (>3 mg/L),	
Abnormal fecal calprotectin (>250 mg/kg)	
Abnormal fecal lactoferrin (>7.24 µg/g)	

In addition, summaries by age (2 to 11 years, including 2 to 5 years and 6 to 11 years, 12 to 17 years), and weight (<40 kg, including <30 kg and 30 to <40 kg; ≥40 kg) will be provided separately overall for demographics and baseline disease characteristics.

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

Further, a randomization listing will be provided for the FAS.

6.4. Appendix 4: Protocol Deviations

In general, major protocol deviations (Section 6.4.1) 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.

Other deviations are as follows:

- Participants who entered the study but did not meet the inclusion/exclusion criteria (Section 6.4.2) by category
- Protocol deviations in study intervention administration (Section 6.4.3)

Protocol deviations will be summarized overall for FAS through Week I-8, and by treatment group and overall for the FASR analysis set (from Week M-0 through Week M-44).

In addition to the summary tables, the following listings will be provided from Week I-0 through Week M-44:

- List of participants with major protocol deviations
- List of participants who did not meet study selection criteria
- 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 44 DBL 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
- Minor Protocol Deviations (PD) – Study Procedures
- 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: UC 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 include: 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.

6.5. 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 UC disease-specific concomitant medications at baseline will be presented overall by the FAS analysis set. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 UC disease-specific concomitant medication. The following UC 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 to 5 years, 6 to 11 years], 12 to 17 years), and weight (<40 kg [<30 kg, 30 to 40 kg], ≥ 40 kg) will also be provided for the FAS analysis set.

In addition, summaries of UC-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 UC-related biologic medication history will be summarized overall for the FAS.

In addition, summaries of UC medication history (participants who took medications for UC and their length of exposure prior to Week I-0) will be provided by 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 Safety Randomized Analysis Set.

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 tuberculosis, or opportunistic infection occurring after the first administration of study intervention(s) in participants in this clinical study will be discussed in the CSR.

6.9. Appendix 9: Medications of Special Interest

NA

6.10. Appendix 10: Laboratory Toxicity Grading

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

If a central laboratory value falls within the grading as specified below 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 (/mm ³)	Increase		>4000 - 20,000	>20,000	
Lymphocytes (/mm ³)	Decrease	<LLN - 800	<800 - 500	<500 - 200	<200
Neutrophils (/mm ³)	Decrease	<LLN - 1500	<1500 - 1000	<1000 - 500	<500
Platelets (/mm ³)	Decrease	<LLN - 75,000	<75,000 - 50,000	<50,000 - 25,000	<25,000
Total WBC count (/mm ³)	Increase			>100,000	
Total WBC count (/mm ³)	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	>1.5 - 3.0 x ULN if	>3.0 - 10.0 x ULN if	>10.0 x ULN if baseline

		baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	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

6.11. Appendix 11: Prohibited Medication Changes (Category 3 of the Intercurrent Events)

ICE category 3 for all

Had prohibited changes in UC 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 UC.
2. Increase above baseline in the dosage of oral budesonide or oral beclomethasone dipropionate due to worsening UC.
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 UC.
4. No oral budesonide or oral beclomethasone dipropionate at baseline and initiation of oral budesonide or oral beclomethasone dipropionate due to worsening UC.
5. An initiation of rectal corticosteroids (foam or enema; excludes suppositories) after baseline due to worsening UC.
6. Any switch from oral budesonide/oral beclomethasone dipropionate to other oral corticosteroids or parenteral corticosteroids due to worsening UC.

5-ASA compounds:

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

Immunomodulator agents:

1. Increase above baseline in the dosage of AZA/6-MP or MTX due to worsening UC.
2. No AZA, 6-MP, or MTX at baseline and initiation of AZA, 6-MP, or MTX after baseline due to worsening UC.
3. Switch between AZA/6-MP and MTX due to worsening UC.

Protocol-prohibited medications:

Initiation of any of the following immunomodulatory agents after baseline:

1. IV corticosteroids.

2. Immunomodulatory agents other than 6-MP, AZA, and MTX (including, but not limited to, 6-TG, cyclosporine, Mycophenolate Mofetil (MMF), tacrolimus, sirolimus, thalidomide, tofacitinib, and other Janus kinase inhibitors).
3. More than one antibiotic initiated for the treatment of UC.
4. Parenteral nutrition administered via a central line.
5. Biologic agents (including, but not limited to, TNF α 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 Protocol Section 5.3 [Lifestyle Considerations]).

6.12. Appendix 12: Rescue Medications (Category 4 of the Intercurrent Events)

Following a LOR, any initiation or increase in the dose of 6-MP/AZA/MTX, oral budesonide, oral beclomethasone dipropionate, or oral corticosteroids (prednisone equivalent) above the dose received at baseline will be considered a rescue medication. Any participant who uses rescue medication after a confirmed loss of response will be considered a treatment failure from the time of the use of rescue medication onwards.

6.13. Appendix 13: Mayo Score

Mayo scoring system for assessment of ulcerative colitis activity**Stool frequency^a**

- 0 = Normal number of stools for this participant
- 1 = 1-2 stools more than normal
- 2 = 3-4 stools more than normal
- 3 = 5 or more stools more than normal

Rectal bleeding^b

- 0 = No blood seen
- 1 = Streaks of blood with stool less than half the time
- 2 = Obvious blood with stool most of the time
- 3 = Blood alone passed

Findings of endoscopy

- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern)
- 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment^c

- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

^a Each participant serves as his or her own control to establish the degree of abnormality of the stool frequency.

^b The daily bleeding score represents the most severe bleeding of the day.

^c The physician's global assessment acknowledges the 3 other criteria, the participant's recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the participant's performance status.

6.14. Appendix 14: Grading Criteria for the Histological Evaluation of Disease Activity in Ulcerative Colitis

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

Ref: Geboes K , Riddell R , Ost A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut 2000; 47: 404-409.

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 that meet the following inclusion and exclusion criteria:

1. Phase 3 global clinical studies.
2. Using a landmark endpoint approximately 1 year after study start.
3. Randomized withdrawal study design.
4. Approved study interventions for the treatment of moderate to severe UC in adults.
5. The placebo group at maintenance are based on responders at the induction period.
6. Have clinical remission endpoint defined or can be derived based on data as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline (without requiring sustained remission at multiple timepoints).

For the purpose of the meta-analyses for the placebo rate to be descriptively compared with the Secondary Endpoint **Symptomatic Remission at Week M-44**, the studies will be chosen that meet the following inclusion and exclusion criteria:

1. Phase 3 global clinical studies.
2. Using a landmark endpoint approximately 1 year after study start.
3. Randomized withdrawal study design.
4. Approved study interventions for the treatment of moderate to severe UC in adults.
5. The placebo group at maintenance are based on responders at the induction period.
6. Have symptomatic remission endpoint defined or can be derived based on data as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline.

6.15.2. Meta-Analysis Statistical Details

The meta-analysis for the historical placebo control used the ‘metafor’ package in R⁸. The meta-analytic models were fitted with the `rma.uni()` function.

For a set of $i = 1, 2, \dots, k$ independent studies, the random-effects model was fitted using REML random-effects model using the `rma.uni()` function with:

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

Weighted estimation (with sample size based weights) was used where

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

$\overline{\theta_w}$ is the weighted average of the true outcomes in the set of k studies, with weights equal to $w_i = n_i$ (the ‘sample size’ 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 the study j , where r_{AUj} is the response rate in the placebo group in the study j .

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

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

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

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

$$\beta_{kj} \sim N(\mu_k, \tau_k), k = 0, 1, \dots, c$$

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

$$\mu_k \sim N(0, \tau), k = 0, 1, \dots, c$$

$$\tau_k \sim \text{Gamma}(a, b), k = 0, 1, \dots, c$$

where the hyperparameters are set to non-informative 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 CNTO1275PUC3001 study. More specifically, we use the average value for each covariate based on CNTO1275PUC3001 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}

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

$$\theta_{AUP} = \mu_0 + \mu_1 \bar{X}_{1p} + \dots + \mu_c \bar{X}_{cp}$$

6.16.3. Adult Placebo Study Level Data

r_{AV_j} is the proportion of patients on placebo in clinical remission from study j with study level data. Then we have

$$Y_{AV_j} \sim \text{Bin}(n_j, r_{AV_j}), \text{ and } j = 1, \dots, m$$

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

$$\theta_{AV_j} \sim N(\mu_{AV}, \tau_{AV})$$

The hyperparameters will be modeled with non-informative priors,

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

Where the hyperparameters are set to non-informative 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 weighted average 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 CNTO1275PUC3001 study.

$$Y_{Pi} \sim \text{Bernoulli}(r_p)$$

$$\theta_p = \log\left(\frac{r_p}{1 - r_p}\right)$$

where θ_p is set to be non-informative prior.

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 in adult studies of ustekinumab in UC 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 $\mu\text{g/mL}$
- 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

6.17.3. Study Design

This is an exploratory sub-study within a Phase 3 multicenter, interventional study of ustekinumab in pediatric UC (CNTO1275PUC3001). Participants who lose response during Study CNTO1275PUC3001 and have an 8 weeks post-dose serum ustekinumab concentration of <1.4 $\mu\text{g/mL}$ 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 (LOR) 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 $\mu\text{g/mL}$ 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 SC 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 Schedule of Activities. 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-up q4w. 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 PUCAI score and partial Mayo 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 medication. If a participant is <18 years and, in the opinion of the investigator, would benefit from further treatment at the completion of the substudy, the participant may be enrolled in 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 in Study CNTO1275PUC3001, 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 a 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, 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 (CNTO1275PUC3001 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 partial Mayo score from initiation of the q4w dose regimen to Week M-44 (or 16 weeks of q4w exposure, whichever is longer).

- Change in the PUCAI score from initiation of the q4w dose regimen to Week M-44 (or 16 weeks of q4w exposure, whichever is longer)
- Proportion of participants in partial Mayo response from initiation of q4w dose regimen to Week M-44 (or 16 weeks of q4w exposure, whichever is longer).
- Proportion of participants in PUCAI remission from initiation of q4w dose regimen to Week M-44 (or 16 weeks of q4w exposure, whichever is longer).
- 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 $<1.4 \mu\text{g/mL}$ (at Week M-8 or M-32). Therefore, based on a sample size of approximately 100 participants, the Sponsor expects approximately 10 participants will be eligible for the substudy, and approximately 6 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 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 will be summarized for all participants who receive at least 1 dose of ustekinumab in the substudy. The following analyses will be used to assess the safety of participants in the substudy:

frequency and type of AEs, SAEs, 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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