Janssen Research & Development*

Clinical Protocol

Protocol Title

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

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Short Title

Efficacy, Safety, and Pharmacokinetics of Ustekinumab in Pediatric Participants with Moderately to Severely Active Crohn's Disease

Protocol CNTO1275CRD3004; Phase 3
Amendment 7
STELARA®(ustekinumab)

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

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 7	06 March 2023
Amendment 6	25 May 2022
Amendment 5	21 May 2021
Amendment 4	02 February 2021
Amendment 3	21 October 2020
Amendment 2	14 October 2020
Amendment 1	26 June 2020
Original Protocol	17 December 2019

Amendment 7 (06 March 2023)

Overall Rationale for the Amendment: To add an interim analysis of participants with body weight ≥40 kg to support a submission to the EMA.

The changes made to the clinical protocol CNTO1275CRD3004 as part of Protocol Amendment 7 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.19 Appendix 19: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Synopsis; Section 4.1: Overall Design	Added paragraph describing new interim analysis: **End of study analyses will occur after Week M-44 when all participants will have completed the study. In addition, an interim analysis of the data will be performed when at least 36 randomized participants with body weight ≥40 kg at Week I-0 and Week M-0 have completed the Week M-44 visit or terminated the main study participation prior to Week M-44. The interim analysis results will be used for the EMA submission of participants with body weight ≥40 kg. At the time of the interim analysis, the treatment regimen will only be unblinded for the participants who meet the criteria for the interim analysis (ie, at least 36 randomized participants with body weight ≥40 kg who have completed the Week M-44 visit or terminated the main study participation prior to Week M-44).**	To add an interim analysis to support a submission to the EMA.
Synopsis: sample size determination	Added paragraph regarding new interim analysis: **Confidence intervals (CI) will be provided for evaluation as needed. See SAP for details.**	To clarify the synopsis.
Synopsis: statistical analyses	Added a sentence in the first paragraph: **For the EMA submission, randomization of 36 participants with body weight ≥40 kg is considered sufficient to adequately characterize the PK of ustekinumab in this subgroup.**	To add an interim analysis to support a submission to the EMA.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3: Schedule of Activities, Table 1 Table 2	The note for serum biomarker has been updated as: **For children with body weight ≤25 kg, collection of serum biomarkers must occur at Screening.** For children with body weight >25 kg, collection of serum biomarkers may occur at I-0, **but NOT at both Screening and I-0.** **For children with body weight >25 kg, collection of serum biomarkers may occur at I-0 if it was NOT obtained at Screening. Do NOT obtain additional sample if it was taken at Screening.**	To clarify the collection of serum biomarkers for children with body weight >25 kg versus ≤25 kg.
Table 1, 2, and 3.	Study Procedure – Induction has been updated as: If the first or the last day of a visit window coincides with a holiday **and/or a site closure**, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.	To clarify the visit window period.
Table 3.	A visit has been added at M-40 for "serum ustekinumab concentration". A visit has been added at M-16 for the collect and review PCDAI electronic diary.	Only for substudy participants. The visit was missing.
Section 4.1: Overall Design	Added a paragraph describing the interim analysis database lock: **A DBL to support the interim analysis for the EMA submission for randomized participants with body weight ≥40 kg will occur when at least 36 randomized participants with body weight ≥40 kg at Week I-0 and Week M-0 have received at least 1 administration of study intervention during maintenance and have completed the Week M-44 visit, or terminated the main study participation prior to Week M-44. Participants who meet this criterion and who had PK samples collected at the Week I-0, M-0, and M-8 visits will be included in the PK analysis.**	To add interim analysis DBL for EMA submission.
Section 4.2: Scientific Rationale for Study Design Blinding, Control, Study Phase/Periods, Intervention Groups	Added a paragraph describing the new unblinded group of sponsor personnel: **A limited group of sponsor personnel will have access to the unblinded treatment assignment only for the participants included in the interim analysis.**	To add limited unblinded group for EMA submission.
Section 6.3: Measures to Minimize Bias: Randomization and Blinding	Note added describing the unblinded group of sponsor personnel: **Sponsor personnel will remain blinded to maintenance treatment assignment until after**	To add an interim analysis to support a submission to the EMA.

Section Number and Name	Description of Change	Brief Rationale
	the DBL following the M-44 visit, with the exception of a PK sponsor representative independent of study conduct to review the PK interim analysis (see DMC SAP for further details) and a sponsor unblinded group for preparing the EMA submission for the participants ≥40 kg included in the interim analysis (Further details will be provided in the unblinding plan, including the list of sponsor personnel who will have access to unblinded information at the time of the interim analysis).	
Section 9.2: Sample Size Determination	Added a subsection explaining the sample size determination for the EMA submission for participants ≥40 kg: **9.2.1 Sample Size Determination for the EMA Submission for Participants ≥40 kg:** **Optimal design analysis was performed for this study using FIM-based methods to determine the appropriate sample size needed to adequately characterize ustekinumab PK in pediatric CD participants ≥40 kg. Based on the PIP commitment, at least 24 participants with body weight <40 kg are planned to be enrolled in this study. Thus, the maximum number of participants with body weight ≥40 kg may not be expected to exceed 66 (for a total of 90). Accordingly, optimization analyses for the subgroup of participants with body weight ≥40 kg were performed with the assumption that 66 participants will provide the maximum information obtainable in the study. From the FIM optimization analysis, no substantial PK information is expected to be gained if the number of pediatric participants with body weight ≥40 kg increases from 36 to 66. With 36 participants, approximately 92% of the information needed to characterize ustekinumab PK is obtained when compared with the information obtained from 66 participants. Accordingly, 36 participants with body weight ≥40 kg would ensure adequate characterization of the PK of ustekinumab in this subgroup.**	To add sample size justification for the EMA submission.
Section 9.3: Populations for Analyses	Added the EMA population: **EMA Randomized Analysis Set for Participants with Body Weight ≥40 kg (ERAS): At least 36 randomized participants with body weight ≥40 kg at Week I-0 and Week M-0, who received at least 1 administration of study intervention during maintenance, and completed the Week M-44 visit or terminated**	To add the analysis population for the interim analysis used to support the EMA submission of participants ≥40 kg.

Section Number and Name	Description of Change	Brief Rationale
	the main study participation prior to Week M-44.	
Section 9.4: Statistical Analyses	Added a paragraph explaining the statistical analysis for the EMA submission: **The analyses to support the EMA submission will be based on at least 36 randomized participants who had body weight ≥40 kg at Week I-0 and Week M-0 and had completed the Week M-44 visit or terminated study participation prior to Week M-44. All efficacy analyses that are specified for the main study will be performed with exception of the US-specific endpoints analyses and some supplementary analyses. All safety analyses and selected other analyses (including PK and immunogenicity) that are specified for the main study will be performed. Details of the analyses to support the EMA submission will be provided in the SAP.**	To add an interim analysis to support a submission to the EMA.
Section 9.4.9 Safety Analyses Clinical Laboratory Tests Section 10.13.2.1: Phase 3-4 Liver Chemistry Stopping Criteria and Follow-up Assessments	Updated the liver chemistry stopping criteria: (ALT or AST ≥3xULN and total bilirubin ≥2xULN **(>35% direct) or INR >1.5).**	Need to update the Hy's law description in the protocol.
Section 9.4.10. Other Analyses Pharmacokinetic Analyses	Second paragraph updated as following: Serum ustekinumab concentrations will be summarized overall through Week I-8 for the 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 ~~also~~ be summarized ~~overall (combined q8w and q12w)~~ for PK All Responder Analysis Set (PKASRES) (responder, delayed responder).	To clarify PK analyses.
Section 9.5. Interim Analysis	The new paragraph below has been added: **An interim analysis of the data will be performed when at least 36 randomized participants with body weight ≥40 kg at Week I-0 and Week M-0 have completed the Week M-44 visit or terminated study participation prior to Week M-44. The interim analysis results will be used for the EMA submission for participants with body weight ≥40 kg.**	To add an interim analysis to support a submission to the EMA.

Section Number and Name	Description of Change	Brief Rationale
Section 10.17 Appendix 17 : Exposure Optimization Substudy	Added some clarification to the study design: Participants will continue to follow the study protocol Schedule of Activities, **with the exception of Study Home Visits and at-Home Study Intervention. Substudy participants who regain clinical response may have Study Intervention Administration at Home and/or Study Site or Home visits.** Removed previously deleted PK analysis from Table 6: schedule of activities for substudy.	To clarify the study design of the exposure estimation substudy.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

STELARA® (ustekinumab) is a fully human immunoglobulin G1 kappa monoclonal antibody which binds with high affinity to the p40 submit common to both interleukin (IL)-12 and IL-23. The mechanism of action of ustekinumab is prevention of IL-12/23p40 binding to the IL-12Rβ1 cell surface receptor shared by both cytokines. Through this mechanism of action, ustekinumab effectively neutralizes IL-12 T helper 1 (Th 1)- and IL-23 T helper 17 (Th 17)-mediated cellular responses.

OBJECTIVES AND ENDPOINTS

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

Objectives

Primary Objectives

The **global** primary objectives of this study are, in pediatric participants with moderately to severely active Crohn's disease:

- To evaluate the efficacy of ustekinumab dosing in inducing clinical remission.
- To evaluate the safety profile of ustekinumab.
- To evaluate ustekinumab exposure (pharmacokinetics [PK]).

The **US-specific** primary objectives of this study are, in pediatric participants with moderately to severely active Crohn's disease:

- To evaluate the efficacy of ustekinumab dosing in maintaining clinical remission among participants who were in clinical response in induction.
- To evaluate the safety profile of ustekinumab.
- To evaluate ustekinumab exposure (PK).

Secondary Objectives

The **global** and **US-specific** secondary objectives of this study are, in pediatric participants with moderately to severely active Crohn's disease:

- To evaluate the efficacy of intravenous (IV) ustekinumab during the induction period.
- To evaluate the efficacy of subcutaneous (SC) ustekinumab during the maintenance period among participants who were in clinical response in induction.

Endpoints

Primary Endpoint

The **global** primary endpoint is clinical remission at Week I-8.

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

Secondary Endpoints

The **global** secondary endpoints are:

- Clinical remission at Week I-6 as assessed by sPCDAI.
- Clinical response at Week I-8.
- Clinical response at Week I-6 as assessed by sPCDAI.
- Endoscopic response at Maintenance Week 8 (Week M-8) as assessed by SES-CD.*
- Clinical response at Week M-8.*

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

The endpoints below will be evaluated for participants who are clinical responders at Week I-8:

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

The **US-specific** secondary endpoints are:

- Clinical remission at Week I-8.
- Clinical remission at Week I-6 as assessed by sPCDAI.
- Clinical response at Week I-8.
- Clinical response at Week I-6 as assessed by sPCDAI.
- Endoscopic response at Week M-8 as assessed by SES-CD.*
- Clinical response at Week M-8.*

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

The endpoints below will be evaluated for participants who are clinical responders at Week I-8:

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

Hypothesis

Global Hypothesis

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

US-Specific Hypothesis

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

OVERALL DESIGN

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

End of study analyses will occur after Week M-44 when all participants will have completed the study. In addition, an interim analysis of the data will be performed when at least 36 randomized participants with body weight ≥40 kg at Week I-0 and Week M-0 have completed the Week M-44 visit or terminated the main study participation prior to Week M-44. The interim analysis results will be used for the EMA submission of participants with body weight ≥40 kg. At the time of the interim analysis, the treatment regimen will only be unblinded for the participants who meet the criteria for the interim analysis (ie, at least 36 randomized participants with body weight ≥40 kg who have completed the Week M-44 visit or terminated the main study participation prior to Week M-44).

An external Data Monitoring Committee (DMC) will be commissioned for this study to monitor safety data on an ongoing basis until all participants complete the Week M-44 visit or terminate the study prior to Week M-44. 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 to evaluate the ustekinumab dosage for participants <40 kg (as measured at Week I-0).

NUMBER OF PARTICIPANTS

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

INTERVENTION GROUPS AND DURATION

Induction Period

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

For participants with body weight <40 kg:

- 250 mg/m^2 IV

For participants with body weight ≥40 kg:

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

Maintenance Period

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

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

Early Escape Criteria (Induction Nonresponders)

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

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

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

    OR

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

        - If a participant is documented to have low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit), the participant will be eligible for enrollment in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to every 4 weeks (q4w) (See Appendix 17 [Section 10.17]). If determined to be medically appropriate in the judgment of the investigator,

participants who meet the Early Escape criteria may receive approved rescue therapies while they await the Week M-8 ustekinumab trough level result to determine eligibility for the Exposure Optimization Substudy.

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

Loss of Response

All participants randomized into the maintenance period will be assessed for loss of response (LOR) based on PCDAI or short pediatric Crohn's Disease Activity Index (sPCDAI) score.

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

1. An increase in the PCDAI >12.5 above the reference PCDAI score, or an increase in the sPCDAI ≥10 above the reference sPCDAI score, at 2 consecutive visits at least 7 days apart. The reference PCDAI is Week M-0 for induction responders and Week M-8 for delayed induction responders.

AND

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

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

Participants who have LOR will be eligible for a dose adjustment; those who have LOR and have documented low ustekinumab exposure will be eligible for the Exposure Optimization Substudy.

Dose Adjustment Criteria:

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 clinical response at Week M-8), participants who experience LOR 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).

Participants will be assessed 16 weeks after dose adjustment. If the participant is not in clinical response or sPCDAI clinical response at that time, and does not have low exposure, the participant will be withdrawn from the study intervention and return for the~~ir~~ final safety visit (approximately 20 weeks after the administration of the last study intervention).

If a participant experiences LOR, is dose adjusted (or sham dose adjusted) to ustekinumab q8w, achieves response, and subsequently experiences a second LOR with documented low ustekinumab exposure*, the participant may be eligible for the optional Exposure Optimization Substudy (Appendix 17 [Section 10.17]).

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

Exposure Optimization Substudy

- If a participant has not achieved response by Week M-8, and is documented to have low exposure (defined as an ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit), the participant will be eligible to be enrolled in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to q4w (Appendix 17 [Section 10.17]).
- If a participant has achieved response by Week M-8 and in the maintenance phase has LOR at any time after Week M-8 and has low exposure*, he/she may be enrolled in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to q4w (Appendix 17 [Section 10.17]) (*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).

EFFICACY EVALUATIONS

Efficacy evaluations will include the following:

- PCDAI/sPCDAI score(s)
- Crohn's Disease Activity Index (CDAI) score
- C-reactive protein (CRP)
- Fecal calprotectin and fecal lactoferrin
- IMPACT-III
- Fistula assessment
- Ileocolonoscopy for SES-CD and SEMA-CD scores
- Histologic Assessments: Global Histology Activity Score (GHAS), Geboes score, and Robarts Histopathology Index (RHI)
- Height, weight, and body mass index (BMI) to determine age and sex-specific z-scores

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected for measurement of serum concentrations of ustekinumab and antibodies to ustekinumab as indicated in the Schedule of Activities. Serum samples will be analyzed to determine concentrations of ustekinumab using a validated, specific, and sensitive immunoassay method and will be used to evaluate various ustekinumab PK parameters.

BIOMARKER AND HISTOLOGIC EVALUATIONS

Blood samples for PK assessment may also be used for serum-based biomarker analyses. These analyses will include, but not be limited to, IL-17A and IL-22 and will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to Crohn's disease or the mechanism of action of ustekinumab. Ileocolonic biopsy samples will be collected during ileocolonoscopy to assess the effect of study intervention on gene expression and for the histological assessment of disease and improvement. Fecal samples will be collected from all participants and microbiome and associated products analysis will be conducted to evaluate the association between inflammatory proteins and microbial activities with ustekinumab treatment and/or Crohn's disease.

IMMUNOGENICITY EVALUATIONS

Antibodies to ustekinumab will be evaluated in serum samples collected for PK analysis. The titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to ustekinumab and/or further characterize the immunogenicity of ustekinumab.

SAFETY EVALUATIONS

Safety evaluations will include the assessment of adverse events (AEs; at the visit and those occurring between evaluation visits), tuberculosis evaluation and other infection assessment, clinical laboratory blood tests (complete blood count and serum chemistries), physical examinations, height, weight, vital signs, concomitant medication review, observations for an infusion reaction (an AE, apart from laboratory abnormalities, that occurs during or within 1 hour after the infusion of study intervention), injection-site reactions, and/or allergic reactions.

STATISTICAL METHODS

Sample Size Determination

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

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

For the EMA submission, randomization of 36 participants with body weight ≥40 kg is considered sufficient to adequately characterize the PK of ustekinumab in this subgroup.

Statistical Analyses

Data primarily will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, interquartile range, minimum and maximum, as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Confidence intervals (CI) will be provided for evaluation as needed. See SAP for details.

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

Primary Efficacy Analysis

Global Primary Analysis

The global primary analysis population includes all participants who received an administration of study intervention at Week I-0. A summary of the proportion of participants who are in clinical remission at Week I-8, will be provided, as well as a 95% confidence interval (CI).

US-Specific Primary Analysis

The US-specific primary analysis population includes all participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and received at least 1 administration of study intervention during maintenance.

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

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

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

Secondary Efficacy Analysis

The analysis population for secondary endpoints through Week I-8 includes all participants who received one administration of study intervention at Week I-0. For the secondary endpoints in induction, the proportion of participants who meet the endpoint at Week I-8 will be summarized overall, and a 95% CI will be provided.

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

Pharmacokinetic Analyses

Descriptive statistics of the serum ustekinumab concentrations will be calculated at each sampling time point. These concentrations will be summarized over time. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or Statistical Analysis System datasets. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

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

Immunogenicity Analyses

Incidence of antibody (evaluable, treatment-emergent ADA positive, treatment-emergent ADA negative) status and neutralizing antibodies to ustekinumab will be summarized overall through Week I-8 for 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.

Summaries for Week M-0 through Week M-44 will be provided by intervention group, irrespective of dose adjustment, for all participants who were randomized into the maintenance period of the study, received at least 1 administration of ustekinumab during maintenance, and had appropriate samples for detection of

antibodies to ustekinumab (q8w, q12w, overall). The summaries will also be provided for the participants fulfilling these criteria and who were in clinical response to ustekinumab induction therapy at Week I-8.

Biomarker Analyses

Changes in serum protein analytes, fecal biomarkers, and biopsy ribonucleic acid 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 selected markers and response to treatment will be explored.

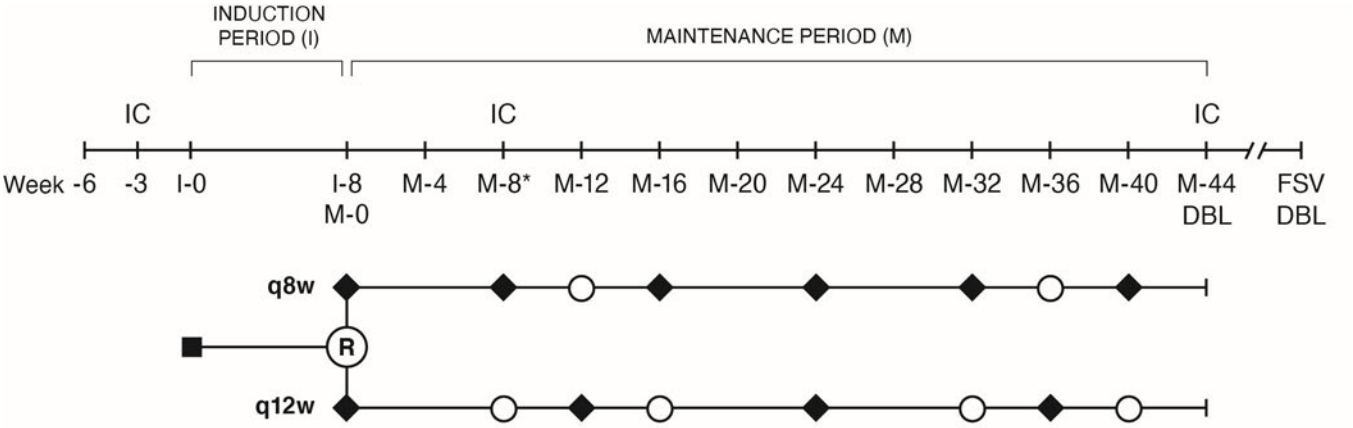
Safety Analyses

The following analyses will be used to assess the safety of participants in the study: frequency and type of AEs, serious adverse events (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), AEs within one hour of IV infusion, and injection-site reactions.

Safety analyses will include summaries of AEs and laboratory parameters. The summaries will be based on the population of participants who received at least 1 administration of study intervention in induction at Week I-0 (induction period) and the population of participants who were randomized into the maintenance period of the study and received at least 1 administration of study intervention during maintenance (maintenance period).

1.2. Schema

Figure 1: Schematic Overview of the CNTO1275CRD3004 Study



■ = Intravenous ustekinumab: 250 mg/m² IV for participants with <40 kg body weight; 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.

◆ = Subcutaneous ustekinumab: 90 mg for participants with ≥40 kg body weight; 60 mg/m² for participants with <40 kg body weight.

○ = SC Placebo

DBL = Database Lock FSV = Final Safety Visit IC = Ileocolonoscopy R = Randomization

*** Nonresponders at Week M-8:**

1. If Week M-8 ustekinumab trough concentration is low, option to enter substudy.
   - If choose not to enter substudy, must withdraw study intervention with approximately 20 week safety follow-up.
2. If Week M-8 ustekinumab trough concentration is not low, must withdraw study intervention with approximately 20 week safety follow-up.

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1.3. Schedule of Activities (SoA)

Table 1: Screening Period: Schedule of Activities

Study Period	Screening	NOTES
	Within 6 Weeks	
Study Procedure		Screening should occur within 6 weeks before the Week I-0 visit. Blood sampling in participants with a body weight ≤20 kg must be divided between visits during the screening period and other visits as required for countries outside of Japan. Blood sampling in participants in Japan weighing <26 kg must be divided between visits during the screening period and other visits as required. Contact the sponsor for details of the recommended sampling sequence.
Screening/Administrative		
Informed consent/assent (ICF)	X	
Inclusion/exclusion criteria	X	
Medical history and demographics	X	
Diet history	X	
IGRA testing/Tuberculin skin test	X	All participants will undergo IGRA testing (including either QuantiFERON®-TB or T-Spot®). In addition to IGRA testing, tuberculin skin testing (Appendix 10 [Section 10.10]) should also be considered in participants less than 5 years old, if preferred by local health authorities, or if the investigators believe based on their judgment that both tests are clinically indicated to evaluate a participant at high risk for latent TB.
Chest radiograph	X	Chest radiograph should be obtained during the screening period unless one was obtained 6 months prior to the first administration of study intervention and the findings are recorded in the study source documents. Chest radiographs should be reviewed to assess for potential undiagnosed pulmonary pathologies that may include extraintestinal manifestations of IBD, malignancies, and prior or current infection.
HBV and HCV testing	X	Details are provided in Appendix 12 (Section 10.12).
HIV testing	X	HIV testing is required in those study participants who are greater than 6 years old only when birth history is unknown (ie, adopted) or have exposure risks (eg, parents with HIV or with risk factors) or at the discretion of the study investigator. HIV testing in study participants who are less than 6 years old where testing would otherwise be required do not need testing provided that there is a record of a negative HIV test at birth. This is acceptable at the discretion of the study investigator as long as it is entered into the study record.
Highly sensitive urine pregnancy test	X	Must be performed for females who have undergone menarche and are of childbearing potential.

Table 1: Screening Period: Schedule of Activities

Study Period	Screening	NOTES
	Within 6 Weeks	
Stool for enteric pathogens	X	Stool studies for enteric pathogens including a stool culture and *Clostridioides difficile* (formerly known as *Clostridium difficile*) test (*C. difficile* toxin/GDH with Reflex to PCR testing) will be performed by the central laboratory. Results from local laboratory studies performed during the current episode of disease exacerbation and within 4 months prior to the first administration of study intervention may be used in place of central testing. Additional testing (eg, ova and parasites or *Escherichia coli* 0157:H7 assessments) may be performed at the investigator's clinical discretion. If previous results are unavailable, the central laboratory should be used to perform the tests at screening.
Confirmation of Crohn's disease diagnosis	X	Confirmation of Crohn's disease or fistulizing Crohn's disease with active colitis, ileitis, or ileocolitis, confirmed at any time in the past by endoscopy and histology. Radiographic findings may provide supporting evidence.
Acceptable evidence of immunity to measles (as representative for MMR administration) and varicella	X	Confirm that the participant is up to date with all immunizations in agreement with current local immunization guidelines for immunosuppressed participants before Week I-0.
Provide participant diaries (CDAI, PCDAI) and training	X	Provide participants with the take-home electronic diaries and provide training on diary completion. Participants will be instructed to complete the dairies for 7 days prior to the Week I-0 visit and all other applicable visits indicated in the SoA. The timing of diary completion should be coordinated with the site and should not overlap with preparation for the screening ileocolonoscopy procedure.
Safety Assessments		
Physical examination	X	
Vital signs	X	Temperature, pulse/heart rate, respiratory rate, and blood pressure.
Weight	X	
Height	X	
AE review	X	
Concomitant medication review	X	
CD-related surgeries/ hospitalizations review	X	Collect information on events occurring prior to the ICF.
Efficacy Assessments		
Ileocolonoscopy	X	Ileocolonoscopy should be performed within approximately 3 weeks prior to the administration of study intervention at Week I-0.[a] A SES-CD and a SEMA-CD score will be assessed by a central endoscopist. All study ileocolonoscopies should be performed with

Table 1: Screening Period: Schedule of Activities

Study Period	Screening	NOTES
	Within 6 Weeks	
		study software to permit central review of the video of the ileocolonoscopy and scoring using the criteria of the SES-CD and the SEMA-CD (Section 8.1.7). (In case back-up software would need to be used, this should be recorded in the source documents.)
Stool sample (fecal calprotectin)	X	Stool studies for fecal calprotectin may be performed at either the central or local laboratory. Note: In case Inclusion Criterion 5.2 is otherwise met, the fecal calprotectin assessment is not needed.
PCDAI score	X	The investigator will complete the questionnaire on a tablet.
CRP	X	
Clinical Laboratory Assessments		
Hematology, chemistry	X	
ESR	X	
Biomarkers		
Ileocolonic Biopsy (RNA, histology)	X	The screening biopsy samples for histology and RNA analyses will be collected during the screening ileocolonoscopy performed within approximately 3 weeks prior to the first study intervention administration.[a]
Serum biomarkers	X	For children ≤25 kg, collection of serum biomarkers must occur at Screening. For children >25 kg, collection of serum biomarkers may occur at I-0, but NOT at both Screening and I-0.

a. A video ileocolonoscopy recorded within 3 months prior to the Week I-0 visit may be used in case of rescreening of a participant who had an ileocolonoscopy but failed the initial screening for another reason, on a case-by-case basis, after consultation with the sponsor. This is also applicable to the histologic and RNA analyses results obtained from the ileocolonic biopsy samples collected during the initial screening.

Abbreviations: AE=adverse event; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; GDH=glutamate dehydrogenase antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IBD=inflammatory bowel disease; ICF=informed consent/assent form; IGRA=interferon gamma release assay; IV=intravenous; MMR=measles, mumps, rubella; PK=pharmacokinetic; PCR=polymerase chain reaction; PCDAI=Pediatric Crohn's Disease Activity Index; RNA=ribonucleic acid; sPCDAI=short Pediatric Crohn's Disease Activity Index; SEMA-CD=Simple Endoscopic Mucosal Assessment-Crohn's Disease; SES-CD=Simplified Endoscopic Score-Crohn's Disease; TB=tuberculosis; Week I-0=Induction Week 0.

Table 2: Induction Period: Schedule of Activities

Study Period	Induction				Early Term	Safety F/U	NOTES
Study Week Name	I-0	I-3	I-6	I-8			
Study Week	0	3	6	8		FSV	
Study Procedure – Induction	• Visit dates are based on the participant's original induction date (Week I-0); visit windows are ±4 days (ie, plus or minus 4 days). If the first or the last day of a visit window coincides with a holiday and/or a site closure, the window can be extended with 2 business days. This will not be considered a protocol deviation. • If discontinuation of study intervention administration occurs before or at Week I-8, the Week I-8 assessments should be completed, and a safety follow-up visit should be scheduled approximately 20 weeks after the participant's last study intervention administration. • If multiple sample collections are scheduled for the same timepoint, it is recommended that samples are collected in the following sequence: clinical laboratory assessments, PK, immunogenicity, and serum biomarkers.						
Administrative							
Inclusion/exclusion criteria	X	This review should be performed prior to study intervention administration.					
Study Intervention Administration							
Administer study intervention	X	All assessments including collection of blood samples are to be completed before study intervention administration, unless otherwise specified. It is recommended that PRO (ie, IMPACT-III questionnaire) assessments be completed prior to study intervention administration.					
Safety Assessments							
Physical examination				X	X	X	
TB evaluation / other infection assessment	X			X	X	X	If the evaluation raises suspicion for TB infection or the participant has had a close contact exposure to TB, study intervention must be withheld and an immediate and thorough investigation must be undertaken, including consultation with a physician specializing in TB to determine if treatment is warranted.
Vital signs	X			X	X	X	Temperature, pulse/heart rate, respiratory rate, and blood pressure. At the Week I-0 visit with IV study intervention administration vital signs will be obtained before, approximately every 30 minutes during, and twice (at approximately 30-minute intervals) after completion of the IV infusion.

Table 2: Induction Period: Schedule of Activities

Study Period	Induction				Early Term	Safety F/U	NOTES
Study Week Name	I-0	I-3	I-6	I-8			
Study Week	0	3	6	8		FSV	
Weight	X	X	X	X	X	X	
Height	X	X	X	X	X	X	
Highly sensitive urine pregnancy test	X			X	X	X	Must be performed before any study intervention administration for females of childbearing potential.
AE review	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	
Diet review / history	X			X			
CD-related surgeries / hospitalizations	X	X	X	X	X	X	
Study intervention infusion site evaluation	X						
Efficacy Assessments							
Review PCDAI and CDAI electronic diary information	X			X	X		PCDAI and CDAI diaries will be completed by all participants and should be reviewed (in the Yprime portal) by the investigator or site personnel to confirm completion.
PCDAI score	X			X	X		The investigator will complete the PCDAI questionnaire on a tablet.
sPCDAI score		X	X				The investigator will complete the sPCDAI questionnaire on a tablet.
Fistula examinations	X			X			
IMPACT-III	X				X		Required only if participant is ≥10 years of age at Week I-0. The IMPACT-III assessments should be completed remotely on the handheld device, approximately 1 week prior to the study visit.
Stool sample (fecal calprotectin, fecal lactoferrin)	X	X	X	X	X		
CRP	X	X	X	X	X		

Table 2: Induction Period: Schedule of Activities

Study Period	Induction				Early Term	Safety F/U	NOTES
Study Week Name	I-0	I-3	I-6	I-8			
Study Week	0	3	6	8		FSV	
Clinical Laboratory Assessments							
Hematology, chemistry	X			X	X	X	
ESR	X			X	X	X	
Nutritional parameters (25-hydroxyvitamin D, MMA, and iron)	X				X		Nutritional parameters should be collected at Week I-0 prior to the infusion. In children <17 kg, these blood samples should be collected during the screening period. The results of the test will be sent to the investigator and recommendations will be provided for any follow-up treatment or retesting.
Clinical Pharmacology Assessments							
Serum ustekinumab concentration	X	X	X	X	X	X	At the induction infusion visit (Week I-0), blood samples for PK analysis should be collected before the start of the infusion and approximately 60 minutes after completion of the infusion. At the other visits, blood samples for PK analysis should be collected prior to administering the study intervention. The same blood draws can be used to collect serum samples for measuring ustekinumab concentration and antibodies to ustekinumab.
Antibodies to ustekinumab	X			X	X	X	
Biomarkers							
Serum biomarkers			X	X			For children >25 kg, collection of serum biomarkers may occur at I-0 if it was NOT obtained at Screening. Do NOT obtain additional sample if it was taken at Screening. Participants who have received biologic therapy for the treatment of Crohn's disease prior to the I-0 visit and have had a biologic drug washout duration of <5 half-lives may have a blood test for the prior biologic drug level at Week I-8.
Additional fecal biomarkers	X			X	X		

Abbreviations: AE=adverse event; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; F/U=follow-up; FSV=Final Safety visit; I=induction; IV=intravenous; MMA=methylmalonic acid; PCDAI=Pediatric Crohn's Disease Activity Index; PK=pharmacokinetic; PRO=participant-reported outcome; RNA=ribonucleic acid; sPCDAI=Short Pediatric Crohn's Disease Activity Index; TB=tuberculosis; Term=Termination

Table 3: Maintenance Period: Schedule of Activities

Study Period	Maintenance										Loss of Response	Early Term	Safety F/U	NOTES
Study Week Name	**M-0[a,b]**	**M-4**	**M-8**	**M-12**	**M-16**	**M-24**	**M-32**	**M-36**	**M-40**	**M-44**				Maintenance visit dates are based on the participant's M-0 visit date ±10 days. (If the first or the last day of a visit window coincides with a holiday and/or a site closure, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.)
Study Week	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**44**	**48**	**52**			**FSV**	
Study Visit Location	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**H**	**S**	**S**	**S**	**S**	**S = Study Site; H = Home** Home visits may occur at home at the discretion of the primary investigator (PI), caregiver, or participant, and upon completion of training. If it is determined by the PI, caregiver, or participant that they will not participate in home visits, the caregiver and participant will come to the clinic study site to complete the visit.
Study Procedure – Maintenance	• All assessments including collection of blood samples are to be completed before study intervention administration, unless otherwise specified. Participants/caregivers will have the option to administer study intervention at home at Weeks M-12, M-24, M-36, and M-40 after being properly trained. • Although Week M-0 assessments should be completed at Week I-8, participants may be able to complete the Week M-0 assessments within 4 days after Week I-8. At the investigator's discretion, the window may be extended up to 8 days to allow appropriate treatment of and/or recovery from nonserious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) before administration of study intervention. • If discontinuation of study intervention administration occurs after Week M-0 but before or at Week M-8, the early termination visit assessments should be completed, and a safety follow-up visit should be scheduled approximately 20 weeks ±10 days after the last study intervention administration. • If discontinuation of study intervention administration occurs after Week M-8 but before or at Week M-44, the Week M-44 assessments should be completed, and a safety follow-up visit should be scheduled approximately 20 weeks after the last study intervention administration. • Participants who do not enter the LTE should complete a safety follow-up visit approximately 20 weeks after their last study intervention administration.													

Table 3: Maintenance Period: Schedule of Activities

Study Period	Maintenance										Loss of Response	Early Term	Safety F/U	NOTES
Study Week Name	M-0[a,b]	M-4	M-8	M-12	M-16	M-24	M-32	M-36	M-40	M-44				Maintenance visit dates are based on the participant's M-0 visit date ±10 days. (If the first or the last day of a visit window coincides with a holiday and/or a site closure, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.)
Study Week	8	12	16	20	24	32	40	44	48	52			FSV	
	• If multiple sample collections are scheduled for the same timepoint, it is recommended that samples are collected in the following sequence: clinical laboratory assessments, PK, immunogenicity, and serum biomarkers.													
Study Intervention Administration														
Randomization	X	All participants who complete Week I-8 will be randomized at Week M-0 to receive ustekinumab as a q8w or q12w SC regimen												
Assessment for Early Escape Criteria and Induction Nonresponders status			X	X										Participants who were not in clinical response at Week I-8 will be evaluated for clinical response (see Section 4.1.1).
Study Intervention Home Administration Training	X		X											Optional for participants and/or caregivers electing home visits only.
Study Intervention Administration at Home or Study Site	S		S	H	S	H	S	H	H					S = Study Site; H = Home Study intervention administration may occur at home or in the Study Site, at the discretion of the PI.
Study Intervention Home Administration Diary				X		X		X	X					At-home visits, participants will be instructed to record study intervention administrations with time and date information and whether study intervention was self-administered or given by a caregiver in the Study Intervention Home Administration Diary.

Table 3: Maintenance Period: Schedule of Activities

Study Period	Maintenance										Loss of Response	Early Term	Safety F/U	NOTES
Study Week Name	**M-0[a,b]**	**M-4**	**M-8**	**M-12**	**M-16**	**M-24**	**M-32**	**M-36**	**M-40**	**M-44**				Maintenance visit dates are based on the participant's M-0 visit date ±10 days. (If the first or the last day of a visit window coincides with a holiday and/or a site closure, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.)
Study Week	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**44**	**48**	**52**			**FSV**	
Safety Assessments														
Physical examination										X		X	X	
TB evaluation / other infection assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	If the evaluation raises suspicion for TB infection or the participant has had a close contact exposure to TB, study intervention must be withheld and an immediate and thorough investigation must be undertaken, including consultation with a physician specializing in TB to determine if treatment is warranted.
Vital signs			X	X	X	X	X	X	X	X	X	X	X	Temperature, pulse/heart rate, respiratory rate, and blood pressure will be obtained before SC injection when visits occur at the Study Site.
Weight			X		X		X			X	X	X	X	
Height			X		X		X			X	X	X	X	
Highly sensitive urine pregnancy test	X		X	X	X	X	X	X	X	X	X	X	X	Must be performed before any study intervention administration for females of childbearing potential.
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diet review / history		X	X	X	X	X	X	X	X	X	X	X	X	

Table 3: Maintenance Period: Schedule of Activities

Study Period	Maintenance										Loss of Response	Early Term	Safety F/U	NOTES
Study Week Name	**M-0[a,b]**	**M-4**	**M-8**	**M-12**	**M-16**	**M-24**	**M-32**	**M-36**	**M-40**	**M-44**				Maintenance visit dates are based on the participant's M-0 visit date ±10 days. (If the first or the last day of a visit window coincides with a holiday and/or a site closure, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.)
Study Week	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**44**	**48**	**52**			**FSV**	
CD-related surgeries / hospitalizations		X	X	X	X	X	X	X	X	X	X	X	X	
Study intervention injection-site evaluation	X		X	X	X	X	X	X	X		X	X		Visual inspection of injection-site will be performed ≥30 minutes after injection. Participants/caregivers administering study intervention at home will receive detailed instructions on how to monitor and report potential injection-site reactions. This may include evaluation by the study team via video or photographic image, where local regulations permit.
Efficacy Assessments														
Collect and review CDAI electronic diary			X							X	X	X		CDAI diary tools will be provided to all participants to complete for the 7 days prior to Weeks M-8 and M-44 and for LOR and early termination visits. Diary completion is not mandatory for unscheduled LOR and early termination participants. The investigator or site personnel will check completion of participants' CDAI diary in the yPrime Portal.
Collect and review PCDAI electronic diary			X		X		X			X	X	X		PCDAI diary tools will be provided to all participants to complete for the 7 days prior to Weeks M-8, M-16, M-32, and M-44 and for LOR and early termination visits. Diary completion is not mandatory for unscheduled LOR and early termination participants. The investigator or site personnel will check completion of paticipants' PCDAI diary in the Yprime portal.

Table 3: Maintenance Period: Schedule of Activities

Study Period	Maintenance										Loss of Response	Early Term	Safety F/U	NOTES
Study Week Name	**M-0[a,b]**	**M-4**	**M-8**	**M-12**	**M-16**	**M-24**	**M-32**	**M-36**	**M-40**	**M-44**				Maintenance visit dates are based on the participant's M-0 visit date ±10 days. (If the first or the last day of a visit window coincides with a holiday and/or a site closure, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.)
Study Week	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**44**	**48**	**52**			**FSV**	
PCDAI score			X		X		X			X	X	X		The investigator will complete the questionnaire on a tablet. The final PCDAI score will be available on the Tablet and also in the yPrime portal. At the LOR visit, the PCDAI assessment will consider the most recent laboratory results, including local laboratory results.
sPCDAI score		X		X		X		X	X		X			The investigator will complete the questionnaire on a tablet. The sPCDAI may be used if laboratory test values are not available including for those participants who lose response. During home visits an abdominal examination will not be conducted and will be computed without the abdominal exam item.
Fistula examinations			X		X		X			X	X	X	X	A dedicated form for fistula examinations will be completed in addition to the PCDAI and sPCDAI.

Table 3: Maintenance Period: Schedule of Activities

Study Period	Maintenance										Loss of Response	Early Term	Safety F/U	NOTES
Study Week Name	**M-0[a,b]**	**M-4**	**M-8**	**M-12**	**M-16**	**M-24**	**M-32**	**M-36**	**M-40**	**M-44**				Maintenance visit dates are based on the participant's M-0 visit date ±10 days. (If the first or the last day of a visit window coincides with a holiday and/or a site closure, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.)
Study Week	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**44**	**48**	**52**			**FSV**	
Ileocolonoscopy			X							X		X		• Ileocolonoscopy should be performed within approximately 3 weeks prior to the Week M-8 visit and within approximately 3 weeks prior to the Week M-44 visit. For participants in early termination prior to Week M-44, an ileocolonoscopy is recommended but not required. • A SES-CD score will be assessed by the central endoscopist. All study ileocolonoscopies should be performed with study software to permit central review of the video of the ileocolonoscopy and scoring using the criteria of the SES-CD and the SEMA-CD (Section 8.1.7). (In case back-up software would need to be used, this should be recorded in the source documents.) • The sponsor suggests that at least 48 hours must elapse between an ileocolonoscopy with polypectomy, deep biopsies, or bleeding and the study intervention administration visit. • If performed on the day of the study visit, the 7 days prior to the start of ileocolonoscopy preparation should be used to calculate the PCDAI.
IMPACT-III										X		X		Required only if participant is ≥10 years of age at Week I-0 and had previously completed the questionnaire. The IMPACT-III assessments should be completed remotely on the handheld device,

Table 3: Maintenance Period: Schedule of Activities

Study Period	Maintenance										Loss of Response	Early Term	Safety F/U	NOTES
Study Week Name	**M-0[a,b]**	**M-4**	**M-8**	**M-12**	**M-16**	**M-24**	**M-32**	**M-36**	**M-40**	**M-44**				Maintenance visit dates are based on the participant's M-0 visit date ±10 days. (If the first or the last day of a visit window coincides with a holiday and/or a site closure, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.)
Study Week	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**44**	**48**	**52**			**FSV**	
														approximately 1 week prior to the study visit and prior to the collection of blood samples and endoscopy at Week M-44.
Stool sample (fecal calprotectin, fecal lactoferrin)			X			X				X	X	X		Home stool collection kits will be provided, and participants will be given instructions on how to collect, store and deliver stool samples to the study site or designated laboratory. Stool samples may be collected during study-site visits for participants who were unable to collect a stool sample at home. If still unable to provide a stool sample at the time of the visit, participants may provide the sample within 4 days after the visit.
CRP			X			X				X	X	X		
Clinical Laboratory Assessments														
Hematology, chemistry		X	X		X	X	X	X		X	X	X	X	Hematology and chemistry may be collected remotely in circumstances where blood samples are not able to be collected on-site or shipped out in the timeframe described in the protocol. Please contact the sponsor if an outside laboratory is used.
ESR			X		X		X			X	X	X		
Nutritional parameters (25-hydroxyvitamin D, MMA, and iron)		X								X		X		For children <16 kg (for participants in Japan: <17 kg), nutritional parameters may be collected prior to the Week M-44 visit.
Stool for enteric pathogens											X			Stool studies for enteric pathogens will include a stool culture and *Clostridioides difficile* (formerly known as *Clostridium difficile*) test (*C. difficile* toxin/GDH with

Table 3: Maintenance Period: Schedule of Activities

Study Period	Maintenance										Loss of Response	Early Term	Safety F/U	NOTES
Study Week Name	M-0[a,b]	M-4	M-8	M-12	M-16	M-24	M-32	M-36	M-40	M-44				Maintenance visit dates are based on the participant's M-0 visit date ±10 days. (If the first or the last day of a visit window coincides with a holiday and/or a site closure, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.)
Study Week	8	12	16	20	24	32	40	44	48	52			FSV	
														Reflex to PCR testing) and may be performed by a local laboratory. Additional testing (eg, ova and parasites or *Escherichia coli* 0157:H7 assessments) may be performed at the investigator's clinical discretion.
Clinical Pharmacology Assessments														
Serum ustekinumab concentration		X	X	X	X	X	X	X	X[c]	X	X	X	X	Blood samples for PK analysis should be collected prior to administering the study intervention.
Antibodies to ustekinumab			X			X				X	X	X	X	
Biomarkers														
Ileocolonic Biopsy (RNA, histology)			X							X		X		
Serum biomarkers						X				X		X		
Additional fecal biomarkers						X				X		X		
Other														
Exit survey													X	The exit survey is optional.

a. Except for study intervention administration, assessment for TB and other infections, occurrence of AEs, changes in concomitant medications, injection-site reactions, the highly sensitive urine pregnancy test, and fistula examination, no new data will be collected for these procedures at this visit; data from the study procedures performed at Week I-8 will be used for Week M-0.

b. All participants will be assessed for LOR (Section 4.1.2) during the maintenance period. Participants who have LOR will be eligible for a dose adjustment (Section 4.1.3); those who have LOR and have documented low ustekinumab exposure will be eligible for the Exposure Optimization Substudy (Appendix 17 [Section 10.17]). Participants who undergo dose adjustment will proceed to visits every 4 weeks. Participants who are not in clinical response (or sPCDAI clinical response) within 16 weeks after dose adjustment will be withdrawn from study intervention and return for their final safety visit (approximately 20 weeks after the administration of the last study intervention).

Table 3: Maintenance Period: Schedule of Activities

Study Period	Maintenance										Loss of Response	Early Term	Safety F/U	NOTES
Study Week Name	M-0[a,b]	M-4	M-8	M-12	M-16	M-24	M-32	M-36	M-40	M-44				Maintenance visit dates are based on the participant's M-0 visit date ±10 days. (If the first or the last day of a visit window coincides with a holiday and/or a site closure, the visit window can be extended with 2 business days. This will not be considered a protocol deviation.)
Study Week	8	12	16	20	24	32	40	44	48	52			FSV	

c. Required only for substudy participants who are still in the study at M-40

Abbreviations: AE=adverse event; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; F/U=follow-up; FSV=Final Safety Week; GDH=glutamate dehydrogenase; I=induction; IV=intravenous; LOR=loss of response; LTE=long-term extension; M=maintenance; MMA=methylmalonic acid; PCR=polymerase chain reaction; PI=primary investigator; PK=pharmacokinetic; PRO=participant-reported outcome; PCDAI=Pediatric Crohn's Disease Activity Index; q8w=every 8 weeks; q12w=every 12 weeks; RNA=ribonucleic acid; SES-CD=Simplified Endoscopic Score-Crohn's disease; sPCDAI=Short Pediatric Crohn's Disease Activity Index; TB=tuberculosis; Term=Termination.

2. INTRODUCTION

STELARA® (ustekinumab) is a fully human immunoglobulin G1 kappa monoclonal antibody which binds with high affinity to the p40 subunit common to both interleukin (IL)-12 and IL-23. The mechanism of action of ustekinumab is prevention of IL-12/23p40 binding to the IL-12Rβ1 cell surface receptor shared by both cytokines. Through this mechanism of action, ustekinumab effectively neutralizes IL-12 T helper 1 (Th 1)- and IL-23 Th 17-mediated cellular responses.

Ustekinumab (subcutaneous [SC] formulation) has been approved for the treatment of psoriasis in adults, adolescents, and pediatric patients 6 years and older with moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy, and for psoriatic arthritis (PsA) in adults. Ustekinumab has also been approved for the treatment of Crohn's disease and ulcerative colitis in adults using intravenous (IV) induction dosing followed by SC maintenance dosing.

Crohn's disease is an idiopathic inflammatory bowel disease (IBD) that can affect any portion of the intestinal tract with focal, asymmetric, transmural, and granulomatous inflammation and is characterized by transmural infiltration of lymphocytes and macrophages, granulomas, fissuring ulceration, and submucosal fibrosis.[5,16,39,45]

The cardinal clinical features of both pediatric and adult Crohn's disease include abdominal cramps, diarrhea, cachexia, fever, anemia, lower right quadrant mass, rectal bleeding, and perianal fissures/fistulae.[12,13] Many patients also may display prominent extraintestinal manifestations. These commonly include arthralgia/arthritis, erythema nodosum, oral ulcers, and uveitis.[5,11,12,37]

The principal pathologic features of Crohn's disease in both adult and pediatric disease include discontinuous focal ulcerations, fistula formation, granulomas, and perianal involvement.[7,16,39,45] Crohn's disease is characterized by chronic inflammation that may extend through all layers of the intestinal wall, involving the mesentery and regional lymph nodes. Intestinal involvement is discontinuous; "skip areas" of apparently normal tissue separate severely involved segments. Anatomical distribution for pediatric Crohn's disease is similar to that in adults; in about 30% of cases, gross pathologic involvement is limited to the small intestine, usually the terminal ileum; 30% display only colonic involvement; and 40% manifest ileocolonic involvement.[11,19,50]

The natural history of Crohn's disease comprises a progression from intestinal inflammation to the development of strictures and/or penetrating disease (ie, with fistulas and/or abscesses). Intestinal obstruction ultimately occurs in 20% to 30% of patients and fistula formation affects 15% to 32% of patients.[45] Fistulizing Crohn's disease has the poorest prognosis, with surgical resection usually required after 3 to 4 years.[11,19,50] Adults and children show similar patterns of progression, with purely inflammatory disease in 60% to 80% of patients at diagnosis and increasing proportions with stricturing and penetrating disease over time.[11,19,39,45] Approximately 10% of both adults and children with Crohn's disease will develop perianal disease.[39]

A growing body of scientific and clinical evidence suggests that diet and nutritional status play a significant role in the treatment and management of pediatric Crohn's disease. Nutritional factors that impact treatment strategies and outcomes in pediatric Crohn's disease may include

disease-related food restrictions/poor nutrient intake; malabsorption of nutrients; chronic or increased nutrient losses; hypermetabolism; and drug-nutrient interactions. The short-term effects may be seen as undernutrition and micronutrient deficiencies while long-term effects can include impaired growth and developmental delays.

Impaired linear growth has been reported in up to 46% of children with Crohn's disease[13,18] while delayed puberty has been detected in up to 85% of patients with Crohn's disease diagnosed at childhood.[13] Inflammation, undernutrition and corticosteroid usage contribute to decreased height velocity. Increased cytokine production acts both on the hepatic expression of insulin-like growth factor 1 and at chondrocytes of the growth plates of long bones. Growth hormone insensitivity caused by deranged immune function is a major mechanism in growth retardation.[42] Glucocorticoids and inflammation inhibit bone formation, though their impact on skeletal modeling remains unclear. Although corticosteroids can suppress growth, decreased height at diagnosis demonstrates that this finding is a consequence of the disease and not merely an adverse effect of treatment. Current treatment strategies for Crohn's disease that include anti-tumor necrosis factor therapy have been shown to improve patients' growth rate; however, linear growth deficiencies are still common. In pediatric patients with Crohn's disease, prolonged diagnostic delay, high initial activity index, and stricturing/penetrating type of behavior may cause growth deficiencies (in weight and height) and delayed puberty, with several studies reporting that these patients may not reach an optimal bone mass. Long-term control of active inflammation and an adequate intake of nutrients are both fundamental in promoting normal puberty.

In addition to the impaired growth caused by malnutrition, Crohn's disease in children creates challenges with respect to psychological, educational, and social development that are difficult to reverse.[11]

Patients with IBD may also suffer from sleep disturbances, which reduce their quality of life (QoL) and may also affect medical morbidity.[25] Not surprisingly, the presence of Crohn's disease can increase the risks for clinical depression.[17]

Currently, REMICADE® (infliximab) and HUMIRA® (adalimumab) are the only approved biologic therapies for the treatment of pediatric Crohn's disease in the United States (US) and European Union. Both of these biologics are tumor necrosis factor alpha (TNFα) antagonist therapies. As in adults, a sizable portion of children never respond, respond initially and lose response, or are intolerant to both conventional and TNFα antagonist therapies. Thus, considerable unmet medical need remains among children with Crohn's disease for additional safe and effective long-term therapies with a different mechanism of action.

For patients with moderate or severe disease, remission is induced with either corticosteroids or exclusive enteral nutrition (EEN). Treatment with EEN is offered as an alternative to corticosteroids for induction of remission in children with Crohn's disease. Exclusive enteral nutrition may be particularly appropriate for patients with growth failure and/or those who are corticosteroid-dependent.

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

The term “study intervention” used throughout the protocol refers to study drug, as defined in Section 6.1.

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

The term “participant” throughout the protocol refers to the common term “subject” In this study, “participant” also refers to the pediatric participant and/or his or her parent(s) or legal guardian.

2.1. Study Rationale

Ustekinumab has been studied in a Phase 3 program of adults with moderately to severely active Crohn’s disease which demonstrated that ustekinumab is an effective therapy with a safety profile consistent with other approved indications that include psoriasis, PsA, and ulcerative colitis. Ustekinumab is approved for the treatment of adults with moderately to severely active Crohn’s disease.

Ustekinumab has the potential to offer pediatric participants with moderately to severely active Crohn’s disease a safe and effective therapy with a single IV induction dose followed by maintenance SC dosing.

2.2. Background

Pharmacokinetics

In induction studies of adult participants with Crohn’s disease (UNITI-1 [CNTO1275CRD3001] and UNITI-2 [CNTO1275CRD3002]), following a single IV administration of ustekinumab, median serum ustekinumab concentrations were approximately dose proportional and were detectable at all sampling timepoints through Week 8. Median peak serum ustekinumab concentrations 1 hour after the Week 0 infusion were 41.9 µg/mL and 126.1 µg/mL for the 130 mg and ~6 mg/kg dose groups, respectively, while the corresponding peak concentrations were 39.8 µg/mL. At Week 8, the median serum ustekinumab concentrations were 6.36 µg/mL and 2.09 µg/mL for the ~6 mg/kg and 130 mg and groups, respectively.

In the maintenance study of adult participants with Crohn’s disease (IM-UNITI [CNTO1275CRD3003]), following maintenance treatment with ustekinumab 90 mg SC every 8 weeks (q8w) or every 12 weeks (q12w), steady state was reached at approximately 8 weeks for participants receiving ustekinumab q8w, or at 12 weeks for participants receiving ustekinumab q12w maintenance doses. Median steady-state trough serum ustekinumab concentrations over time in the ustekinumab q8w group (1.97 µg/mL to 2.24 µg/mL) were approximately 3-fold the concentrations in the ustekinumab q12w group (0.61 µg/mL to 0.76 µg/mL). Following maintenance doses of ustekinumab 90 mg SC q8w or q12w, serum ustekinumab concentrations were sustained through Week 44 in almost all participants, with a smaller proportion of participants

with undetectable ustekinumab trough concentrations over time in the 90 mg q8w group (3.2% to 4.9%) compared with those in the 90 mg q12w group (11.1% to 19.1%). The median ustekinumab concentration in participants in the placebo group was below detectable levels by Week 16.

In pediatric participants with Crohn's disease in UniStar (CNTO1275CRD1001), after a single IV administration of the low-induction dose (3 mg/kg or 130 mg) or the high-induction dose (9 mg/kg or 390 mg) of ustekinumab, mean and median serum ustekinumab concentrations were approximately dose proportional at all sampling timepoints through Week 8. Median (mean) peak serum ustekinumab concentrations 1 hour after the Week 0 infusion were 50.5 µg/mL (51.3 µg/mL) and 150.2 µg/mL (148.7 µg/mL) for the low-induction and high-induction doses, respectively. At the end of induction at Week 8, median (mean) serum ustekinumab concentrations were 1.18 µg/mL (1.56 µg/mL) and 2.53 µg/mL (4.76 µg/mL) for the low-induction and high-induction doses, respectively.

Following SC administration of ustekinumab at Week 8 to pediatric participants with Crohn's disease in UniStar, the impact of the difference in induction doses at Week 0 had diminished by Week 16. The median (mean) serum ustekinumab concentration at Week 16 was 1.04 µg/mL (1.47 µg/mL) in the low-induction dose group in comparison with 0.59 µg/mL (1.80 µg/mL) in the high-induction dose group.

Serum ustekinumab concentrations observed in the overall pediatric Crohn's disease population were generally comparable to those observed in the reference adult Crohn's disease population. However, at the dose regimens studied in UniStar, a pattern towards lower median or mean serum ustekinumab concentrations was observed in participants in the <40 kg body weight subgroup compared with participants in the ≥40 kg body weight subgroup and compared with the reference adult Crohn's disease population. Median or mean serum ustekinumab concentrations in the ≥40 kg body weight subgroup were generally comparable with those in the reference adult population.

Efficacy/Safety Studies

The efficacy and safety of ustekinumab in adults with moderately to severely active Crohn's disease have been evaluated in 3 Phase 3 IBD studies (UNITI-1 [CNTO1275CRD3001], UNITI-2 [CNTO1275CRD3002], and IM-UNITI [CNTO1275CRD3003]).[43]

UNITI-1 (CNTO1275CRD3001) and UNITI-2 Studies (CNTO1275CRD3002)

UNITI-1 and UNITI-2 were both randomized, double-blind, placebo-controlled, parallel-group, multicenter studies to evaluate the safety and efficacy of ustekinumab induction therapy in participants with moderately to severely active Crohn's disease. The participant population evaluated in UNITI-1 were those who had failed or were intolerant to anti-TNFα therapy, whereas participants in UNITI-2 had demonstrated an inadequate response or failed to tolerate conventional therapy for Crohn's disease (but had not failed TNFα antagonists), and had elevated C-reactive protein (CRP), or calprotectin, or endoscopic evidence of active Crohn's disease.

In UNITI-1 and UNITI-2, participants were randomized to receive a single dose of IV ustekinumab of either 130 mg or a weight-range based ustekinumab dose of approximately 6 mg/kg or placebo. At Week 6, all participants were evaluated for the primary endpoint of clinical response.

UNITI-1

Ustekinumab-induced clinical response (defined as a reduction from baseline in the Crohn's Disease Activity Index [CDAI] score of ≥10 points or CDAI score <150 points) and clinical remission (a CDAI score of <150 points) in this study of participants with demonstrated prior failure (primary or secondary nonresponse) or intolerance to 1 or more TNFα antagonists. For the primary endpoint as well as all 4 major secondary endpoints, statistical significance was met for both ustekinumab IV doses (~6 mg/kg and 130 mg).

UNITI-2

Ustekinumab-induced clinical response (a reduction from baseline in the CDAI score of ≥100 points or CDAI <150 points) and clinical remission (a CDAI score of <150 points) in this study of participants who had failed conventional therapy (ie, corticosteroids or immunomodulators [6-mercaptopurine (6-MP), azathioprine (AZA), or methotrexate (MTX)]), but had not failed TNFα antagonists. For the primary endpoint as well as all 4 major secondary endpoints, statistical significance was met for both ustekinumab doses (~6 mg/kg and 130 mg).

All participants in UNITI-1 and UNITI-2 who received study intervention at Week 0 and completed the Week 8 visit were eligible to enter the maintenance study IM-UNITI; those who were randomized to ustekinumab induction therapy and were induced into clinical response at Week 8 entered as the primary efficacy population (responders). Participants not entering IM-UNITI had a final safety follow-up visit approximately 20 weeks after study intervention administration at Week 0.

IM-UNITI (CNTO1275CRD3003) Maintenance Study

IM-UNITI was a Phase 3, multicenter, placebo-controlled, parallel-group, double-blind, randomized-withdrawal study to evaluate the safety and efficacy of ustekinumab maintenance therapy in participants with moderately to severely active Crohn's disease induced into clinical response with ustekinumab in the induction studies, UNITI-1 or UNITI-2. The maintenance portion of the study continued to Week 44. The long-term extension (LTE) period of the study began at Week 44 through Week 272. The study was unblinded to investigators and participants after the Week 44 analyses were completed.

The participants in the primary efficacy population (responders after ustekinumab induction treatment) were randomized to receive 1 of the following 3 SC regimens: Placebo, ustekinumab 90 mg SC q12w, and ustekinumab 90 mg SC q8w. Participants who demonstrated a loss of response (LOR) were eligible for a dose adjustment to ustekinumab 90 mg SC q8w. Of the randomized participants, ustekinumab demonstrated statistically significant results for maintaining clinical remission and clinical response (across the broad population included in the maintenance study and for both maintenance dosing regimens, 90 mg q12w and 90 mg q8w administered SC).

Participants not in clinical response to ustekinumab induction treatment (nonresponders) received ustekinumab 90 mg SC at Maintenance Week 0 (Week M-0) in IM-UNITI. If these ustekinumab induction nonresponders achieved clinical response at Week 8, they continued to receive ustekinumab 90 mg SC q8w through Week 40 (delayed responders). The majority of these participants who continued to receive ustekinumab were in clinical response at Week 44.

Participants who completed the safety and efficacy evaluation at Week 44 of study CNTO1275CRD3003 and who, in the opinion of the investigator, may benefit from continued treatment had the opportunity to participate in the LTE to receive the same SC treatment regimen that they were receiving at the end of the maintenance study (either placebo or 90 mg SC ustekinumab q12w or q8w), without further dose adjustment. Treatment with ustekinumab 90 mg SC q12w and q8w maintained clinical remission in over 70% of participants through the third year of treatment.

Clinical Study in Pediatric Participants: UniStar (CNTO1275CRD1001) Study

The UniStar study (CNTO1275CRD1001) was a Phase 1, randomized, double-blind PK study of IV ustekinumab induction followed by SC ustekinumab maintenance in pediatric participants, from 2 through <18 years old, with moderately to severely active Crohn's disease. Pharmacokinetics, efficacy and safety of ustekinumab were evaluated through Week 16. Participants received 1 of 2 ustekinumab IV induction doses at Week 0:

- a low IV induction dose: 130 mg in participants with body weight ≥40 kg and 3 mg/kg in participants with body weight 10 kg to <40 kg, or

- a high IV induction dose: 390 mg in participants with body weight ≥40 kg and 9 mg/kg in participants with body weight 10 kg to <40 kg

The induction dose was followed by a SC maintenance dose (2 mg/kg in participants with body weight 10 kg to <40 kg; 90 mg in participants with body weight ≥40 kg) at Week 8. Median or mean serum ustekinumab concentrations through Week 6 were generally comparable between the overall pediatric population and adult participants with Crohn's disease. From Week 8 through Week 16, median (and mean) serum ustekinumab concentrations were generally lower in the overall pediatric population compared with the corresponding reference adult population. No participant tested positive for antibodies against ustekinumab through Week 16 of the study.

At Week 8, the proportions of participants in the low-induction dose group and in the high-induction dose group in clinical response (defined as a reduction from baseline in the Pediatric Crohn's Disease Activity Score (PCDAI) score of ≥15 points) were 47.8% and 47.7%, respectively. At Week 8, the proportions of participants in the low-induction dose group and in the high-induction dose group in clinical remission (defined as a PCDAI score ≤10 points) were 21.7% and 19.0%, respectively. The proportions of participants in clinical response and clinical remission at Week 16 were similar to those at Week 8.

Clinically meaningful endoscopic improvement (defined as a reduction in the Simple Endoscopic Score for Crohn's Disease [SES-CD] of ≥3 points from baseline) at Week 16 was achieved for 42.1% of participants in the low-induction dose group and 33.3% of participants in the high-induction dose group. Endoscopic healing (defined as the complete absence of any mucosal ulcerations among participants who presented with ulceration in at least 1 ileocolonic segment at induction baseline) at Week 16 was achieved by 15.8% of participants in the low-induction dose group and 11.1% of participants in the high-induction dose group.

The proportions of participants in the low-induction dose group and in the high-induction dose group reporting an adverse event (AE) during or within 1 hour of an infusion at Induction Week 0 (Week I-0) were 4.3% and 0%, respectively.

Through Week 16, the proportions of participants in the low-induction dose group reporting at least 1 AE, serious adverse event (SAE), or infection were 82.6%, 26.1%, and 39.1%, respectively. The proportions of participants in the high-induction dose group reporting at least 1 AE, SAE, or infection, were 61.9%, 4.8%, and 38.1%, respectively.

No injection-site reactions, malignancies, or deaths were reported through Week 16; 1 serious infection (abscess, intestinal) was reported at safety follow-up.

2.3. Benefit-Risk Assessment

2.3.1. Risks for Study Participation

All therapies have the potential to cause adverse experiences. Ustekinumab, an IL-12/23 blocker, has a well-defined safety profile and has been extensively studied for the following approved indications: adults with psoriasis, PsA, Crohn's disease, ulcerative colitis (UC), and also in pediatric participants with plaque psoriasis.

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Clinical worsening of Crohn's disease	The benefit-risk of ustekinumab in the treatment of moderately to severely active Crohn's disease has been established in adults, but not in children.	• During the study, participants will be permitted to continue treatment of Crohn's disease with certain concomitant medications (Section 6.8.1) and will be eligible for dose adjustment from q12w to q8w, if they meet criteria for LOR (Section 4.1.2).

		• Participants may be discontinued from study intervention if not in clinical response by Maintenance Week 8 (Week M-8) (Section 7.1) or if they need to initiate protocol-prohibited medications (Sections 6.8.2 and 7.1). Participants not in clinical response with low exposure may be eligible for the optional substudy and eligible for dose adjustment every 4 weeks (q4w).
Risks Due to Study Intervention (Ustekinumab)		
Serious infections	Ustekinumab is a selective immunosuppressant and may have the potential to increase the risk of infections and reactivate latent infections.	• Participants with a history of, or ongoing, chronic or recurrent infectious disease, including human immunodeficiency virus (HIV), Hepatitis B or C, will be excluded from the study. Similarly, participants with evidence of active or untreated latent TB will be excluded from the study (Section 5.2). • Throughout the protocol, participants will be monitored for signs and symptoms of infection, including, but not limited to, TB, sepsis, and pneumonia (Sections 7.1 and 8.3.6). • Live viral or live bacterial vaccinations will be restricted (Section 5.2)
Hypersensitivity reactions, including serious hypersensitivity reactions	Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported in postmarketing experience with ustekinumab.	• Participants with known allergy, hypersensitivity, or intolerance to ustekinumab or its excipients will be excluded from the study. Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1). • For injections that occur at the site, appropriately trained personnel and medications

		must be available to treat hypersensitivity reactions, including anaphylaxis (Section 8.2.6). • For injections that will occur at home, participants will be instructed on how to monitor for, identify, and react to potential injection-site reactions (Section 8.2.6).
Malignancy	Ustekinumab is a selective immunosuppressant. Immunosuppressive agents have the potential to increase the risk of malignancy. Some participants who received ustekinumab in clinical studies developed cutaneous and noncutaneous malignancies	• Participants who have the presence or history of any malignancy including lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location, and monoclonal gammopathy of undetermined significance, or clinically significant hepatomegaly or splenomegaly will be excluded from the study (Section 5.2). • Participants who develop a malignancy during the study will be discontinued from study intervention (Section 7.1).
Immunosuppression	It is unknown if ustekinumab in combination with other immunosuppressives increases the risk of diseases associated with immunosuppression, such as infections or malignancy.	• In order to minimize the theoretical increased risk of infection or malignancy with the combination of ustekinumab with immunosuppressive therapy, the baseline dose of oral corticosteroids on study entry is limited. • Certain immunomodulators (MTX, 6-MP, or AZA) are allowed in the study as they have been studied in combination with ustekinumab previously and did not appear to influence the safety of ustekinumab. • Adequate washout or restriction of other

		medications with immunosuppressive effects or potential for immunosuppression are provided in Sections 5.1 and 5.2.
Risks Due to Study Procedures		
Risks associated with the endoscopy procedure including bleeding and ileocolonic perforation	These risks are well recognized but are rare.[4,36]	Trained and experienced endoscopists will be performing the procedure during this study.

Detailed information about the safety profile and risks for ustekinumab, including a table of adverse drug reactions, may be found in the ustekinumab IB.

2.3.2. Benefits for Study Participation

Although the clinical benefit of ustekinumab, an IL-12/23 antagonist, has been established in adults with moderately to severely active Crohn's disease, it remains to be confirmed in pediatric participants as the clinical development program is ongoing. While it is possible that participants in this study may not benefit from the study intervention, the Phase 1 UniStar study with ustekinumab that enrolled children between 2 to <18 years of age with moderate to severely active Crohn's disease demonstrated clinical benefit. Further, as ustekinumab has already been established as safe and efficacious for adults with moderately to severely active Crohn's disease and UC, the sponsor anticipates that pediatric participants with Crohn's disease may benefit from treatment with ustekinumab. Participants may also have some benefit from the participation in a clinical study irrespective of receiving study intervention, due to regular visits and assessments monitoring their overall health. Lastly, while not directly benefiting the participant, results from this clinical study will inform on the overall safety and efficacy of ustekinumab in treating moderately to severely active Crohn's disease in pediatric participants ages 2 to 18, which would benefit other pediatric patients with Crohn's disease.

2.3.3. Benefit-Risk Assessment for Study Participation

Taking into account the measures to minimize risk to participants participating in this study, the potential risks identified in association with ustekinumab are justified by the anticipated direct clinical benefits that may be afforded to participants with moderately to severely active Crohn's disease. Crohn's disease is a debilitating disease with high morbidity for which approved pharmacologic treatments are still quite limited. The basic pathogenesis and etiology of Crohn's disease is likely the same in pediatric and adult populations. Ustekinumab is an IL-12/23 blocker that is approved for treatment of Crohn's disease in adults with demonstrated efficacy and safety that would provide a novel pharmacologic mechanism of action for pediatric patients with Crohn's disease. Known risks of the medication are highlighted in Section 2.3.1 and there are multiple strategies to minimize risk for the study population. Participants in this study will be extensively evaluated during screening and excluded from participation if they have any relevant risk factor to limit the chance of untoward and adverse effects in this study. Study sites are selected based on

experience and qualification to run pediatric Crohn's disease studies, and careful monitoring will be performed throughout the study.

The same Data Monitoring Committee (DMC), consisting of at least one medical expert in the relevant therapeutic area and at least one statistician, will be used for studies CNTO1275CRD3004 and CNTO1275PUC3001 and will be established to monitor safety data on an ongoing basis until all participants reach the Maintenance Week 44 (Week M-44) visit or terminate the study prior to the Week M-44 visit (Section 9.6). 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 to evaluate the ustekinumab dosage for participants <40 kg (as measured at Week I-0). The DMC responsibilities, authorities, and procedures will be documented in the DMC charter. Refer to Committees Structure in Appendix 15 (Section 10.15.6), Regulatory, Ethical, and Study Oversight Considerations for details.

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

3. OBJECTIVES AND ENDPOINTS

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

The objectives, primary and secondary endpoints and hypothesis found in Section 3.1 refers to the global objectives and endpoints.

The objectives, primary and secondary endpoints and hypothesis found in Section 3.2 refers to the US-specific objectives and endpoints.

The population definitions are defined in Section 3.3 and endpoint definitions are defined in Section 3.4.

3.1. Global Objectives, Endpoints and Hypothesis

Global Objectives	Global Endpoints
Primary	
• To evaluate the efficacy of ustekinumab dosing in inducing clinical remission in pediatric participants with moderately to severely active Crohn's disease.	The primary endpoint is clinical remission at Week I-8.

Global Objectives	Global Endpoints
• To evaluate the safety profile of ustekinumab in pediatric participants with moderately to severely active Crohn's disease.	• AEs, SAEs, AEs leading to discontinuation of study intervention, and AEs of interest (eg, infections, Section 8.3.7). • 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-6 as assessed by sPCDAI. • Clinical response at Week I-8. • Clinical response at Week I-6 as assessed by sPCDAI. • Endoscopic response at Week M-8* as assessed by SES-CD. • Clinical response at Week M-8.* *These endpoints are evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction.
• To evaluate the efficacy of SC ustekinumab during the maintenance period among participants who were in clinical response in induction.	• Clinical remission at Week M-44. • Endoscopic response at Week M-44 as assessed by SES-CD. • Clinical response at Week M-44. • Corticosteroid-free clinical remission at Week M-44. • Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8.

Global Objectives	Global Endpoints
Other	
• To evaluate the effects of ustekinumab on the following factors: – Histologic assessments – Serum and fecal biomarkers – Growth – Nutritional parameters	• Histologic assessments based on the Global Histology Activity Score (GHAS), Geboes score, and Robarts Histopathology Index (RHI). Change from baseline in: • CRP concentrations. • Fecal calprotectin and fecal lactoferrin levels. • 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, methylmalonic acid (MMA), and iron levels at Weeks M-4 and M-44.
• To evaluate the effect of ustekinumab on Crohn's disease-related QoL.	• Change from baseline in IMPACT-III scores at Week M-44 for participants ≥10 years of age at Week I-0.

GLOBAL HYPOTHESIS

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

3.2. US-specific Objectives, Endpoints and Hypothesis

US-specific Objectives	US-specific Endpoints
Primary	
• To evaluate the efficacy of ustekinumab dosing in maintaining clinical remission in pediatric participants with moderately to severely active Crohn's disease.	The primary endpoint is clinical remission at Week M-44. This endpoint will be assessed among participants who are in clinical response at Week I-8.
• To evaluate the safety profile of ustekinumab in pediatric participants with moderately to severely active Crohn's disease	• AEs, SAEs, AEs leading to discontinuation of study intervention, and AEs of interest (eg, infections, Section 8.3.7). • Clinical laboratory hematology and chemistry.

US-specific Objectives	US-specific Endpoints
	• Reactions temporarily associated with an IV infusion (induction period) and SC injection-site reactions (maintenance period).
• To evaluate ustekinumab exposure (PK)	• Serum ustekinumab concentrations
Secondary	
• To evaluate the efficacy of IV ustekinumab during the induction period.	• Clinical remission at Week I-8. • Clinical remission at Week I-6 as assessed by sPCDAI. • Clinical response at Week I-8. • Clinical response at Week I-6 as assessed by sPCDAI. • Endoscopic response at Week M-8* as assessed by SES-CD. • Clinical response at Week M-8.* *These endpoints are evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction.
• To evaluate the efficacy of SC ustekinumab during the maintenance period among participants who were in clinical response in induction.	• Endoscopic response at Week M-44 as assessed by SES-CD. • Clinical response at Week M-44. • Corticosteroid-free clinical remission at Week M-44. • Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8.
Other	
• To evaluate the effects of ustekinumab on the following factors:	
– Histologic assessments	• Histologic assessments based on the GHAS, Geboes score, and RHI.
	Change from baseline in:
– Serum and fecal biomarkers	• CRP concentrations. • Fecal calprotectin and fecal lactoferrin levels.
– Growth	• Height, weight, and BMI (measured with age and sex-specific z-scores) at Weeks I-8 and M-44.
– Nutritional parameters	• 25-hydroxyvitamin D, MMA, and iron levels at Weeks M-4 and M-44.

US-specific Objectives	US-specific Endpoints
• To evaluate the effect of ustekinumab on ~~UC~~ Crohn's disease-related QoL	• Change from baseline in IMPACT-III scores at Week M-44 for participants ≥10 years of age at Week I-0.

US-SPECIFIC HYPOTHESIS

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

3.3. Population Definitions

Induction Responders: Participants who are in clinical response at Week I-8.

Induction Nonresponders: Participants who are not in clinical response at Week I-8.

All Responders: Induction and delayed responders combined. Delayed responders are defined as Induction nonresponders who are in clinical response at Week M-8 after a single SC dose of ustekinumab.

Exposure Optimization Substudy Participants: Participants who are eligible for and enroll in the Exposure Optimization Substudy with adjustment to q4w interval dosing (see Appendix 17 [Section 10.17]), including induction nonresponders with low steady-state ustekinumab trough exposure, and participants with LOR and low steady-state trough exposure.

3.4. Endpoint Definitions

Clinical remission: PCDAI score ≤10 points

Short Pediatric Crohn's Disease Activity Index (sPCDAI) clinical remission: Short PCDAI score ≤10 points

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

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

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

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

CDAI clinical remission: CDAI score <150 points.

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

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

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

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

Endoscopic remission (assessed by SES-CD): A SES-CD score ≤2, in participants with a baseline SES-CD score of ≥3.

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

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

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

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

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

4. STUDY DESIGN

4.1. Overall Design

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

A diagram of the study design is provided in Section 1.2.

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

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

For participants with body weight <40 kg:

- 250 mg/m^2 IV

For participants with body weight ≥40 kg:

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

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

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

Further information on the study interventions is provided in Section 6.1. 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 (see Section 7.1).

During the maintenance period, at Week M-0 and Week 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 Maintenance Week 12 (Week M-12), Week M-24,

Week M-36, and Week M-40, the participant or the participant's caregiver will have the option to conduct study visits remotely and to administer study intervention at home.

Please refer to Section 6.8.1. for details about allowed concomitant treatments for Crohn's disease.

The primary endpoint is:

- **Global** – clinical remission at Week 1-8
- **US-specific** – clinical remission at Week M-44. This endpoint will be assessed among participants who are in clinical response at Week I-8.

End of the main study analyses will occur after Week M-44 when all participants will have completed the study. In addition, an interim analysis of the data will be performed when at least 36 randomized participants with body weight ≥40 kg at Week I-0 and Week M-0 have completed the Week M-44 visit or terminated the main study participation prior to Week M-44. The interim analysis results will be used for the EMA submission for participants with body weight ≥40 kg. At the time of the interim analysis, the treatment regimen will only be unblinded for the participants who meet the criteria for the interim analysis (ie, at least 36 randomized participants with body weight ≥40 kg who have completed the Week M-44 visit or terminated the main study participation prior to Week M-44).

Database locks are:

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

Additional DBLs other than the ones specified above may be performed.

A PK interim analysis to evaluate the ustekinumab dosage for participants <40 kg (as measured at Week I-0) will be performed when ~20 participants <40 kg from both the CNTO1275CRD3004 and CNTO1275PUC3001 studies (combined) complete the Week M-8 visit (see Section 9.5).

4.1.1. Early Escape Criteria (Induction Nonresponders)

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

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

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

  OR

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

     - If a participant is documented to have low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit), the participant will be eligible for enrollment in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to q4w (See Appendix 17 [Section 10.17]). If determined to be medically appropriate in the judgment of the investigator, participants who meet the Early Escape criteria may receive approved rescue therapies (Section 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 µg/mL from blood sample drawn at the Week M-8 visit) must be discontinued from study intervention and complete a safety follow-up visit approximately 20 weeks after the last administration of study intervention.

4.1.2. Loss of Response During the Maintenance Period

All participants randomized into the maintenance period will be assessed for LOR. During home study visits, participants who experience LOR will be transitioned to a study-site visit to complete their current visit (Section 6.1.4).

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

1. An increase in the PCDAI >12.5 above the reference PCDAI score, or an increase in the sPCDAI ≥10 above the reference sPCDAI score, at 2 consecutive visits at least 7 days apart, from Week M-0 for induction responders and Week M-8 for delayed induction responders.

AND

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

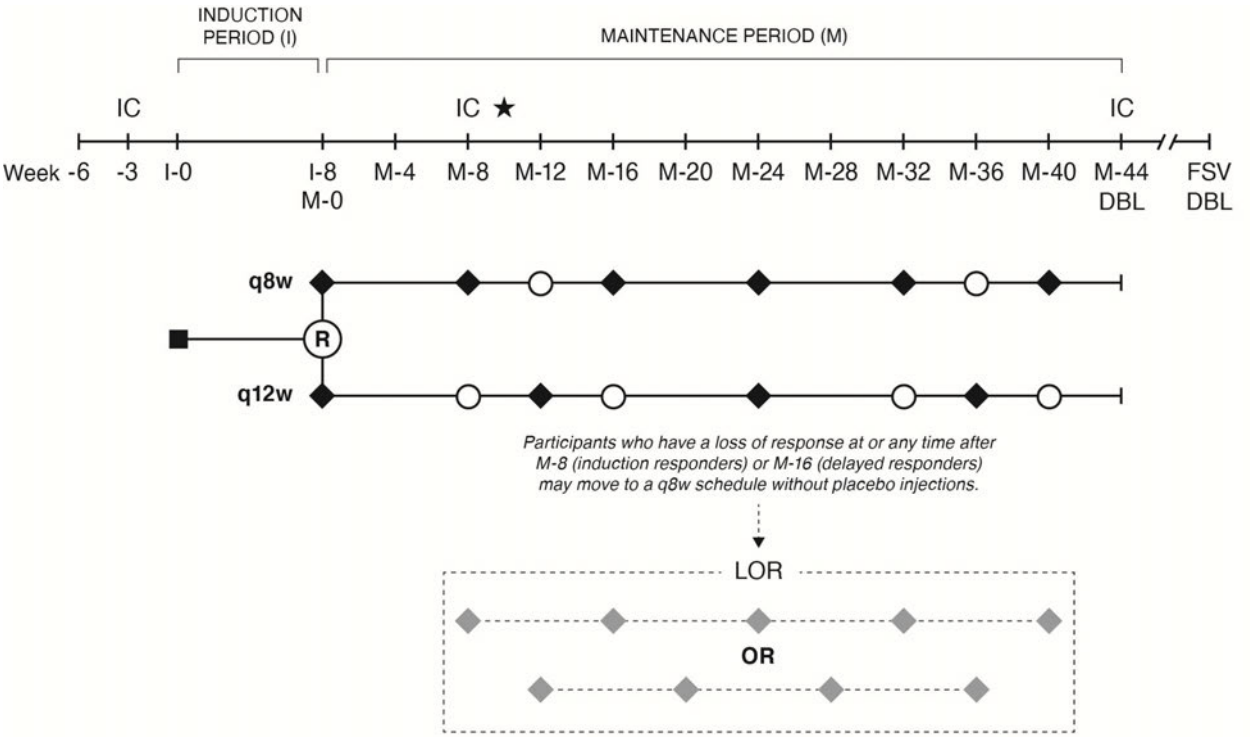
Note: Participants for whom LOR is suspected will need to provide a stool sample for enteric pathogen testing, which will include a stool culture and a *Clostridioides difficile* test. In case of a positive test, a participant can be considered as having LOR if still showing symptoms that meet the criteria,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

Participants who have LOR will be eligible for a dose adjustment (Section 4.1.3), those who have LOR and have documented low ustekinumab exposure will be eligible for the Exposure Optimization Substudy.

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

Participants who lose response during the maintenance period of the main study and have a trough serum ustekinumab concentration of <1.4 µg/mL during the maintenance period (M-8 or M-32) will be eligible to enroll in this optional, open-label q4w substudy (Appendix 17 [Section 10.17]). Loss of response is defined in the main protocol. All eligible participants must sign informed consent/assent (based on intuitional requirements) prior to entry into the substudy.

Figure 2: Loss of Response During the Maintenance Period



■ = Intravenous ustekinumab: 250 mg/m² IV for participants with <40 kg body weight; 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.

◆ = Subcutaneous ustekinumab: 90 mg for participants with ≥40 kg body weight; 60 mg/m² for participants with <40 kg body weight.

○ = SC Placebo

◆ = SC Ustekinumab: Maintenance dose q8w for participants who have loss of response

★ The following participants are eligible for enrolling in the Exposure Optimization Substudy:
- Induction nonresponders at Week M-8 with low 8-week steady-state ustekinumab trough concentration.
- Those with LOR at Week M-8 or later with low 8-week steady-state ustekinumab trough concentration (at Week M-8 or M-32).

DBL = Database Lock FSV = Final Safety Visit IC = Ileocolonoscopy
LOR = Loss of Response R = Randomization

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4.1.3. 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 clinical response at Week M-8), participants who experience LOR (Section 4.1.2 and Figure 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 a 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 the 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 q4w until clinical response or sPCDAI clinical 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 clinical response or sPCDAI clinical response 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 (see Appendix 17 [Section 10.17]) 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.

4.1.4. Rescue Medication During the Maintenance Period

If determined to be medically appropriate in the judgment of the investigator, dose adjustment (Section 4.1.3) or entry into q4w substudy (Appendix 17 [Section 10.17]) should precede institution of Crohn's disease-specific therapies in participants meeting study-specific LOR criteria.

Rescue therapies include:

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

If the above medical therapies are initiated or medication doses increased based on medical necessity after meeting LOR criteria, participants can continue study intervention and should continue to attend all study visits and have all assessments. Treatment failures due to Crohn's disease medication changes will be defined in the Statistical Analysis Plan (SAP).

Rescue therapies for oral corticosteroids are limited to 2 courses of corticosteroids up to 1.5 mg/kg/day (maximum 40 mg prednisone equivalents per day) once daily for up to 3 weeks followed by a tapering period of up 10 weeks of corticosteroids for Crohn's disease as clinically indicated. Second-generation oral steroids with lower systemic effect such as budesonide and beclomethasone dipropionate may be used to treat worsening of Crohn's disease in place of systemic steroids. Their use counts towards 1 of the 2 steroid courses.

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

4.1.5. Long-Term Extension

If in response, participants <18 years old may be eligible to enter an LTE trial after completion of the M-44 visit, or completion of 16 weeks of follow-up post LOR dose adjustment (Section 4.1.3) or substudy entry (Appendix 17 [Section 10.17]) (whichever is longer). Details of the LTE will be provided in a separate protocol, including separate parental consent and child assent form(s).

If participants do not consent/assent to the LTE study, they will continue safety follow-up for approximately 20 weeks after the administration of the last study intervention. The study will end when the last participant has either completed Week M-44 and transitioned into the LTE study, completed their final safety visit (approximately 20 weeks after the administration of the last study intervention), or terminated study participation, whichever is later.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

Maintenance Phase

Randomization at Week M-0 will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints. To maintain the blind, participants will receive placebo at visits they are not scheduled to receive ustekinumab (ie, participants who are randomized to receive ustekinumab SC q8w will receive ustekinumab at Weeks M-0, M-8, M-16, M-24, M-32, and M-40 and placebo at Weeks M-12 and M-36, and participants who are randomized to receive ustekinumab SC q12w will receive ustekinumab at Weeks M-0, M-12, M-24, and M-36, and placebo at Weeks M-8, M-16, M-32, and M-40).

Participants who qualify for early escape at Week M-8 have the option to be discontinued from study intervention and complete a safety follow-up visit approximately 20 weeks after the last administration of study intervention.

Alternatively, participants may remain in the study until the results from the M-8 ustekinumab trough concentration level become available.

A limited group of sponsor personnel will have access to the unblinded treatment assignment only for the participants included in the interim analysis.

Exposure Optimization Substudy

Blinding is not applicable in the optional Exposure Optimization Substudy.

- If the ustekinumab trough concentration is <1.4 µg/mL, the participant will be eligible to enroll in the optional q4w Exposure Optimization Substudy (Appendix 17 [Section 10.17])

Participants who choose not to enroll in the q4w Exposure Optimization Substudy must be discontinued from study intervention (Section 7.1) and complete a safety follow-up visit approximately 20 weeks after the last administration of the intervention.

Participants who experience LOR will no longer receive placebo injections but will continue to receive active study intervention q8w. Participants who experience LOR with low exposure opting to participate in the Exposure Optimization Substudy will no longer receive placebo injections but will continue to receive active study intervention q4w.

Biomarker Collection

Biomarker samples will be collected to evaluate the cellular and molecular mechanism of action of ustekinumab or help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention (Section 8.6). Serum biomarkers will be collected from whole blood in all participants to assess pharmacodynamic (PD) markers associated with the response to ustekinumab. Ileal and colonic biopsies will also be obtained from all participants pre-treatment during endoscopy at screening and post-treatment to assess cellular and molecular changes within the intestinal mucosal tissue. The goal of the biomarker analyses is to evaluate the PD of ustekinumab and aid in evaluating the intervention-clinical response relationship.

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

4.2.1. Participant Input into Study Design

Prior to finalizing the study protocol, the sponsor conducted a qualitative research project. The aims were to collect information on the pediatric patients' experience with IBD and to describe the impact of the disease on the patient, the patient's family unit, and the patient's treatment preferences and willingness to participate in the drug development process. The project focused on describing the patient's views and identifying barriers to participation in clinical research, along with modifiable components of the present Crohn's disease study protocol that could be adapted to optimize study enrollment, retention, and the overall patient experience.

The methods for this project included conducting in-depth interviews, both in person and via webcam. A total of 7 interviews were conducted with adolescent patients ages 13 to 18 years old (n=4) and caregivers (n=3) from a pediatric gastrointestinal (GI) practice. Approximately half of the interviewees had prior clinical study experience. Additionally, an experienced Principal Investigator and Clinical Trial Coordinator were interviewed, and information was collected to understand their view of the proposed pediatric study design and to identify ways to enhance the patient's clinical study experience.

The information (data) from this project was used to help inform to the following study design/elements of this study:

- Moved the timepoint for Week I-8 ileocolonoscopy exam to Week M-8 to allow for more time for onset of endoscopic response.
- Minimize the number and amount of required blood samples.
- Include home visit options during the maintenance period of the study to reduce the amount of time missed from school, as well as after-school activities.
- Use of at-home electronic diaries and questionnaires rather than paper diaries and questionnaires to decrease the length of time needed for study-site visits.
- Minimize the use of placebo SC injections; the study design does not provide placebo SC injections to participants who are nonresponders or who experience a LOR and have a dose adjustment.

4.2.2. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent/assent voluntarily will be enrolled. Younger children who are unable to understand the risks, benefits, and potential AEs of the study will be enrolled following parental consent or consent from a legally acceptable representative. Assent from children will be obtained as described below.

When referring to the signing of the informed consent/assent form (ICF), the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Written consent/assent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by applicable local regulations as well as study site and/or patient preferences. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending

on applicable local and institutional policies. For the purposes of this study, all references to participants who have provided consent (and assent as applicable) refers to the participants and his or her parent(s) or the participant's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent(s) still want them to participate.

This study will be investigating 2 different dose regimens that are currently approved in the European Union (EU) for treatment of adult Crohn's disease, q8w and q12w. No child enrolled in this study will receive an inferior treatment.[47] Rather, in order to maintain study blinding and reduce bias in assessing the efficacy of the 2 regimens approved in adults, placebo injections will be administered at selected visits. Under US regulations, these placebo injections represent a minor increase over no greater than minimal risk and will be clearly described in the ICF.[38,51] For jurisdictions where minimal risk refers to the risks experienced by participants in those aspects of their everyday life that relate to the research, the use of a placebo injection represents no more than minimal risk and minimal burden. Further, dose adjustment from q12w to q8w (see Section 4.1.3) (or q4w with low exposure for the Exposure Optimization Substudy, see Appendix 17 [Section 10.17]) also has to be integrated for any participants with LOR. While the inclusion of a sham dose adjustment from q8w to q8w (no change in the dosing regimen in the q8w group) is necessary to maintain the study blind, it does not represent an inferior treatment and does not change the risk-benefit profile. Further information on the use of placebo injections and associated risks in the ICF can be found in Informed Consent and Assent Form in Appendix 15 (Section 10.15).

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study. Total blood volume to be collected in this study is in line with the allowable blood sample volumes described in the EU guideline on clinical trials conducted with minors (EU Guideline: Ethical considerations for clinical trials on medicinal products conducted with minors).[10]

4.2.3. Rationale for Target Population

This study will enroll participants with Crohn's disease who have not adequately responded to or have not tolerated biologic therapy (ie, TNFα antagonist or vedolizumab) or conventional therapies (ie, steroids and immunomodulators) or who are corticosteroid dependent. Although children with inflammatory bowel disease are most likely to be diagnosed when they are over the age of 10, approximately 15% will be younger, including a cohort with very-early-onset IBD (VEO-IBD) who are under the age of 6.[6,26] Natural history studies have demonstrated that just under half of children with VEO-IBD are being treated with biologics within the first few years of their diagnosis.[27]

Thus, although few biologic therapies are approved for use in pediatrics, particularly children under 6 years of age, the inclusion criteria reflect biologics with an approved pediatric indication as well as biologic therapies that are only approved for adults with Crohn's disease and are

currently summarized for use in pediatric gastroenterology society guidelines. Many children are not being treated with conventional medications due to their side effect profile.[48] Often, these children have received treatment with biologics that are either approved in pediatrics or included in pediatric guidelines, but they have either not achieved remission or lost response.

4.3. Justification for Dose

The following ustekinumab dose regimens will be evaluated in the proposed Phase 3 pediatric Crohn's disease study, CNTO1275CRD3004:

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

For participants with body weight <40 kg:

- 250 mg/m^2 IV

For participants with body weight ≥40 kg:

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

In the maintenance period, starting at Week M-0, all participants who complete the induction period will be randomized in a 1:1 ratio stratified by induction response and weight to receive 1 of 2 SC ustekinumab dose regimens in a blinded fashion:

- Ustekinumab q8w: 90 mg for ≥40 kg body weight and 60 mg/m^2 for <40 kg body weight
- Ustekinumab q12w: 90 mg for ≥40 kg body weight and 60 mg/m^2 for <40 kg body weight

The ustekinumab dose regimens planned for this Phase 3 pediatric Crohn's disease study were determined based on the following considerations.

Previous studies of the anti-TNF monoclonal antibodies (mAbs) infliximab, golimumab, and adalimumab, and the anti-IL12/IL23 mAb ustekinumab in pediatric participants with Crohn's disease have demonstrated similar exposure-response (E-R) relationships in children and adults. These findings support the goal of achieving similar systemic drug exposures in pediatric and adult participants with Crohn's disease.

The PK and exposure-response relationship of ustekinumab in adult participants with Crohn's disease have been characterized using data from several late phase clinical studies including 2 Phase 3 induction (CNTO1275CRD3001 and CNTO1275CRD3002) and 1 maintenance (CNTO1275CRD3003) clinical study. Based on the data from these studies, a posology consisting of a weight-tiered induction dose approximating 6 mg/kg ustekinumab IV (ie, 260 mg [weight ≤55 kg], or 390 mg [weight >55 kg and ≤85 kg], or 520 mg [weight >85 kg]), followed by a

maintenance dose of 90 mg SC given q8w (or q12w in some regions) has been shown to be effective for the treatment of Crohn's disease in adult participants and is approved for the treatment of Crohn's disease in adult patients.

With respect to the pediatric Crohn's disease population, the PK, safety, and efficacy of ustekinumab have been evaluated in a Phase 1 study of pediatric participants with Crohn's disease (CNTO1275CRD1001; n=44). In that study, dose regimens comprising of 1 of 2 ustekinumab IV induction doses (3 mg/kg for participants <40 kg and 130 mg for participants ≥40 kg, or 9 mg/kg for participants <40 kg and 390 mg for participants ≥40 kg) followed by a single ustekinumab SC maintenance dose regimen (2 mg/kg for participants <40 kg and 90 mg for participants ≥40 kg) were evaluated. The totality of the data (efficacy and safety) from CNTO1275CRD1001 support the use of the higher induction dose regimen along with the tested maintenance dose.

Based on a partial extrapolation approach which assumes that pediatric and adult patients with Crohn's disease exhibit a similar response at comparable exposures, ustekinumab doses in this Phase 3 pediatric Crohn's disease study (CNTO1275CRD3004) were selected to achieve systemic ustekinumab exposure comparable with those obtained following the approved dose regimen in adult Crohn's disease. To achieve ustekinumab exposure in pediatric participants comparable to those in adults, ustekinumab PK analyses including population PK modeling and simulation based on data from pediatric and adult Crohn's disease participants were considered. These analyses showed that a participant's body weight could account for some of the variability observed in ustekinumab disposition; however, a participant's age was not found to have a significant influence on the PK of ustekinumab after correcting for body size-related PK differences. Accordingly, the data suggest that older pediatric participants whose body size typically fall within the range of those of adults can receive the same dose approved in adults, while pediatric participants with lower body weights should be dosed using a BSA-adjusted dosing strategy.

Results from the CNTO1275CRD1001 study suggested that the mg/kg dose adjustment strategy used in that study did not consistently result in similar exposures in the lowest body weight subgroups. Accordingly, a BSA-based dose adjustment strategy was conservatively adopted for pediatric participants with lower body weight (<40 kg) to minimize the variability of ustekinumab exposure across the lower pediatric weight band. The expectation of consistent exposure following a BSA-adjusted posology was based on existing empirical knowledge and was confirmed from PK simulations and observed PK data from the CNTO1275CRD1001 study. As implemented in the CNTO127CRD1001 study, a 40 kg body weight cutoff was chosen to transition from a BSA-adjusted dose to the fixed adult dose in the CNTO1275CRD3004 study. The 40 kg body weight cutoff is close to the lower range of the body weight distribution of adults with Crohn's disease treated with ustekinumab and is also consistent with the typical body weight cut-offs used in other pediatric studies of mAbs in pediatric IBD.

For induction treatment in this Phase 3 pediatric Crohn's disease study, a single dose of either a BSA-adjusted dose of 250 mg/m^2 in pediatric participants with body weight <40 kg, 260 mg IV for participants with ≥40 to ≤55 kg body weight, 390 mg IV for participants with >55 to ≤85 kg body weight, or 520 mg IV for participants with >85 kg body weight, will be evaluated. The choice

of a single induction dose is supported by the positive E-R relationships and higher magnitude of benefit with the weight-ranged based ~6 mg/kg dose relative to the lower fixed 130 mg dose in adult Crohn's disease in the absence of a dose-related safety signal.

For maintenance treatment in this Phase 3 pediatric Crohn's disease study, participants will receive 1 of 2 maintenance dose regimens of 90 mg SC ustekinumab for participants with body weight ≥40 kg or BSA-adjusted dose of 60 mg/m^2 for participants with body weight <40 kg, administered either q8w or q12w. Both ustekinumab 90 mg q8w and q12w regimens provided clinically meaningful benefits in the adult Crohn's disease study, although the totality of the data suggests that q8w regimen demonstrated modestly greater efficacy. Along with supporting the assessment of E-R during maintenance, the evaluation of these 2 maintenance dose regimens may help confirm the appropriate maintenance dose regimen for pediatric patients with Crohn's disease, also given that both the q12w and q8w dosing regimens are approved across different regions.

To examine the expected systemic ustekinumab exposure from the proposed dose regimen in this pediatric Crohn's disease study, the population PK model developed from both adult and pediatric Crohn's disease data was used to simulate and predict systemic ustekinumab exposure during induction (ie, area under the plasma concentration curve $[AUC]_{0\text{-}8}$ weeks; Figure 3) and maintenance (ie, AUC_{ss} over a SC dose interval of 8 weeks; Figure 4). The covariate distribution used for the simulations were sampled from the covariate data recorded from studies of adults and pediatric participants with Crohn's disease.

Overall, the ustekinumab dose regimens to be evaluated in this Phase 3 pediatric study provide systemic ustekinumab exposures that have been observed to be safe and effective in adults and are expected to be efficacious and safe in pediatric participants with Crohn's disease.

Figure 3: Predicted Ustekinumab Systemic Exposure During Induction in Adult Participants and Pediatric Participants with Crohn's Disease by Body Weight Subgroups, Following a Single IV Infusion of Ustekinumab at Week 0

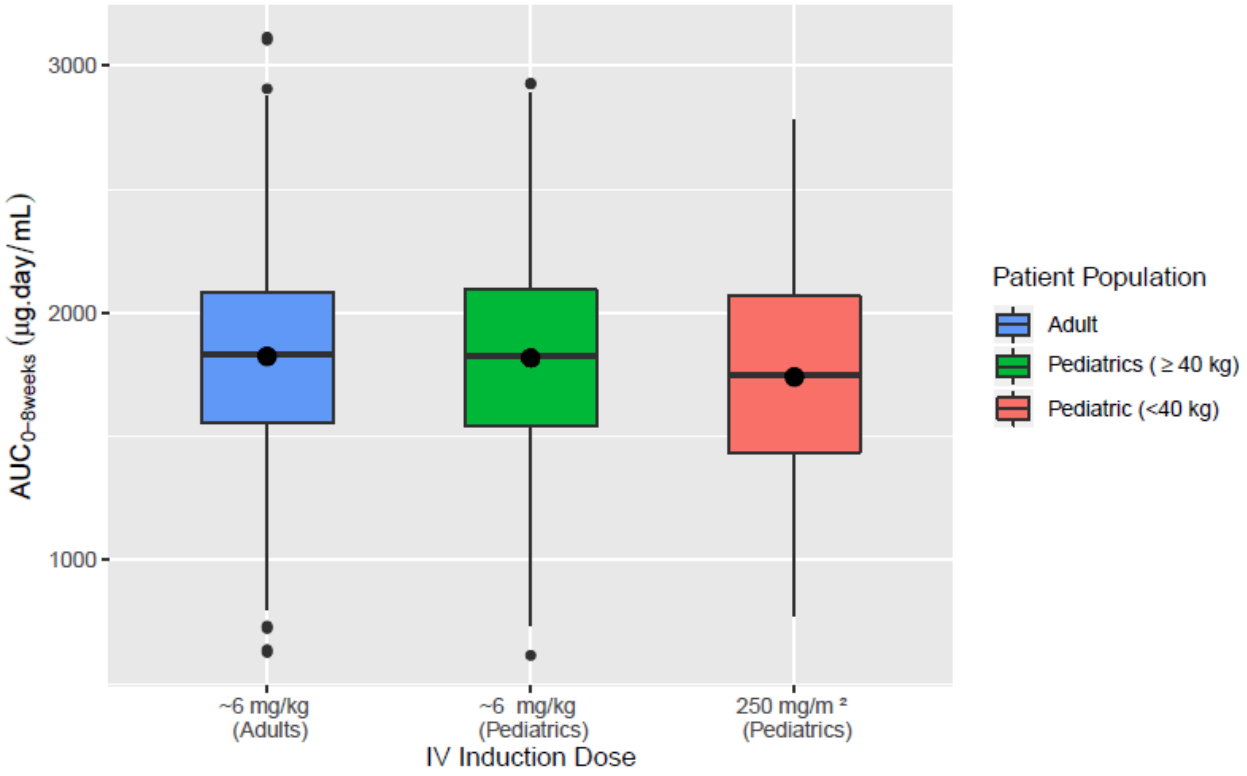
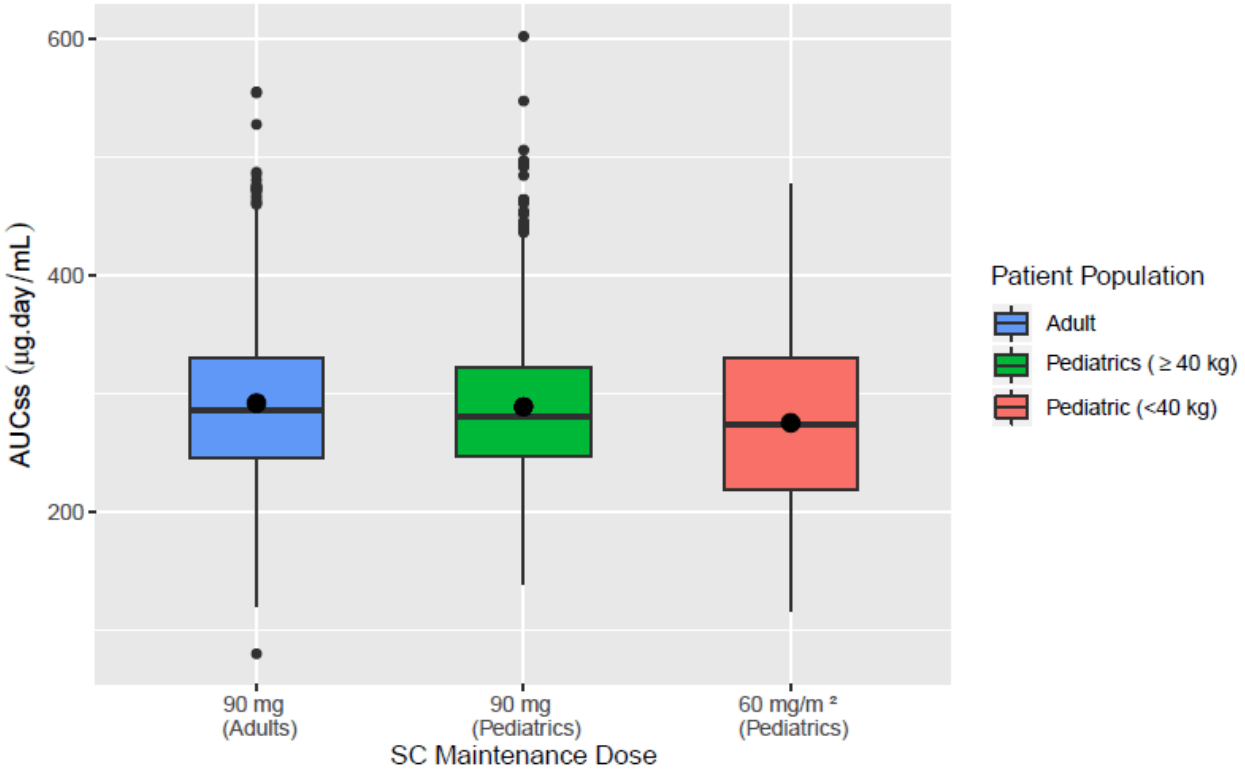


Figure 4: Predicted Ustekinumab Systemic Exposure During Maintenance in Adult Participants and Pediatric Participants with Crohn's Disease by Body Weight Subgroups, Following SC Injections of Ustekinumab every 8 weeks from Week 8 of Induction



4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment as shown in the Schedule of Activities for the last participant in the study. The expected duration of the study is 74 weeks. This includes 6 weeks of screening, 48 weeks of treatment (8 weeks in the induction period followed by 40 weeks in the maintenance period) with study intervention and 20 weeks of safety follow-up after the last study intervention administration. Participants who complete participation at Week M-44 or 16 weeks after dose adjustment (whichever is longer) will be eligible for inclusion into a separate LTE study, unless they have reached 18 years of age. If participants do not participate in the LTE study, they will continue safety follow-up for approximately 20 weeks after the last administration of study intervention. The study will end when the last participant has either completed Week M-44 or 16 weeks after dose adjustment (whichever is longer) and transitioned into the LTE study or completed their final safety visit (approximately 20 weeks after the last administration of study intervention), or terminated study participation, whichever is later. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

Induction and Maintenance Period Through Week M-44

A participant will be considered to have completed the induction and maintenance period of the study if he or she has completed assessments through Week M-44 of the study and has enrolled in the LTE or has completed the final safety visit (20 weeks after the last administration of study intervention) for those who did not enter the LTE.

Participants who prematurely discontinue study intervention for any reason before completion of the Week M-44 assessments of the study will not be considered to have completed the study. However, if they have completed the scheduled follow-up assessments, they can be considered to have completed the study.

Long-Term Extension

Participants who complete Week M-44 and who may benefit from further treatment will be eligible to participate in an LTE study in order to continue to receive ustekinumab, unless they have reached 18 years of age. Details for participation in the LTE study will be provided in a separate protocol and will require a separate consent/assent.

5. STUDY POPULATION

The study population will include pediatric participants 2 to <18 years of age (at the time of the first administration of study intervention at Week I-0) with moderately to severely active Crohn's disease (defined by a PCDAI score >30). Participants must have had an inadequate response and/or intolerance to biologic therapy (ie, TNFα antagonist or vedolizumab) and/or conventional therapies (ie, IV or oral corticosteroids or the immunomodulators AZA, 6-MP, or MTX) or be dependent upon corticosteroids.

Screening for eligible participants will be performed within 6 weeks before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed. On a case-by-case basis after consultation with the sponsor, retesting procedures may exceed the 6-week window and will not be considered protocol deviations.

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

5.1. Inclusion Criteria

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

General

1. 2 to <18 years of age, inclusive (at the time of the first administration of study intervention at Week I-0) with a body weight ≥10 kg.

2. Medically stable on the basis of physical examination, medical history, and vital signs performed at screening. Any abnormalities must be consistent with the underlying illness in the study population and this determination must be recorded in the participant's source documents and acknowledged by the investigator.

3. Criterion modified per Amendment 2

    3.1. Medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel including liver enzymes, other specific tests, or hematology are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and acknowledged by the investigator.

Crohn's Disease Diagnosis and Status

4. Criterion modified per Amendment 4

    4.1. Have Crohn's disease or fistulizing Crohn's disease with active colitis, ileitis, or ileocolitis, confirmed at any time in the past by endoscopy and histology.

5. Criterion modified per Amendment 4

    5.1. Criterion modified per Amendment 6

    5.2. i. Must have moderately to severely active Crohn's disease (as defined by a baseline PCDAI score >30).

    ii. Have ileocolonoscopy with evidence of active Crohn's disease defined as presence of ulceration (which is equal to SES-CD score ≥3) during screening into this study. The ileocolonoscopy procedure must occur within approximately 3 weeks* prior to the administration of study intervention at Week I-0.**

    * A video ileocolonoscopy recorded within 3 months prior to the Week I-0 visit may be used in case of rescreening of a participant who had an ileocolonoscopy but failed the initial screening for another reason, on a case-by-case basis, after consultation with the sponsor.

**If unable to evaluate ulceration due to stricture or inadequate bowel preparation, at least one of the following criteria may instead be applied:

a. An abnormal CRP (>0.3 mg/dL or 3.0 mg/L at screening)

OR

b. Fecal calprotectin of ≥250 mg/kg or ≥250 µg/g at screening

Allowed Concomitant or Prior Medical Therapies for Crohn's Disease

6. Criterion modified per Amendment 6

6.1 Prior or current medication for Crohn's disease must include at least 1 of the following:

Have received biologic therapy for the treatment of pediatric Crohn's disease Appendix 5 (Section 10.5) and have had ≥2-half-lives washout duration prior to first administration of study intervention Appendix 6 (Section 10.6) and have a documented history of failure to respond to or not tolerate the biologic therapy.

OR

Be naïve to biologic therapy (ie, have not demonstrated a history of failure to respond to or failure to tolerate a biologic therapy) **and** have a prior or current Crohn's disease medication history that includes at least 1 of the following:

a. Inadequate response to or failure to tolerate current treatment with oral or IV corticosteroids or immunomodulators (6-MP, AZA, or MTX) (Appendix 7 [Section 10.7]).

OR

b. History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP, AZA, or MTX), Appendix 7 [Section 10.7]).

OR

c. History of corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of Crohn's disease; Appendix 7 [Section 10.7]).

OR

d. Have required more than 3 courses of oral or IV corticosteroids in the past year.

7. Criterion modified per Amendment 2

7.1. Criterion modified per Amendment 4

7.2. Must meet concomitant medication dose stability criteria prior to the first administration of study intervention:

Corticosteroids:

a. If receiving budesonide or beclomethasone dipropionate, the dose must have been stable for at least 2 weeks prior to Week I-0.

b. If receiving oral corticosteroids other than budesonide or beclomethasone dipropionate, the dose must be ≤1.5 mg/kg/day prednisone (or its equivalent) up to 40 mg/day prednisone and must have been stable or discontinued for at least 2 weeks prior to Week I-0.

c. If IV, or rectal corticosteroids have recently been discontinued, they must have been stopped for at least 2 weeks prior to Week I-0.

5-ASA, MTX, 6-MP, and AZA compounds:

d. If receiving oral 5-ASA compounds, the dose must have been stable for at least 2 weeks prior to Week I-0.

e. If oral or rectal 5-ASA compounds have been discontinued, they must have been stopped for at least 2 weeks prior to Week I-0.

f. If receiving MTX, 6-MP, or AZA, the participant must have been taking them for ≥12 weeks and on a stable dose for at least 4 weeks prior to Week I-0.

g. If the MTX, 6-MP, or AZA have been recently discontinued, they must have been stopped for at least 4 weeks prior to Week I-0.

Antibiotics:

h. If receiving a single antibiotic as a primary treatment of Crohn's disease, the dosage of the medication/antibiotic must have been stable for at least 2 weeks prior to Week I-0. Participants cannot be receiving more than one antibiotic for the primary treatment of Crohn's disease.

Enteral Nutrition

8. If receiving enteral nutrition, must have been on a stable regimen for at least 2 weeks prior to Week I-0.

Malignancy or Increased Potential for Malignancy

9. Criterion deleted per Amendment 1

Contraception and Pregnancy

10. Criterion modified per Amendment 2

    10.1. Before randomization, a female must be either:

        a. Not of childbearing potential

        b. Of childbearing potential and

            - Not sexually active, practicing abstinence, or using a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 16 weeks after the last dose – the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Appendix 14 Contraceptive and Barrier Guidance (Section 10.14).

11. Criterion modified per Amendment 5

    11.1. Criterion modified per Amendment 6

    11.2. Females of childbearing potential must have a negative highly sensitive urine pregnancy test at screening and at Week I-0 prior to study intervention administration.

12. Criterion modified per Amendment 2

    12.1. Females of childbearing potential must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a minimum of 16 weeks after receiving the last dose of study intervention.

13. Criterion modified per Amendment 2

    13.1. During the study and for a minimum of 16 weeks after receiving the last dose of study intervention, a male:

        a. Who is sexually active with a female of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository).

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

c. Must agree not to donate sperm.

Immunization History

14. Criterion modified per Amendment 2

14.1. Criterion deleted per Amendment 6

15. Criterion modified per Amendment 1

15.1. Criterion modified per Amendment 5

15.2. Participants must be up to date with varicella and measles, mumps, and rubella in agreement with current local immunization guidelines for immunosuppressed participants before Week I-0.

Note: For participants who have not received the required vaccine doses due to age or other reasons, an accelerated vaccination schedule can be completed prior to study enrollment, as per local or professional guidelines.

16. Criterion modified per Amendment 1

16.1. If live, attenuated viral vaccine is utilized for any study participants, it is necessary for at least 4 weeks (or longer as indicated on the package insert of the relevant vaccine) to elapse between the vaccination and receipt of initial study intervention.

17. Criterion modified per Amendment 4

17.1. Have negative stool results for enteric pathogens. Stool studies must include a stool culture and *Clostridioides difficile* (formerly known as *Clostridium difficile*) toxin assay (*C. difficile* toxin/glutamate dehydrogenase [GDH] with Reflex to polymerase chain reaction testing). These must have been performed during screening or the current episode of disease exacerbation as long as the stool studies were performed within 4 months prior to the first administration of study intervention. Additional testing (eg, ova and parasites or *Escherichia coli* O157:H7 assessments) may be performed at the investigator's clinical discretion.

Screening Laboratory Test Parameters

18. Have screening laboratory test results as follows:

a. Hemoglobin ≥8.0 g/dL.

b. White blood cells (WBC) ≥2.5 x 10^3 cells/µL (SI: ≥2.5 x10^9 cells/L).

c. Neutrophils ≥1.5 x 10^3 cells/ µL (SI: ≥1.5 x10^9 cells/L).

d. Platelets ≥100 x 10^3 cells/ µL (SI: ≥100 x10^9 cells/L).

e. Serum alanine transaminase (ALT) and aspartate transaminase (AST) levels not exceeding 2 times the upper limit of normal for the central laboratory.

f. Serum creatinine not to exceed:

1) 0.5 mg/dL (SI: 44 µmol/L) for ages 2 to 5 years.

2) 0.7 mg/dL (SI: 62 µmol/L) for ages 6 to 10 years.

3) 1.0 mg/dL (SI: 88 µmol/L) for ages 11 to 12 years.

4) 1.2 mg/dL (SI: 106 µmol/L) for ages ≥13 years.

Other

19. Parent(s) (preferably both if available or as per local requirements) or their legally acceptable representative must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to allow the child to participate in the study. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Informed Consent Process in Appendix 15 (Section 10.15, Regulatory, Ethical, and Study Oversight Considerations). An adolescent who signs the assent form will be given the opportunity to sign an adult ICF at a later visit when they reach the age of majority during the study to indicate that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

20. Must be willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Crohn's Disease Diagnosis and Status

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

2. Criterion modified per Amendment 6

   2.1. Currently has or is suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained and adequately treated at least 3 weeks prior to first administration of study intervention, or 8 weeks prior to first administration of study intervention for intra-abdominal abscesses, provided that there is no anticipated need for any further surgery. Participants with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses identified.

3. Has had any kind of bowel resection within 6 months or any other intra-abdominal surgery within 3 months prior to Week I-0.

4. Presence of a stoma.

Concomitant or Previous Medical Therapies Received

5. Criterion modified per Amendment 1

   5.1. Criterion modified per Amendment 6

   5.2. Has received any of the following prescribed medications or therapies within the specified period:

      a. Has ever received ustekinumab or a biologic agent targeting IL-12/23 or IL-23, including, but not limited to, briakinumab, brazikumab, guselkumab, mirikizumab (formerly LY3074828), and risankizumab.

      b. Has ever received thalidomide or related agents.

      c. Has received natalizumab within 12 months of Week I-0.

      d. Has received agents that deplete B or T cells (eg, rituximab, alemtuzumab, or visilizumab) within 12 months of Week I-0

      e. or continue to manifest depletion of B or T cells more than 12 months after completion of therapy with lymphocyte depleting agents.

      f. Has received vedolizumab with <2 half-lives washout period (Appendix 6 [Section 10.6]) prior to Week I-0.

      g. Has received other immunomodulatory agents (eg, 6-thioguanine [6-TG], cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil) within 8 weeks prior to Week I-0.

h. Has received anti-TNFα biologic agents with <2 half-lives washout period (Appendix 6 [Section 10.6]) prior to Week I-0.

i. Has used any investigational intervention within 4 weeks prior to Week I-0 or within 5 half-lives of the investigational intervention, whichever is longer.

j. Has used apheresis (ie, Adacolumn apheresis, Cellsorba apheresis) within 2 weeks prior to Week I-0.

k. Have used laxatives, except preparations for endoscopy or other procedures, within 1 week prior to screening procedures.

l. Has initiated enteral nutrition therapy <3 weeks prior to the first administration of study intervention at Week I-0. (Participants who are on a stable regimen ≥2 weeks prior to the anticipated first administration of study intervention at Week I-0 may be considered for enrollment [Section 5.1]).

m. Has an indwelling catheter.

n. Is on total (complete) or partial (supplemental) parenteral nutrition or anticipated to require during enrollment in the study. If recently on total (complete) or partial (supplemental) parenteral nutrition, much have stopped therapy at least <3 weeks before first administration of study intervention.

o. Is on rectal therapy for Crohn's disease with either 5-ASA medications or corticosteroids.

p. Is on IV steroids

q. Is on more than one antibiotic prescribed for the treatment of Crohn's disease

Infections or Predisposition to Infections

6. Criterion modified per Amendment 6

6.1. Have a history of latent or active granulomatous infection histoplasmosis, or coccidioidomycosis, or have had a nontuberculous mycobacterial infection prior to screening.

7. Have a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis, chronic cystitis), an open, draining, or infected skin wound, or a skin ulcer.

8. Have clinically significant immune deficiency syndrome (eg, severe combined immunodeficiency syndrome, T-cell deficiency syndromes, B-cell deficiency syndromes, or chronic granulomatous disease) and/or monogenic cause of IBD. With children who carry a diagnosis of VEO-IBD, an evaluation for immunodeficiency and monogenic forms of IBD should have been performed.

9. Have a known history of infection with HIV or test positive at screening.

10. Has evidence of herpes zoster infection within 8 weeks prior to Week I-0.

11. Have a known history of hepatitis C infection or test positive at screening.

12. Have a hepatitis B infection. Participants must undergo screening for hepatitis B virus (HBV, Appendix 12 [Section 10.12]). At a minimum, this includes testing for hBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total).

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

13. Have had a Bacille Calmette-Guerin vaccination within 12 months of screening visit.

14. Criterion modified per Amendment 1

    14.1. Criterion modified per Amendment 4

    14.1. Criterion modified per Amendment 6

    14.2. Received, or are expected to receive, any live virus or bacterial vaccination within 4 weeks prior to the first administration of study intervention.

15. Criterion modified per Amendment 6

    15.1 A medical history of or current nontuberculous mycobacterial infection or clinically significant opportunistic infection (eg, pneumocystosis, invasive aspergillosis, progressive multifocal leukoencephalopathy) at any time.

16. Criterion modified per Amendment 6

    16.1. Meet ANY of the following tuberculosis (TB) screening criteria:

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

a. Have a history of active TB or show signs or symptoms suggestive of active TB upon medical history and/or physical examination at screening.

b. Have a history of latent TB.

c. Have had recent close contact with a person with active TB.

d. Have a positive IGRA test result within 2 months prior to the first administration of study intervention.

Note: Tuberculin skin testing (TST) should also be considered in participants less than 5 years old. Indeterminate/borderline results should be handled as outlined in Section 8.3.6.1.

e. Have a chest radiograph or chest computed tomography within 3 months prior to the first administration of study intervention with evidence of TB. Chest imaging must be performed as part of the screening, unless country or site guidelines do not recommend a chest radiograph, as a necessary screening process prior to initiation of anti-TNFα therapies AND IGRA/TST testing is negative.

17. Criterion modified per Amendment 6

17.1. Have a chest radiograph during screening or within 6 months prior to the first administration of study intervention that shows an abnormality suggestive of an undiagnosed pulmonary pathology that may include extraintestinal manifestations of IBD, a malignancy, or current active infection.

18. Have had a serious infection (eg, hepatitis, pneumonia, or pyelonephritis), have been hospitalized for an infection, or have been treated with parenteral antibiotics for an infection within 2 months prior to first administration of study intervention. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

NOTE: For COVID-19-related exclusion, see Exclusion Criterion 31.

Malignancy or Increased Potential for Malignancy

19. Presence or history of any malignancy including presence or history of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (eg, nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or

periaortic areas), and monoclonal gammopathy of undetermined significance, or clinically significant hepatomegaly or splenomegaly.

Coexisting Medical Conditions or Past Medical History

20. Have a history of moderate or severe progressive or uncontrolled liver or renal insufficiency; or significant cardiac, vascular, pulmonary, GI, endocrine, neurologic, hematologic, psychiatric (including suicidality), or metabolic disturbances.

21. Is currently undergoing or has previously undergone allergy immunotherapy for a history of anaphylactic reactions.

22. Has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients (refer to current IB).

23. Has poor tolerability of venipuncture or lack of adequate venous access for required blood sampling.

24. Has a serious allergic reaction to latex.

25. Have a transplanted organ (with the exception of a corneal transplant performed >3 months prior to first administration of study intervention).

26. Has any condition that, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

27. Has a history of drug or alcohol abuse according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), within 1 year before screening.

Other Exclusions

28. Criterion modified per Amendment 4

    28.1. Received an investigational intervention including any investigational vaccines or used an invasive investigational medical device within 3 months before the planned first dose of study intervention or is currently enrolled in an investigational study. Receipt of an investigational vaccine for COVID-19 is not an automatic exclusion criterion; discuss with medical monitor.

29. Criterion modified per Amendment 6

    29.1. Are pregnant, nursing, or planning pregnancy while enrolled in this study or within 16 weeks after the last dose of study intervention.

30. Criterion modified per Amendment 6

30.1 A child of an employee or a child who is a first-degree relative of an employee, or a child of the investigator who has direct involvement in the proposed study as well as the children of family members of the employees or the investigator may not participate in the study at the study site at which the family member is employed. The child may participate in the study at a different study site that does not employ any first-degree family members.

Additional Infections or Predisposition to Infections:

31. Criterion modified per Amendment 6

31.1. During the 6 weeks prior to first administration of study intervention, have had ANY of the following (regardless of vaccination status): (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features of COVID-19 without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection:

- Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

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

  AND

  (ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the first administration of study intervention

NOTES on COVID-related exclusion:

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

Other Exclusions

32. Plans to father a child while enrolled in this study or within 16 weeks after the last dose of study intervention.

NOTE: Investigators should ensure that all available study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 15 (Section 10.15).

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Criterion modified per Amendment 5

    1.1. Criterion modified per Amendment 6

    1.2. Refer to Section 6.8, Concomitant Therapy, for details regarding prohibited and restricted therapy during the study.

    It is recommended that participants are up to date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. It is strongly recommended that participants will have completed a locally approved (including emergency-use-authorized) COVID-19 vaccination regimen at least 2 weeks prior to the first administration of study intervention. Study participants should follow applicable local vaccine labeling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.8.3).

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Criterion modified per Amendment 6

    3.1. All females of childbearing potential must have a negative highly sensitive urine pregnancy test at all visits when study intervention is to be administered.

4. If sexually active, females must remain on a highly effective method of birth control during the study and for 16 weeks after receiving the last administration of study intervention.

5. All males who are sexually active with a female of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository), or who is sexually active with a female who is pregnant must use a condom.

6. Criterion deleted per Amendment 6

7. Must agree not to receive a live virus or live bacterial vaccination during the study. Participants may request an exception from the sponsor to this lifestyle restriction. If approved by the sponsor, the participant will be allowed to receive a live vaccination and to remain in the study. However, study intervention may be withheld for a period of time as specified by the sponsor.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log, which reports on all participants who were seen to determine eligibility for inclusion in the study, to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification number and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent/assent will be used.

If, during the screening period, a participant has not met all inclusion criteria or has met any exclusion criteria or is unable or unwilling to adhere to the lifestyle considerations of the study, the participant is considered to be a screen failure and is not eligible to be enrolled in the study.

In general, if a participant is a screen failure, but at some timepoint in the future is expected to meet all of the participant eligibility criteria, the participant may be rescreened after a new informed consent/assent has been obtained. Participants who are rescreened should be assigned a new participant number and will restart a new screening period.

Completion of screening and enrollment procedures must occur within the specified screening window of 6 weeks.

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

Additional criteria for retesting and rescreening are outlined below and in the Retesting and Rescreening Plan.

Retesting

Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the screening period, as long as this is done within the specified screening window of within 6 weeks. On a case-by-case basis after consultation with the sponsor, retesting may exceed the 6-week window and will not be considered protocol deviations.

Rescreening

Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened only after consultation with the sponsor. Participants who are rescreened will be assigned a new participant number, undergo the informed consent/assent process, and then start a new screening period. On a case-by-case basis after consultation with the sponsor, rescreening procedures may exceed the 6-week window and will not be considered protocol deviations.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Additional information for delayed administration of study intervention between Week I-8 and Week M-0 will be considered on a case-by-case basis after consultation with the sponsor (Schedule of Activities, Table 3). Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.16.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

Intravenous study intervention (including the flush) should be administered over a period of not less than 1 hour, and not more than 2 hours. The infusion (including the flush) should be completed within 8 hours of preparation of the study intervention.

Subcutaneous study intervention will utilize either the prefilled syringe (PFS) with an UltraSafe Passive™ Needle Guard (PFS-U) presentation or the liquid-in-vial (LIV) presentation.

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Ustekinumab and placebo for ustekinumab will be manufactured and provided under the responsibility of the sponsor. Refer to the ustekinumab IB for a list of excipients.

Instructions on the preparation and administration of study intervention will be provided in the Site Investigational Product Procedures Manual (SIPPM).

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.16.

6.1.1. Combination Product

- For this protocol, the term combination product refers to the single integral drug device combination.
- The sponsor-manufactured combination product for use in this study is the PFS assembled with a PFS-U. Additional details on the PFS-U are provided in Section 6.1.2.2 and the ustekinumab IB.
- All combination product deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the study. For studies using a combination product, these deficiencies will be reported as product quality complaints (PQCs; Appendix 8 [Section 10.8]: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting) and appropriately managed by the sponsor.

6.1.2. Physical Description of Study Interventions

6.1.2.1. Induction Period

For participants with body weight <40 kg: Ustekinumab 5 mg/mL LIV will be supplied as a single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume). In addition to ustekinumab, the solution contains L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, L-methionine, ethylenediaminetetraacetic acid disodium salt dihydrate, and water for injection at pH 6.0. No preservatives are present. After the dose is calculated, the ustekinumab 5 mg/mL liquid formulation will be diluted to an appropriate concentration using an appropriate diluent for IV administration.

For participants with body weight ≥40 kg: Multiple vials of ustekinumab 5 mg/mL LIV, described above, will be diluted to an appropriate concentration using an appropriate diluent for IV administration.

6.1.2.2. Maintenance Period

For randomized participants with body weight <40 kg: Ustekinumab 90 mg/mL LIV will be supplied as a single-use, sterile solution in 2 mL vials. Each 1 mL of ustekinumab solution contains 90 mg ustekinumab, L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, and water for injection at pH 6.0. No preservatives are present. Ustekinumab 90 mg/mL can be used for SC administration at a dose strength of 45 mg in 0.5 mL nominal volume. As doses are determined based upon the BSA of participants, the contents of the vial(s) are withdrawn using a standard graduated syringe to the required dose volume.

For randomized participants with body weight ≥40 kg: Ustekinumab will also be supplied in a PFS-U in a strength of 90 mg in 1 mL nominal volume for SC administration. Each 1 mL of ustekinumab solution in the PFS contains 90 mg ustekinumab L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, and water for injection at pH 6.0. No preservatives are present. The needle cover on the PFS contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Placebo administrations will have the same appearance as the respective ustekinumab administrations.

6.1.3. Dose Regimens

6.1.3.1. Induction Period

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

For participants with body weight <40 kg:

- 250 mg/m^2 IV

For participants with body weight ≥40 kg:

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

6.1.3.2. Maintenance Period

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

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

Further information on the study interventions is provided in Section 6.1.2. Ustekinumab doses from Week M-0 through Week M-40 will be based on the participants' weight and height obtained at each visit or based on participant weight and height at the last on-site study 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 (see Section 7.1). For induction nonresponders who do not achieve clinical response based on the PCDAI by Week M-8 (ie, a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30), the Week M-8 ustekinumab trough concentration will determine eligibility for the Exposure Optimization Substudy (Appendix 17 [Section 10.17]), or requirement for study withdrawal.

Beginning at Week M-8 for induction responders and beginning at Week M-16 for delayed responders (induction nonresponders who are in clinical response at Week M-8), participants who experience LOR (Section 4.1.2) will be eligible for dose adjustment as follows (unless they have documented low ustekinumab exposure at Week M-8, in which case they will be eligible for the Exposure Optimization Substudy):

- 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 a LOR will remain on ustekinumab q8w (a sham adjustment).

At the first scheduled study-site visit (after Week M-8 for induction responders and after Week M-16 for delayed responders) that participants experience LOR, they will have a dose adjustment and transition to q8w dosing without any placebo injections. If during any home visit a participant reports worsening of their symptom history sub-scores, they will be instructed to withhold administration of study intervention and instructed to schedule a study-site visit to be evaluated for LOR and eligibility for a dose adjustment.

For the first dose, participants may receive a study intervention 4 weeks after the prior study intervention if the LOR occurs between their scheduled study intervention injections in order to maintain study blinding.

Participants who are not in clinical response within 16 weeks after dose adjustment and have normal ustekinumab exposure will be withdrawn from study intervention and return for their final safety visit (approximately 20 weeks after the administration of the last study intervention).

Participants who lose response and have low ustekinumab exposure* may be eligible to participate in an optional Exposure Optimization Substudy with q4w dosing and safety visits (see Appendix 17 [Section 10.17]) 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.

6.1.4. Optional Home Study Intervention Administration

Study sites and their participants will be offered the option of administering study intervention at home during the maintenance period. At Week M-0, Week M-8 and Week M-16, SC study intervention will be administered (or supervised) by a study-site staff member.

During visits Week M-0 and M-8, the participant and the participant's caregiver may be trained to administer SC study intervention. Training of the participants/caregivers will occur at the investigative site under the supervision of a health care provider (HCP). In addition, participants/caregivers will receive detailed instructions on how to monitor for potential injection-site reactions or allergic reactions including anticipatory guidance on seeking medical care. At-home visits, participants will be questioned about safety assessments by phone or video chat by site staff and/or by a home health aide.

After being properly trained, at Week M-12, Week M-24, Week M-36, and Week M-40, participants or the participant's caregiver will have the option of administering study intervention at home. Participants <40 kg (and/or their caregiver) will also be trained on how to draw up the blinded study intervention. Instructions will be provided to record study intervention administrations with time and date information and whether study intervention was self-administered or given by a caregiver, and if so, whether SC administration was completed, in the participant's Study Intervention Home Administration Diary. Any participant/caregiver who is unable or unwilling to administer study intervention at home will be asked to return to the study site for the administration of study intervention and study visit assessments.

Participants will be instructed to complete all protocol-specified activities prior to the home administration of study intervention, (ie, laboratory blood tests, home diaries, questionnaires, and remote site visit with study staff, Section 8). After all study visit activities have been completed, the study-site staff will instruct the participant whether to proceed with home administration of study intervention or to return to the study site for an in-person visit, prior to administration of study intervention.

Participants who are instructed to withhold at-home study intervention administration at visit weeks M-12, M-24, M-36, and M-40, will be instructed to bring the unused study intervention/syringe to the study site and will undergo an evaluation for LOR.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C), not frozen, and protected from light. Vigorous shaking of the product should be avoided. Prior to administration, the product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow color), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used.

Study intervention in glass vials or in PFS-U will be ready to use. The infusions will be prepared according to the participant's BSA (for participants with body weight <40 kg) or weight (for participants with body weight ≥40 kg). The pharmacist (or designated personnel) will prepare the required volume of study intervention to be infused using the appropriate number of vials.

Aseptic procedures must be used during the preparation and administration of the study material. Exposure to direct sunlight should be avoided during preparation and administration.

Participants/caregivers who are able and who have been appropriately trained in at-home administration of study intervention will be instructed on how to transport, store, and administer medication for at-home use as indicated for this protocol.

Refer to the study-site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Since participants and/or their caregiver may be administering study intervention at home at Week M-12, Week M-24, Week M-36, and Week M-40, they will receive detailed instructions for study intervention storage and disposal of used syringes, vials and handling of unused study material. They will also receive detailed instructions about reporting AEs and PQCs (Section 8.3 and Appendix 8 [Section 10.8]). Participants will receive a sharps container to dispose of used syringes. In general, participants will be instructed to return the sharps container and/or cartons in accordance with local guidelines. Participants will record study intervention administrations with time and date information and whether study intervention was self-administered or given by a caregiver, and if so, whether SC administration was completed, in the participant's Study Intervention Home Administration Diary.

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

Home visits may require either study intervention dispensed at the site or shipped direct to a participant (DTP). Participants will be provided site-specific instructions regarding the available options for dispensing and receiving study intervention for home administration.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. At Week M-0, participants (induction responders and induction nonresponders) will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using permuted block randomizations and will be stratified by response status at Week I-8 (induction responder/induction nonresponder) and weight (<40 kg, ≥40 kg). Clinical response status at Week I-8 will be determined by the PCDAI.

The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

To maintain the study blind during the maintenance period, placebo injections will be used, and they will be identical in appearance to ustekinumab. 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 eCRF when the study intervention is dispensed.

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

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

Notes:

- If a participant has documented LOR and the investigator wishes to evaluate if the participant would be eligible for the Exposure Optimization Substudy, the site will be informed of the participant's exposure (ie, low [<1.4 µg/mL] or normal).
- If a participant's ustekinumab trough concentration at the end of the Exposure Optimization Substudy (after at least 3 doses) is >7.2 µg/mL, the site will be informed and the participant will not be able to continue q4week dosing, but may continue q8w dosing in the LTE. (For details on the Exposure Optimization Substudy, refer to Appendix 17 [Section 10.17].)

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.

The postbaseline results of CRP, fecal calprotectin, and fecal lactoferrin tests performed by the central laboratory will not be blinded to the investigative sites.

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.

Sponsor personnel will remain blinded to maintenance treatment assignment until after the DBL following the M-44 visit, with the exception of a PK sponsor representative independent of study conduct to review the PK interim analysis (see DMC SAP for further details) and a sponsor unblinded group for preparing the EMA submission for the participants ≥40 kg included in the interim analysis (Further details will be provided in the unblinding plan, including the list of sponsor personnel who will have access to unblinded information at the time of the interim analysis).

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. If a participant is unblinded by the site, the information must be entered in the appropriate section of the eCRF and in the participant's source documents.

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 (Section 1.3).

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.

6.4. Study Intervention Compliance

Ustekinumab will be administered as an IV infusion (Week I-0) and an SC injection (all time points specified for study intervention administration in the Schedule of Activities except Week I-0).

The details of each study intervention administration will be recorded in the eCRF, including date, start and stop times of the IV infusion and volume infused, and date and time of SC injection.

From Week I-3 through Week I-8, all visits will occur within a range of ±4 days of the scheduled visit. From Maintenance Week 4 through Week M-44, it is expected that all visits will occur within a range of ±10 days of the scheduled visit (Section 1.3). Any visits outside of these ranges should be discussed with the sponsor. If a maintenance study visit occurs outside the specified visit window, the participant should then resume his or her normal dose schedule relative to the Week M-0 visit as soon as possible. After Week M-44, the follow-up safety visit should occur approximately 20 weeks after the last administration of study intervention (within ±10 days of the scheduled visit). Any out of range visit should be documented in the eCRF.

Study-site personnel will maintain a log of all study intervention administered. Study intervention supplies for each participant will be inventoried and accounted for. Information regarding study intervention administrations that are administered outside of the scheduled windows or missed will be recorded. Participant charts and worksheets may be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Although it is understood that treatment may be interrupted for many reasons, compliance with the treatment schedule is strongly encouraged.

When participants/caregivers begin at-home administration of study intervention, they will be instructed to maintain a log of all study intervention administered. All cartons should be returned to the study site at the next study visit. Returning used syringes that reside in the sharps container will depend on local guidelines. Participants (and caregivers) will receive instructions on compliance with study intervention when they begin at-home administration. During the course of

the study, the investigator or designated study-site personnel will be responsible for providing additional instructions to re-educate any participant who is not compliant with administering study intervention.

6.5. Dose Modification

Dose adjustment is described in Section 6.1.3.2.

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

Participants who are <18 years of age at the end of the study and do not discontinue prior to Week M-44 may be eligible to enter into an LTE which will be described in a separate protocol. If a participant has reached 18 years of age by the end of participation in the study and is not able to access ustekinumab commercially, the participant may be eligible for post-study access to ustekinumab via a country-specific mechanism. If post-study access is not possible, enrollment in the LTE may be permitted on a case-by-case basis.

6.7. Treatment of Overdose

For this study, any dose of ustekinumab greater than the highest dose at a single dosing visit (exceeding 250 mg/m^2 IV for participants with <40 kg body weight, 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, and 520 mg IV for participants with >85 kg body weight or exceeding 90 mg SC for participants with ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight) will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

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

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.8. Concomitant Therapy

For all enrolled participants, prestudy therapies including prescription or over-the-counter medications, vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens administered up to 30 days before first dose of study intervention must be recorded in the eCRF at screening.

Concomitant therapies must be recorded throughout the study beginning with the screening process and through the final safety visit in the eCRF. This includes medications given for endoscopies and sedation that occur during the study.

The use of the following permitted medications must be recorded in the concomitant medication eCRF. The recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication.

- Over-the-counter medications, vitamins, minerals, or herbal supplements
- Prescription therapies, including special diets, or dietary supplements

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies (Section 6.8.2) are administered.

6.8.1. Crohn's Disease-Specific Allowed Medications/Therapies

The following concomitant medications/therapies for Crohn's disease are allowed in this study: oral 5-ASAs, oral corticosteroids, immunomodulators (ie, 6-MP, AZA, MTX), enteral therapy, and single antibiotics for the treatment of Crohn's disease. These treatments must be stable for 2 to 4 weeks prior to first administration of study intervention at Week I-0 [see Inclusion Criterion 7]. If there is a concern for drug toxicity, dose reduction can always occur.

The following medication/therapy changes 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 a single antibiotic for the treatment of Crohn's disease at Week I-0, the 5-ASA or antibiotic can be discontinued at any time during the course of the study, though preferably after Week M-44.
- For participants on enteral therapy for treatment of Crohn's disease, the enteral therapy may be reduced after Week M-12.
- For participants receiving 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 induction responders as follows.
  - Recommended tapering schedule for oral prednisone-equivalent corticosteroids:
    - Participants receiving >20 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until 0 mg/day.
    - Participants receiving ≤20 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.
  - Tapering of budesonide or beclomethasone dipropionate should follow local clinical practice.

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

Refer to Section 4.1.4 for rescue therapies.

6.8.2. Prohibited Concomitant Medications/Therapies

Participants who initiate the following medications/therapies at any time during study participation (both induction and maintenance periods) should be discontinued from further study intervention administration and should have a final safety follow-up visit approximately 20 weeks after their last study intervention administration.

- IV corticosteroids.
- Immunomodulatory agents other than 6-MP, AZA, and MTX (including, but not limited to, 6-TG, cyclosporine, MMF, tacrolimus, sirolimus, thalidomide, tofacitinib, and other Janus kinase inhibitors).
- More than one antibiotic initiated for the treatment of Crohn's disease.
- Parenteral nutrition administered via a central line.
- Biologic agents (including, but not limited to TNFα antagonists, abatacept, anakinra, rituximab, vedolizumab, natalizumab, visilizumab, and alemtuzumab).
- A biologic therapy targeted at IL-12 and/or IL-23 (eg, commercial ustekinumab, guselkumab, risankizumab, brazikumab, tildrakizumab).
- Investigational drugs.
- A live virus or bacterial vaccine, unless approved by the sponsor (see Section 5.3, Lifestyle Considerations).

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

6.8.3. Vaccinations (Including COVID-19)

Non-live vaccines are allowed to be administered during this study.

When considering use of locally approved non-live vaccines (including emergency-use-authorized COVID-19 vaccines) in study participants, follow applicable local vaccine labeling, guidelines, and standards of care for participants receiving immune-targeted therapy.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant (or the participant's parent/legal representative) withdraws consent or assent to receive study intervention.
- The investigator or sponsor believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant or is planning a pregnancy within the study period. Refer to Appendix 14 (Section 10.14), Contraceptive Guidance and Collection of Pregnancy Information.
- The participant initiates treatment with prohibited therapies for Crohn's disease and other indications (Section 6.8.2).
- The participant is an induction nonresponder who meets the Early Escape criteria and does not have low exposure or who does not wish to participate in the optional substudy.
- The participant experiences LOR during the maintenance period of the study and is not in clinical response after 16 weeks from dose adjustment.
- The participant experiences LOR and low exposure leading to substudy entry and does not achieve clinical response after 16 weeks after substudy entry.
- The participant requires more than 2 courses of corticosteroids for Crohn's disease, or more than 1 antibiotic for the treatment of Crohn's disease through the Week M-44 visit.
- The participant has a disease-related surgery that represents a lack of efficacy of study intervention or that will preclude the future ability to assess efficacy using instruments required for demonstration of efficacy endpoints.
- The participant develops a serious or systemic opportunistic infection.
- The participant misses 2 consecutive doses of ustekinumab after Week I-8 because body weight is below the 10 kg limit.
- The participant meets **ANY** of the following TB-related conditions:
  - A diagnosis of active or latent TB is made.
  - A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.
  - A participant undergoing evaluation has chest imaging with evidence of TB and/or a positive IGRA test result and/or 2 indeterminate/borderline IGRA test results. Indeterminate/borderline results should be handled as outlined in Section 8.3.6.
- The participant experiences an SAE related to either an injection or infusion, including severe hypersensitivity reactions. Discontinuation of ustekinumab administration must also be

considered for participants who develop a nonserious but severe infusion or injection-site reaction.

- The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) after an injection of study intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- The participant has severe liver test abnormalities, as described in Section 7.1.1 and Appendix 13 (Section 10.13).
- The participant has a malignancy including squamous cell skin cancer.

Refer to the Schedules of Activities (Table 2 and Table 3) for instructions on assessments for the final study visit.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions in Appendix 13 (Section 10.13) Liver Safety: Suggested Actions and Follow-up Assessments, or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.1.2. Temporary Discontinuation

This is not applicable.

7.1.3. Rechallenge

This is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent or assent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent/assent, then no additional assessments are allowed. Study intervention assigned to the withdrawn participant may not be assigned to another participant. Additional participants will not be entered. If a participant discontinues study intervention but does not withdraw from the study, end of intervention efficacy and safety assessments should be obtained.

Withdrawal of Consent/Assent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent/assent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

7.2.1. Withdrawal From the Main Study and the Use of Biomarker Samples

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

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

Withdrawal From the Biomarker Samples While Remaining in the Main Study

The participant may withdraw consent/assent for use of biomarker samples for research while remaining in the study (refer to Appendix 15 [Section 10.15]). The participant may withdraw consent/assent after samples have been obtained. In such a case, the biomarker samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent/assent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 15 [Section 10.15]). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant and/or their parent or legal guardian to reschedule the missed visit as soon as possible, to counsel the participant and/or their parent or legal guardian on the importance of maintaining the assigned visit schedule, to

ascertain whether the participant and/or their parent or legal guardian wishes to or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant and/or their parent or legal guardian (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's and/or their parent's or legal guardian's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant and/or their parent/legal representative continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, and safety measurements applicable to the study.

During screening, each participant and/or their parent or legal guardian will be provided with electronic diaries to enter study-related data. Study-site personnel will train the participants on how to use and complete the diaries, including instructions to capture the data according to the study design and not to wait until the study-site visit to record information. Participants will be provided with written instructions on how to get additional support, if needed, for completion of the diaries.

All visit-specified participant-reported outcome (PRO) assessments (ie, IMPACT-III) should ideally be conducted/completed at home or at the study sites before any tests, procedures, or other consultations to prevent influencing participant responses. Refer to the PRO completion instructions on the administration of PROs. All other efficacy evaluations should be completed before study intervention administrations.

If multiple sample collections are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: clinical safety laboratory assessments, PK, immunogenicity, and biomarkers. Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and on laboratory requisitions.

Additional highly sensitive urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study; and

- Prior to each study intervention administration.
- At final efficacy visit.
- At early termination visit.

- At final safety visit.
- If experiencing a delayed menstrual period (over 1 month between menstrual cycles) or infrequent or irregular menstrual cycles to confirm absence of pregnancy.

The total blood volume to be collected from each participant will be approximately 150 mL (or 175 mL for participants in Japan).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Guidelines for handling of assessments affected by the COVID-19 pandemic are found in Appendix 16 (Section 10.16).

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. The sample should be drawn from a different arm than the IV line at the Week I-0 visit, or if using an IV line that is also being used to deliver medication, the line should be flushed and cleared of any residual medication that may be remaining prior to each PK sample being drawn. When using an IV line to draw PK samples, the first 1 mL of blood should be drawn and discarded prior to obtaining the sample. Intravenous line maintenance should be followed as per the standard of care. At visits where serum concentration and antibodies to ustekinumab will be evaluated, 1 blood draw of sufficient volume can be used.

For at-home visits, blood draws for serum concentration and antibodies to ustekinumab and clinical laboratory tests will be performed by a home health care aide, study-site personnel, or other designate. The study sites will arrange for transfer of blood samples to the study site's laboratory for further processing and shipping to the central laboratory. Study sample handling and processing instructions will be provided in a home study visit guidance document.

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

Instructions for the order in which the sample collection will proceed, sample collection, handling, storage, and shipment of samples are found in the site instruction manuals that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the site instruction manuals.

Study-specific Materials

The investigator will be provided with the following supplies, including, but not limited to:

- Ustekinumab IB
- SIPPM
- Laboratory Manual
- Retesting and rescreening plan

- Biopsy Manual
- IWRS Manual
- eCRF guidelines
- Sample ICF/assent forms
- Electronic PRO (ePRO) device and User Manual
- ePRO questionnaires and PRO completion instructions
- Participant diaries
- Endoscopic imaging kit and manual
- eConsent tablet device and site user guide, if the study site is participating in electronic informed consent/assent

8.1. Efficacy Assessments

Efficacy evaluations will include the following:

- PCDAI/sPCDAI
- CDAI
- CRP
- Fecal calprotectin and fecal lactoferrin
- IMPACT-III
- Fistula assessment
- SES-CD score
- Simplified endoscopic mucosal assessment for Crohn's disease (SEMA-CD)
- Histologic assessments: GHAS, Geboes score, and RHI
- Height, weight, and BMI (age and sex-specific z-scores)

The PCDAI will be the primary tool for assessing disease activity response to ustekinumab. The degree of inflammation will be assessed by measuring serum CRP concentrations, fecal calprotectin, and fecal lactoferrin. Stool samples will be collected and analyzed to evaluate changes in fecal markers that may reflect ustekinumab treatment. The well-being of participants will be measured using the IMPACT-III assessment. For participants with fistulizing disease, fistula closure will also be assessed. Endoscopic response and improvement will be assessed by ileocolonoscopy. Growth during the study will be assessed using age and sex-specific z-scores for height, weight, and BMI.

For PROs:

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

- The PRO instrument will be available for regulators and for IRB/IEC submissions, and will be provided separately in a companion manual with the instruments that will be submitted with the protocol.
- The PRO and AE data will not be reconciled with one another.

The Schedule of Activities summarizes the frequency and timing of efficacy measurements applicable to this study (Section 1.3 [Table 2 and Table 3]).

8.1.1. PCDAI (sPCDAI)

The assessment of remission and response in children with Crohn's disease will be evaluated with the PCDAI (Appendix 2 [Section 10.2]).[21,22] The PCDAI is a validated, patient-reported and clinician-administered composite index designed for use in children ages 3.5 to 19 years old with Crohn's disease. Longitudinal studies have demonstrated that the PCDAI is a reliable and valid assessment and is responsive to changes of disease activity. Based on clinical study, cut-offs for disease severity and a definition of clinically meaningful change have been established.[21,22] The 11-item PCDAI covers 5 general disease activity domains: symptom history scores (3 items: abdominal pain, stool frequency; and general well-being); laboratory scores (3 items: hematocrit [HCT],%; erythrocyte sedimentation rate [ESR], mm/hr; albumin, g/dL); growth scores (2 items: weight and height), physical examination scores (2 items: abdomen and aperirectal disease), and extraintestinal manifestations.

The sPCDAI, a shorter version of the PCDAI, will also be used to evaluate remission and response. The sPCDAI is composed of the following 6 PCDAI items: abdominal pain, general well-being, weight, stool, abdominal exam, and extraintestinal manifestations.[24,46]

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

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

The PCDAI scale will be completed during the induction and maintenance periods of the study according to the timepoints specified in the Schedule of Activities. All items are summed to derive the total score. The total PCDAI score ranges from 0 to 100 with higher scores indicating greater disease activity. A PCDAI score ≤10 points is considered to be indicative of clinical remission, and clinical response is defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30.[7,21,22] The 6-item sPCDAI score ranges from 0 (no disease activity) to 90 (severe disease activity), with higher scores also indicating more active disease.

8.1.2. CDAI

Assessment of response in children with Crohn's disease will also use the CDAI (Appendix 3 [Section 10.3]). The CDAI is a validated, patient-reported and clinician-administered composite index that is a reliable, discriminative disease activity index, and is responsive to changes occurring during the intervals used in clinical studies.[7,40,41] The 8-item CDAI covers 4 general disease activity domains: history scores, patient-reported symptoms (3 items: 1 week daily recall of daily abdominal pain, number of liquid or soft stools, general well-being); laboratory score (1 item: HCT, %); extraintestinal manifestations (6 items: arthritis/arthralgia, iritis/uveitis, skin/mouth lesions, peri-anal disease, other fistula, fever >100°C/37.8°C in the last week); use of antidiarrheal agents including lomotil, loperamide, or opiates; presence of an abdominal mass; and current body weight. All items are scored, calculated using a predetermined multiplication factor, and summed to derive the total score ranging from 0 to over 600. Study intervention-induced clinical response in the adult Phase 3 program with ustekinumab in Crohn's disease was defined as a reduction from baseline in the CDAI score of ≥100 points or CDAI <150 points; a CDAI score of <150 points was used to define clinical remission in participants with Crohn's disease treated with study intervention.

The information collected in the electronic diary will be used to calculate the CDAI composite score. The participant and/or parent proxy will be instructed to complete the CDAI diary at least 7 days prior to Weeks I-0, I-8, M-8, and M-44. Each bowel movement will be recorded immediately after going to the toilet and scores for abdominal pain and well-being will be recorded before going to bed. If on any day the participants experience a fever, the temperature will be entered in the diary if the temperature is over 100°F/37.8°C (oral) or 101°F/38.3°C (rectal). Finally, all antidiarrheal medication usage during the past week will be recorded in the diary.

The CDAI will be completed by participants or their parent(s)/legal guardians and investigators during the induction and maintenance periods of the study according to the timepoints specified in the Schedule of Activities. The use of the CDAI will more directly facilitate the extrapolation of results from the current study of ustekinumab in pediatric Crohn's disease to results obtained in the Phase 3 program with ustekinumab in adult Crohn's disease.

8.1.3. C-Reactive Protein

C-reactive protein has been demonstrated to be useful as a marker of inflammation in patients with IBD.[8,15,28,44,49] In Crohn's disease, elevated CRP concentrations have been associated with severe clinical activity, 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 (Section 1.3). CRP will be assayed using a validated, high sensitivity CRP assay. Results of CRP measurement will be released to the investigators by the central laboratory.

8.1.4. 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.[29] Stool samples for fecal calprotectin and lactoferrin concentrations will be collected from all participants at visits indicated in the Schedule of Activities. 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.

8.1.5. IMPACT-III

Disease-related health QoL measures will be assessed in participants who are ≥10 years of age at Week I-0 using the validated IMPACT-III questionnaire (Appendix 4 [Section 10.4]). 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.[33,34] 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.[20,23,32,33,34] The IMPACT-III data will be collected on an electronic device.

8.1.6. Fistula Assessment

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

8.1.7. Ileocolonoscopy

To explore the potential utility of endoscopic improvement endpoints in children, 3 ileocolonoscopies will be performed, one at screening, another at Week M-8, and one at Week M-44 within approximately 3 weeks prior to these timepoints per the Schedule of Activities. All ileocolonoscopies will be video-taped and read by a central reader (process defined in a separate Imaging Charter). Endoscopic response will be assessed using the SES-CD.[3] The SES-CD is a scoring system that was developed to provide a simple yet granular evaluation of endoscopic disease severity in patients with Crohn's disease.[30] In addition, endoscopic reports will be evaluated using the SEMA-CD.[3] This novel instrument, derived from the SES-CD score, uses a simple Likert-like scale to rate the severity of mucosal involvement in the ileum and colon.

8.1.8. Histology

Histologic assessments will be performed using biopsy samples collected during video ileocolonoscopy (see endoscopy manual for biopsy details). Histologic assessments will be conducted by a central reader who is blinded to treatment groups and visit. The GHAS[9], Geboes score[14], and RHI[31] will be used to evaluate histologic improvements and healing. Histologic assessment analyses are considered exploratory and will be summarized in separate technical reports.

8.1.9. 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 SDs a value is from the mean of the data.[35] 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.[51] 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/m^2 for all children of the same age. Z-scores have the same statistical relation to the distribution of the reference around the mean at all ages, which makes results comparable across age groups and indicators. Z-scores are also sex-independent, thus permitting the evaluation of children's growth status by combining sex and age groups. These characteristics of z-scores allow further computation of summary statistics such as means, standard deviations, and standard error to classify a population's growth status.

8.2. Safety Assessments

Safety will be assessed by analyses of the incidence and types of AEs, SAEs, reasonably related AEs, discontinuation of study intervention due to an AE, infections, injection-site reactions, and

AEs during or within 1 hour of an infusion. Targeted safety events of malignancy and serious infection will also be assessed. Safety assessments will also include analyses of laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry), and a summary of maximum National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) toxicity grade for postbaseline laboratory values.

Details regarding the external DMC are provided in Section 9.6.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting and Appendix 8 (Section 10.8), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting. For participants who were enrolled with <5 half-lives washout of a prior biologic, refer to the prescribing information on the prior biologic for additional safety risks that should be monitored until the prior biologic is washed out.

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

Adverse events should include the reporting of any observed effects on organ maturation and growth and development, including fertility.

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

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

8.2.1. Physical Examinations

Physical examinations (including skin examinations) will be performed as specified in the Schedule of Activities. Height and weight will be recorded at screening and will also be recorded at timepoints specified in the Schedule of Activities (Section 1.3).

8.2.2. Vital Signs

Vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be collected at timepoints specified in the Schedule of Activities (Section 1.3). During site visits, vital signs will be obtained before, approximately every 30 minutes during, and twice (at approximately 30-minute intervals) after completion of the IV infusion of ustekinumab during the induction period. Vital signs should be obtained before every SC ustekinumab administration when administered by a healthcare provider during the maintenance period. The vital signs will be recorded in source notes.

8.2.3. Electrocardiograms

This section is not applicable.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Appendix 11 (Section 10.11). The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the central laboratory:

- **Hematology panel**
  - Hemoglobin
  - Hematocrit
  - WBC count with differential
  - Platelet count
- **Serum chemistry panel**
  - sodium
  - potassium
  - chloride
  - blood urea nitrogen (BUN)
  - creatinine
  - aspartate aminotransferase (AST)
  - alanine aminotransferase (ALT)
  - gamma-glutamyltransferase
  - total and direct bilirubin
  - alkaline phosphatase
  - calcium
  - phosphate
  - albumin
  - total protein
  - CRP

  Hematology and chemistry samples may be collected by local laboratories in circumstances where blood samples are not able to be collected on-site or shipped out in the timeframe described in the protocol.

- **Abnormal liver tests:** If laboratory testing for a participant who is enrolled in the study and receiving study intervention reveals an increase of serum aminotransferases (ALT or AST) to ≥3 x upper limit of normal (ULN) and an increase of bilirubin to ≥2 x ULN, study intervention

should be suspended immediately. In addition, initial laboratory tests for ALT, AST, alkaline phosphatase, and total bilirubin should be confirmed by a retest within 48 hours if possible, but no later than 72 hours following notification of test results. Additional clinical and laboratory studies may be performed to evaluate the underlying etiology of abnormal findings.

See Appendix 13 (Section 10.13) for additional information on monitoring and assessment of abnormal liver test.

- **Nutritional parameters**
  - 25-hydroxyvitamin D, MMA, iron
- **Pregnancy testing:** Females of childbearing potential will undergo a highly sensitive urine pregnancy test before all study intervention administration visits and at the Week M-44 and safety follow-up visit and, if applicable, at the LOR and early termination visits. A highly sensitive pregnancy test will be provided by sites to participants who are performing administration of study intervention at home. If used at home, investigators or site staff should instruct participant how to use the test and communicate that the test must be performed prior to dosing. In the event of a positive pregnancy test result, participants will be advised to hold further dosing and must be discontinued from further study intervention according to established protocol procedures.
- **Serology for HBV, HCV, and HIV**
  - Serology for HBV antibody, HBsAg, anti-HBs, and anti-HBc total at screening (HBV deoxyribonucleic acid [DNA] detection will only be performed for participants who test positive for core antibody and negative for surface antibody, Section 10.12 [Appendix 12]).
  - Serology for HCV at screening.
  - Serology for HIV at screening: HIV testing is required in those study participants who are greater than 6 years old and whose birth history is unknown (ie, adopted) or have exposure risks (parents with HIV or with other risk factors) or at the discretion of the study investigator. HIV testing in study participants who are less than 6 years old where testing would be required do not need testing, provided there is a record of a negative HIV test at birth. This is acceptable at the discretion of the study physician as long as it is entered into the study record.

8.2.5. Concomitant Medications

Concomitant medications will be reviewed at each study visit.

8.2.6. Infusion and Injection-site Reactions

AEs Temporally Related to Infusion

Any AE (except laboratory abnormalities) that occur during or within 1 hour after the IV infusion of study intervention may be considered an infusion-related reaction. Minor infusion-related AEs may be managed by slowing the rate of the IV infusion and/or treating with antihistamines and/or acetaminophen (paracetamol) as clinically indicated. If an IV infusion of study intervention is

stopped because of an AE that, in the opinion of the investigator, is not severe or does not result in an SAE (Section 8.3) the infusion may be restarted with caution.

Injection-site Reactions

A study intervention injection-site reaction is any adverse reaction at a SC study intervention injection site. Through Week M-40, the injection sites will be evaluated by site staff or study participant/caregiver for reactions. Participants will be observed for at least 30 minutes after the administration of study intervention for symptoms of an injection-site reaction at the investigative site. Participants/caregivers administering study intervention at home will receive anticipatory guidance on how to monitor and report potential injection-site reactions. This may include evaluation by the study team via video or photographic image, where local regulations permit. If an injection-site reaction is observed, the participant should be treated at the investigator's discretion. Injection-site reactions will be recorded as an AE in the eCRF and source documents.

Allergic Reactions

Before any on-site IV infusion or SC injection, appropriately trained personnel and medications must be available to treat allergic reactions, including anaphylaxis.

For the induction IV infusion, appropriate medical personnel must remain in close proximity to the infusion center for the remaining duration of the infusion, and for 1 hour after the end of the infusion in the event that emergency resuscitation is required. For the maintenance SC injection, appropriate medical personnel must be in attendance at the time of the injection and for at least 30 minutes after the injection. All participants must be observed carefully for symptoms of an allergic reaction (eg, urticaria, itching, hives, more serious events [eg, drop in blood pressure, syncope, tachycardia, trouble breathing, and wheezing]).

If a mild or moderate allergic reaction is observed, paracetamol, nonsteroidal anti-inflammatory drugs, and/or diphenhydramine or locally available alternative may be administered. In the case of a severe allergic reaction (eg, anaphylaxis), SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures are essential and must be available at the study site where the injections or infusions are being given.

For injections that will occur at home, participants and caregivers will receive anticipatory guidance on how to monitor for an allergic reaction and either treat or seek medical care in that situation.

Participants who experience severe adverse reactions related to an infusion or injection must be discontinued from further study intervention administrations and should complete all scheduled visits and complete the final safety follow-up visit approximately 20 weeks after the last study intervention administration, as outlined in the Schedule of Activities.

For moderate or lesser adverse reactions related to an injection or infusion, the participant may be permanently discontinued from further study interventions at the discretion of the investigator.

Participants who experience serious adverse reactions after an infusion or injection that results in bronchospasm with wheezing and/or dyspnea that requires ventilatory support OR that result in symptomatic hypotension with systolic blood pressure <90 mm Hg for children >10 years old or decrease in baseline systolic blood pressure of 30% will not be permitted to receive additional study intervention.

8.2.7. Infections

Study intervention should not be administered to a participant with a clinically important, active infection. Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits as specified in the Schedule of Activities (Section 1.3). If a participant develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study intervention administration must be considered. For an active varicella-zoster infection or a significant exposure to varicella-zoster infection in a participant without a history of chickenpox, study intervention administration should be interrupted until the symptoms have resolved and no active infection is present.

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

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

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study. At each visit, participants (or, when appropriate, a caregiver, surrogate, or the participant's legally acceptable representative) will be questioned about any AEs (eg, "side effects") occurring since the previous visit and the outcomes for any AEs reported at previous visits. At-home visits, participants will receive the same questions about AEs, but questioning will be done at home by phone, video chat, or in person with a home health aide.

Anticipated events will be recorded and reported as described in Appendix 9 (Section 10.9).

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

Further details on AEs, SAEs, and PQCs can be found in Appendix 8 (Section 10.8), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

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

All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported by phone, video chat, or with a home health aide from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 20 weeks after the last dose of study intervention, must be reported using the SAE reporting form.

Serious Adverse Events

All SAEs, as well as PQCs, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately but no later than 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 20 weeks after the last dose of study intervention, must be reported using the SAE reporting form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

Solicited adverse events are predefined local events occurring at the injection site and systemic events for which the participant is specifically questioned and which are noted by participants in their diary (see Section 8, Study Assessments and Procedures).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned. An example would be a laboratory abnormality.

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

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or

PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other HCPs.

Adverse events and the special reporting situation of pregnancy, will be followed by the investigator as specified in Appendix 8 (Section 10.8), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for SAEs

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

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

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

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

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

8.3.5. Pregnancy

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

Follow-up information regarding the outcome of the pregnancy for female participants who become pregnant, or where the pregnancy was the result of male participant and his partner, and any postnatal sequelae in the infant will be required.

8.3.6. Tuberculosis Evaluation

8.3.6.1. Initial Tuberculosis Evaluation

Participant medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant, parent(s), or legal guardian should be asked about past testing for TB, including chest imaging results and responses to tuberculin skin or other TB testing. Investigators should consider TST (see Appendix 10 Tuberculin Skin Testing [Section 10.10]) in addition to IGRA testing to screen for latent TB in participants less than 5 years old, if preferred by local health authorities, or if they believe based on their judgment that both tests are clinically indicated to evaluate a participant at high risk for latent TB.

Participants with a negative IGRA test result (and TST as applicable) are eligible to continue with prerandomization procedures. Participants with a newly identified positive IGRA or TST must be excluded from the study.

Participants with indeterminate/borderline IGRA test results should have the test repeated. If the second IGRA test result is not negative (including indeterminate/borderline), the participant should be excluded from the study.

8.3.6.2. Ongoing Tuberculosis Evaluation

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

- "Has your child had a new cough of >14 days' duration or a change in a chronic cough?"
- "Has your child had any of the following symptoms:"
  - "Persistent fever?"

  - "Unintentional weight loss?"
  - "Night sweats?"
- "Has your child had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

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

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

8.3.7. Adverse Events of Special Interest

Any newly identified malignancy, or case of active TB, or opportunistic infection occurring after the first administration of study intervention(s) in participants participating in this clinical study must be reported by the investigator according to the procedures in Appendix 8 (Section 10.8). Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Pharmacokinetics

Serum samples will be used to evaluate the PK of ustekinumab. Serum collected for the analysis of serum concentrations of ustekinumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period (eg, residue prior biologic level for participants who were enrolled with <5 half-lives washout of a prior biologic) or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

Venous blood samples of approximately 70 mL over the course of the study, will be collected for measurement of serum concentrations of ustekinumab and analytes at the time points indicated in the Schedule of Activities. At Week I-0, blood samples for PK analysis should be collected before the start of the infusion and approximately 60 minutes after completion of the infusion. The same blood draw can be used to collect serum samples for measuring study intervention concentration and antibodies to study intervention. Instructions will be provided for preventing contamination of blood samples during collection at the induction visit at Week I-0 (see Section 8 Sample Collection and Handling).

Venous blood samples will be collected, and each serum sample will be divided into 3 aliquots (1 each for PK, anti-ustekinumab antibodies, and a back-up). Genetic analyses will not be

performed on these serum samples. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the site Laboratory Manual.

8.4.2. Analytical Procedures

Pharmacokinetics

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

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

Serum ustekinumab concentrations over time will be used to evaluate various ustekinumab PK parameters based on blood drawn from participants receiving ustekinumab according to the Schedule of Activities (Section 1.3).

Pharmacokinetic parameters to be estimated include maximum observed serum concentration (C_{max}) and $C_{trough,ss}/C_{min}$ In addition, area under the serum ustekinumab concentration versus time curve calculated from time 0 to a defined time t (AUC_{0-t}), elimination $t_{1/2}$, apparent clearance and volume of distribution will be derived from the analysis.

A population PK analysis approach will be used to characterize the PK of ustekinumab in pediatric participants with Crohn's disease and to evaluate the effect of potential covariates that influence the PK of ustekinumab.

Pharmacokinetic/Pharmacodynamic Evaluations

If feasible, the relationship between serum concentrations and efficacy outcomes in the study will be explored.

8.5. Genetics and Pharmacogenomics

Genetics and pharmacogenomics are not evaluated in this study.

8.6. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to ustekinumab treatment and/or Crohn's disease. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, stool, ileal and colonic biopsy samples collected as specified in the Schedule of Activities. Data collected from these samples will be used for exploratory research that will include the following objectives:

1. To understand the molecular effects of ustekinumab.
2. To understand Crohn's disease pathogenesis.
3. To understand why an individual may respond differently to ustekinumab.

4. To understand the impact of treatment with ustekinumab on intestinal mucosal inflammation in participants with moderately to severely active Crohn's disease.
5. To develop diagnostic tests to identify Crohn's disease populations that may be responsive or non-responsive to treatment with ustekinumab.

Stopping Analyses

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

8.6.1. Pharmacodynamics

Results of PD analyses will be presented in a separate report.

8.6.2. Serum-based Biomarkers

Samples will be collected from all participants. Assays to be performed may include proteins associated with proinflammatory and anti-inflammatory effects, the recruitment and proliferation of cells associated with inflammation and repair, and markers associated with tissue injury or repair. Blood samples for PK assessment may also be used for serum-based biomarker analyses. These analyses will include, but not be limited to, IL-17A and IL-22, and will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to Crohn's disease or the mechanism of action of ustekinumab.

8.6.3. Biopsy-based Biomarkers

Ileal and colonic biopsy samples will be collected from all participants during ileocolonoscopy to assess the effect of study intervention on gene expression and for the histological assessment of disease and improvement. Ileal and colonic biopsy analyses may also examine gene and protein expression associated with the pathogenesis of Crohn's disease.

8.6.4. Fecal Biomarkers

Fecal samples will be collected from all participants as specified in the Schedule of Activities (Section 1.3). Microbiome and associated products analysis will be conducted to evaluate the association between inflammatory proteins, microbial activities and ustekinumab, and/or Crohn's disease. The relationships between microbiome, metabolites, and biomarkers in other tissue samples will also be assessed.

8.7. Immunogenicity Assessments

Antibodies to ustekinumab will be evaluated in serum samples collected from all participants according to the Schedule of Activities (Section 1.3). Additionally, serum samples should also be collected at the final study visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

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

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to ustekinumab will be performed using a validated assay method by or under the supervision of the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention.

8.8. Medical Resource Utilization and Health Economics

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

8.9. Exit Survey

At the safety follow-up visit, participants will be invited to participate in an optional exit survey, which will be conducted to elicit feedback on parent and participant (>12 years of age) satisfaction. Details are provided in Appendix 18 (Section 10.18).

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data are outlined below. Specific details will be provided in the SAP.

9.1. Statistical Hypothesis

The **global** primary hypothesis, used for countries outside of the US, is:

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

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

> The primary hypothesis is that ustekinumab is an effective therapy in pediatric participants with moderately to severely active Crohn's disease. A determination of the efficacy of ustekinumab for the treatment of pediatric Crohn's disease will be made based on the totality of evidence from an assessment of the primary and secondary endpoints. This totality of evidence will include a descriptive comparison of the proportion of pediatric participants in clinical remission at Week M-44 relative to a historical adult placebo control (see Section 9.4.6).

9.2. Sample Size Determination

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

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

The sample size determination for the EMA submission for participants ≥40 kg is provided in Section 9.2.1.

The sample size determination for the global primary endpoint is provided in Section 9.2.2

The sample size determination for the US-specific primary endpoint is provided in Section 9.2.3.

9.2.1. Sample Size Determination for the EMA submission for participants ≥40 kg

Optimal design analysis was performed for this study using FIM-based methods to determine the appropriate sample size needed to adequately characterize ustekinumab PK in pediatric CD participants ≥40 kg. Based on the PIP commitment, at least 24 participants with body weight <40 kg are planned to be enrolled in this study. Thus, the maximum number of participants with body weight ≥40 kg may not be expected to exceed 66 (for a total of 90). Accordingly, optimization analyses for the subgroup of participants with body weight ≥40 kg were performed with the assumption that 66 participants will provide the maximum information obtainable in the study. From the FIM optimization analysis, no substantial PK information is expected to be gained if the number of pediatric participants with body weight ≥40 kg increases from 36 to 66. With 36 participants, approximately 92% of the information needed to characterize ustekinumab PK is obtained when compared with the information obtained from 66 participants. Accordingly, 36 participants with body weight ≥40 kg would ensure adequate characterization of the PK of ustekinumab in this subgroup.

9.2.2. Sample Size Determination for the Global Primary Endpoint

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

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

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

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

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined (Table 4):

Table 4: Populations for Analyses.

Population	Description
All Enrolled Analysis Set	All participants who signed the ICF.
Full Analysis Set (FAS)	All participants who received an administration of study intervention in induction at Week I-0.
Full Randomized Analysis Set (FASR)	All participants who were randomized in the maintenance period of the study and received at least 1 administration of study intervention during maintenance.
Full Clinical Responders Analysis Set (FASCR)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and received at least 1 administration of study intervention during maintenance.
All Responder Analysis Set (FASRES)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab therapy at Week I-8 or Week M-8 and received at least 1 administration of study intervention during maintenance.
Safety Analysis Set	All participants who received an administration of study intervention in induction at Week I-0.
Safety Randomized Analysis Set (SASR)	All participants who were randomized into the maintenance period of the study and received at least 1 administration of study intervention during maintenance.
Safety Clinical Responder Analysis Set (SASCR)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and received at least 1 administration of study intervention during maintenance.

Table 4: Populations for Analyses.

Population	Description
PK Analysis Set (PKAS)	All participants who received an administration of ustekinumab in induction at Week I-0 and have at least one postbaseline sample collection in induction.
PK Randomized Analysis Set (PKASR)	All participants who were randomized into the maintenance period of the study, received at least 1 administration of ustekinumab during maintenance, and have at least one post-Week M-0 sample collection in maintenance.
PK Clinical Responder Analysis Set (PKASCR)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8, received at least 1 administration of ustekinumab during maintenance, and have at least one post-Week M-0 sample collection in maintenance.
PK All Responder Analysis Set (PKASRES)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab therapy at Week I-8 or at Week M-8, and have received at least 1 administration of ustekinumab during maintenance, and have at least one post-Week M-0 sample collection in maintenance.
Immunogenicity Analysis Set (IAS)	All participants who received an administration of study intervention in induction at Week I-0 and have appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 sample collection in induction).
Immunogenicity Randomized Analysis Set (IASR)	All participants who were randomized into the maintenance period of the study, received at least 1 administration of ustekinumab during maintenance, and had appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 post Week M-0 sample collection in maintenance).
Immunogenicity Clinical Responder Analysis Set (IASCR)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8, received at least 1 administration of ustekinumab during maintenance, and have appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 post Week M-0 sample collection in maintenance).
Immunogenicity All Responder Analysis Set (IASRES)	All participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab therapy at Week I-8 or at Week M-8, and have received at least 1 administration of ustekinumab during maintenance, and have appropriate samples for detection of antibodies to ustekinumab (ie, participants with at least 1 post Week M-0 sample collection in maintenance).
EMA Randomized Analysis Set for Participants with Body Weight ≥40 kg (ERAS)	At least 36 randomized participants with body weight ≥40 kg at Week I-0 and Week M-0, who received at least 1 administration of study intervention during maintenance, and completed the Week M-44 visit or terminated the main study participation prior to Week M-44.
Substudy Analysis Set (SSAS)	All participants who entered the exposure optimization substudy and received at least 1 administration of study intervention during the substudy

9.4. Statistical Analyses

This section is a summary of the planned statistical analyses of the endpoints for the main study (ie, at the second DBL), including the primary and secondary efficacy analyses (Section 9.4.6 and 9.4.7), tertiary/exploratory endpoints analyses (Section 9.4.8), safety analyses (Section 9.4.9), and other analyses, including PK (Section 9.4.10).

The analyses to support the EMA submission will be based on at least 36 randomized participants who had body weight ≥40 kg at Week I-0 and Week M-0 and had completed the Week M-44 visit or terminated study participation prior to Week M-44. All efficacy analyses that are specified for the main study will be performed with exception of the US-specific endpoints analyses and some supplementary analyses. All safety analyses and selected other analyses (including PK and immunogenicity) that are specified for the main study will be performed. Details of the analyses to support the EMA submission will be provided in the SAP.

9.4.1 General Considerations

Data primarily will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, median, interquartile range, minimum and maximum, as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Unless otherwise specified, the Wilson Score method will be used to construct the 95% CI for binary endpoints where a proportion and the respective 95% CI are reported. Graphical data displays (eg, line plots) may also be used to summarize the data.

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

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

No multiplicity adjustments will be made in this study.

9.4.2. Primary Endpoint

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.

9.4.3. Secondary Endpoints

Global secondary endpoints are provided in Section 9.4.3.1.

US-specific secondary endpoints are provided in Section 9.4.3.2.

9.4.3.1. Global Secondary Endpoints

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

1. Clinical remission at Week I-6 as assessed by sPCDAI
2. Clinical response at Week I-8
3. Clinical response at Week I-6 as assessed by sPCDAI

4. Endoscopic response at Week M-8 as assessed by SES-CD*
5. Clinical response at Week M-8*

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

The following secondary endpoints of maintenance will be evaluated (evaluated among participants who are clinical responders at Week I-8; induction responders):

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

9.4.3.2. US-Specific Secondary Endpoints

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

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

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

The following secondary endpoints of maintenance will be evaluated (evaluated among participants who are clinical responders at Week I-8; induction responders):

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

9.4.4. Tertiary/Exploratory Endpoints

The following are tertiary/exploratory endpoints. Tertiary/exploratory endpoints may not be limited to the endpoints below. Details will be provided in the SAP.

1. Histologic assessments (based on GHAS, Geboes score, and RHI): Analyses are considered exploratory and will be summarized in separate technical reports.
2. Baseline, postbaseline values and the change from baseline in CRP concentrations at Weeks I-3, I-6, I-8, M-8, M-24, and M-44.
3. Baseline, postbaseline values and the change from baseline in fecal calprotectin and lactoferrin levels at Weeks I-3, I-6, I-8, M-8, M-24, and M-44.
4. Baseline, postbaseline values and the change from baseline in parameters of growth (measured with age and sex-specific z-scores for height, weight, and BMI) at Weeks I-8 and M-44.
5. Baseline, postbaseline values and the change from baseline in 25-hydroxyvitamin D, MMA, and iron at Weeks M-4 and M-44.
6. Change from baseline in IMPACT-III values at Week M-44 for participants ≥10 years of age at Week I-0.
7. PCDAI, sPCDAI, and CDAI score related endpoints over time through Week M-44.
    a. Clinical remission
    b. Clinical remission based on PCDAI <10
    c. Clinical response
    d. Clinical-biomarker response
    e. Corticosteroid-free clinical remission (maintenance only)
    f. Clinical remission among participants who are in clinical remission at Week I-8
    g. Change from baseline (Week I-0) in the PCDAI, sPCDAI, and CDAI scores
    h. Components of the PCDAI, sPCDAI, and CDAI scores
8. 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.
9. SES-CD score related endpoints at Week M-8* and Week M-44.
    a. Endoscopic response
    b. Endoscopic remission
    c. Clinically meaningful endoscopic improvement
    d. Change from baseline (Week I-0) in SES-CD score
10. Endoscopic improvement at Weeks M-8* and M-44
11. Fistula assessments at Weeks I-0, I-8, M-8*, M-16, M-32, and M-44, among participants with fistulas at baseline.
    a. Fistula response
    b. Complete fistula response
11. Crohn's disease-related hospitalizations and surgeries

12. SEMA-CD-related endpoints may be explored

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

9.4.5. Population for Efficacy Analysis

Unless otherwise noted, efficacy analyses will be based on the Full Analysis Set (FAS) for induction endpoints through Week I-8 and Full Clinical Responders Analysis Set (FASCR) for maintenance endpoints from Weeks M-0 through M-44 (refer to Section 9.3 for definition). For the FASCR, participants will be analyzed according to the intervention group to which they were randomized regardless of the intervention they actually received.

9.4.6. Primary Endpoint Analysis

The population is pediatric participants 2 to <18 years of age (at the time of the first administration of study intervention at Week I-0) with moderately to severely active Crohn's disease (defined by a PCDAI score >30), and who have had an inadequate response or intolerance to conventional therapies or biologic therapy or have corticosteroid dependence.

The primary endpoint is:

- **Global:** Clinical remission at Week I-8. The global primary analysis is provided in Section 9.4.6.1.
- **US-specific:** Clinical remission at Week M-44. This endpoint will be assessed among participants who are in clinical response at Week I-8. The US-specific primary analysis is provided in Section 9.4.6.2.

Clinical remission is defined as having a PCDAI score ≤10 points.

9.4.6.1. Global Primary Analysis

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

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

9.4.6.1.1. Global Primary Estimand

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

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

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

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

e. ICEs and their corresponding strategies:

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved clinical remission (PCDAI score ≤10 points) after this event; the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.8)	**Composite Strategy:** Same as above
4. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data at and after the event occurred.
5. Discontinued study intervention due to reasons other than ICEs 2 or 4 as described above	**Composite Strategy:** Same as above

9.4.6.1.2. Global Primary Estimand Analysis

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

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

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

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

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

Additional supplementary estimands and sensitivity analyses for the Global primary endpoint will be outlined in the SAP.

The consistency of efficacy for clinical remission at Week I-8 will be examined in subgroups defined by baseline demographics, baseline clinical disease characteristics, baseline concomitant Crohn's disease medications, and Crohn's disease medication history.

9.4.6.2. US-Specific Primary Analysis

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

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

9.4.6.2.1. US-Specific Primary Estimand

a. **Study intervention:** Ustekinumab (experimental treatment/intervention) SC q8w and SC q12w

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

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

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

e. ICEs and their corresponding strategies:

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a Crohn's disease-related surgery (with the exception of percutaneous drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study intervention	**Composite Strategy:** A participant with this ICE is considered to not have achieved clinical remission (PCDAI score ≤10 points) after this event, the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease	**Composite Strategy:** Same as above
3. Had prohibited changes in Crohn's disease medications (for details, see Section 6.8)	**Composite Strategy:** Same as above

4. Rescue medication used (initiation or increase above baseline) for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders (for details, see Section 4.1.4)	**Composite Strategy:** Same as above
5. Eligible for dose adjustment (ie, met criteria for ~~loss of response~~ LOR) after Week M-8 (including both study intervention regimens)	**Composite Strategy:** Same as above
6. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data at and after the event occurred.
7. Discontinued study intervention due to reasons other than ICEs 2 or 6 as described above	**Composite Strategy:** Same as above

9.4.6.2.2. US-Specific Primary Estimand Analysis

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

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

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

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

Further details will be in the SAP.

Confidence intervals based on other confidence levels (eg, 70% or 80%) may also be explored and will be detailed in the SAP.

Additional supplementary estimands and sensitivity analyses for the US-specific primary endpoint will be outlined in the SAP.

The consistency of efficacy for clinical remission at Week M-44 will be examined in subgroups defined by baseline demographics, baseline clinical disease characteristics, baseline concomitant Crohn's disease medications, and Crohn's disease medication history.

9.4.7. Secondary Endpoints Analyses

The analysis population for secondary endpoints through Week I-8 includes all participants who received one administration of study intervention at Week I-0 (FAS). For the secondary endpoints in induction, the proportion of participants who meet the endpoint at Week I-8 will be summarized overall, and a 95% CI will be provided.

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

Unless otherwise specified, the ICEs for the Global Primary Estimand will apply to endpoints through the induction period and the ICEs for the US-Specific Primary Estimand will apply to endpoints at the maintenance period.

Unless otherwise specified, after accounting for ICEs, participants who have missing data for the endpoints will be considered not to have achieved their respective endpoints. Details can be found in the SAP.

Additional US-specific secondary endpoint analyses are provided in Section 9.4.7.1.

9.4.7.1. Additional US-Specific Secondary Endpoint Analyses

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

The secondary endpoints (defined based on the PCDAI) at Week M-44 will be descriptively compared with the proportion (and 95% CI) of adult participants who met the endpoint (defined

based on the CDAI) at Week M-44 in the CNTO1275CRD3003 study among participants who were clinical responders at Week I-8 (90 mg q8w treatment group). In addition, a 95% CI for the adult placebo rate from CNTO1275CRD3003 will be provided to assess the effect of ustekinumab compared with a historical placebo.

9.4.8. Tertiary/Exploratory Endpoint(s) Analyses

Details of tertiary and exploratory endpoints analyses will be provided in the SAP.

9.4.9. Safety Analyses

All safety analyses will be performed using the Safety Analysis Set population for the induction period and the Safety Randomized Analysis Set population for the maintenance period (refer to Section 9.3 for definitions). In addition, analysis of all AEs during the study (ie, induction and maintenance) will be performed**.**

AEs

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

- Frequency and type of AEs.
- Frequency and type of SAEs.
- Frequency and type of reasonably related AEs as assessed by the investigator.
- Frequency and type of AEs leading to discontinuation of study intervention.
- Frequency and type of infections (including serious infections, and infections requiring oral or parenteral antimicrobial treatment).
- Frequency and type of AEs temporally associated with an infusion during the induction period.
- Frequency and type of injection-site reactions during the maintenance period.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Toxicity grades (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point.

The following summaries of clinical laboratory tests will be used to assess participant safety:

- Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry)

- Shift tables will be provided for selected laboratory parameters (hematology: hemoglobin, hematocrit, platelets, and WBC 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)
- Summary of maximum NCI-CTCAE toxicity grade for postbaseline laboratory values (hematology and chemistry)
- Summary of maximum postbaseline ALT, AST, and total bilirubin relative to ULN
- Summary of number and percentage of participants who met the criteria of possible Hy's law (ie, ALT or AST ≥3xULN and total bilirubin ≥2xULN (>35% direct) or INR >1.5.)
- Listings of participants with any abnormal postbaseline laboratory values of NCI-CTCAE Grade ≥2 will also be provided.

9.4.10. Other Analyses

Pharmacokinetic Analyses

Descriptive statistics of the serum ustekinumab concentrations will be calculated at each sampling time point. These concentrations will be summarized over time. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or Statistical Analysis System datasets. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

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

A population PK analysis approach will be used to determine ustekinumab PK parameters. Relevant covariates will be evaluated for their effect on ustekinumab PK where appropriate. Additional PK data from other studies may be used to supplement the population PK analysis in pediatric participants with Crohn's disease. The results of the population PK analysis will be presented in a separate technical report.

A PK interim analysis to evaluate the ustekinumab dosage for participants <40 kg (as measured at Week I-0) will be performed when ~20 participants from both the CNTO1275CRD3004 and CNTO1275PUC3001 studies (combined) weighing <40 kg complete the Week M-8 visit (see Section 9.5).

Biomarkers Analyses

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

Changes in serum protein analytes, fecal biomarkers, and biopsy ribonucleic acid (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.

Immunogenicity Analyses

Definitions of treatment-emergent, treatment-induced, and treatment-boosted anti-ustekinumab antibodies will be provided in the SAP.

The anti-ustekinumab antibodies summary and analysis will be based on the observed data; therefore no imputation of missing data will be performed.

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

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

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

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

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

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

Pharmacokinetic/Pharmacodynamic Analyses

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

Results of PD analyses will be presented in a separate report.

9.5. Interim Analysis

A PK interim analysis to evaluate the ustekinumab dosage for participants <40 kg (as measured at Week I-0) will be performed. The analysis will be performed when ~20 participants from both the 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) will be reviewing the results of the analysis to evaluate the ustekinumab dosage for participants <40 kg. Details of the PK interim analysis can be found in the DMC SAP.

An interim analysis of the data will be performed when at least 36 randomized participants with body weight ≥40 kg at Week I-0 and Week M-0 have completed the Week M-44 visit or terminated study participation prior to Week M-44. The interim analysis results will be used for the EMA submission for participants with body weight ≥40 kg.

9.6. Data Monitoring Committee

A DMC will be established as noted in Committees Structure in Appendix 15 (Section 10.15), Regulatory, Ethical, and Study Oversight Considerations.

The same DMC, consisting of 2 medical experts in the relevant therapeutic area and one statistician, will be used for studies CNTO11275PUC3001 and CNTO1275CRD3004 and will monitor safety data on an ongoing basis.

The major function of the DMC is to monitor the safety of the study intervention by reviewing the SAEs each month and by reviewing the interim study safety data every 3-months. 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 (see Section 9.5). The first DMC meeting will occur approximately 4 months after the first participant is dosed with study intervention.

The content of the safety summaries, the content of the PK interim analysis, the DMC's role and responsibilities, the general procedures (including communications), and their recommendations on the study conduct are defined and documented in the DMC charter, which will be finalized prior to the first DMC review.

In addition, during the study, the sponsor's study responsible physician (or designee) will regularly review safety data (open-label data for induction, and blinded data for maintenance) from the sites and notify the DMC and appropriate sponsor personnel of any issues.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
6-TG	6-thioguanine
AE	adverse event
ALT	alanine aminotransferase
anti-HBc	hepatitis B virus core antibody
anti-HBs	hepatitis B virus surface antibody
ARC	anticipated event review committee
AST	aspartate aminotransferase
AUC	area under the plasma concentration curve
AZA	azathioprine
BMI	body mass index
BSA	body surface area
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus (Disease) 2019
CRF	case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for AEs
DBL	database lock
DCS	data collection systems
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTP	direct to participant
E-R	exposure-response
eCRF	electronic case report form
EEN	exclusive enteral nutrition
ePRO	electronic participant-reported outcome
ESR	erythrocyte sedimentation rate
EU	European Union
FAS	Full Analysis Set
FASCR	Full Clinical Responders Analysis Set
FASR	Full Randomized Analysis Set
FASRES	All Responder Analysis Set
GCP	good clinical practice
GDH	glutamate dehydrogenase
GHAS	Global Histology Activity Score
GI	gastrointestinal
HBsAg	hepatitis B virus surface antigen
HBcAb	hepatis B core antibody
HBV	hepatitis B virus
HCP	health care provider
HCT	hematocrit
HCV	hepatitis C virus
IAS	Immunogenicity Analysis Set
IASR	Immunogenicity Randomized Analysis Set
IASCR	Immunogenicity Clinical Responder Analysis Set
IASRES	Immunogenicity All Responder Analysis Set
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICE	intercurrent event

ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IGRA	interferon gamma release assay
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LIV	liquid-in-vial
LOR	loss of response
MMA	methylmalonic acid
MMR	measles, mumps, rubella
MTX	methotrexate
PCDAI	Pediatric Crohn's Disease Activity Index
PD	pharmacodynamics
PFS	prefilled syringe
PFS-U	prefilled syringe with UltraSafe Plus™ Passive Needle Guard
PI	primary investigator
PK	pharmacokinetics
PKAS	PK Analysis Set
PKASCR	PK Clinical Responder Analysis Set
PKASR	PK Randomized Analysis Set
PKASRES	PK All Responder Analysis Set
PQC	product quality complaint
PRO	participant-reported outcomes
PsA	psoriatic arthritis
q4w	every 4 weeks
q8w	every 8 weeks
q12w	every 12 weeks
QoL	quality of life
RBC	red blood cell
RHI	Robarts Histopathology Index
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SASCR	Safety Clinical Responder Analysis Set
SASR	Safety Randomized Analysis Set
SC	subcutaneous
SD	standard deviation
SEMA-CD	Simplified Endoscopic Mucosal Assessment for Crohn's disease
SES-CD	Simple Endoscopic Score for Crohn's disease
SI	International System of Units
sPCDAI	short Pediatric Crohn's Disease Activity Index
SS	substudy dosing
SSAS	Substudy Analysis Set
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TNFα	tumor necrosis factor alpha
TST	tuberculin skin testing
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
VEO-IBD	very-early-onset inflammatory bowel disease
WBC	white blood cell
Week I-0	Induction Week 0

Week I-8	Induction Week 8
Week M-0	Maintenance Week 0
Week M-8	Maintenance Week 8
Week M-12	Maintenance Week 12
Week M-16	Maintenance Week 16
Week M-32	Maintenance Week 32
Week M-44	Maintenance Week 44

10.2. Appendix 2: Pediatric Crohn's Disease Activity Index (PCDAI)

HISTORY SCORE (Recall, 1 week)

Abdominal Pain:

None _____ (0 points)

Mild - Brief, does not interfere with activities _____ (5)

Mod/Severe – daily, longer lasting, affects activities, nocturnal _____ (10)

Total _____

Stools (per day):

0 – 1 liquid stools, no blood _____ (0)

Up to 2 semi-formed with small blood or 2-5 liquid _____ (5)

Gross bleeding or ≥ 6 liquid or nocturnal diarrhea _____ (10)

Total _____

Subject Functioning- General well-being

No limitation of activities, well _____ (0)

Occasional difficulty in maintaining age appropriate activities, below par _____ (5)

Frequent limitation of activity, very poor _____ (10)

Total _____

History Score _____ (Max 30)

****

LABORATORY SCORE

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

Laboratory Score_____(Max 20)

GROWTH SCORE

Weight

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

Height

At diagnosis (Refer to percentile chart):

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

Follow-up (Refer to growth velocity chart):

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

Growth Score _____ (Max 20)

****

PHYSICAL EXAMINATION SCORE

Abdomen

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

Perirectal disease

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

Physical Examination Score _____ (Max 20)

****

Extraintestinal Manifestation SCORE

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

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

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

10.3. Appendix 3: Crohn's Disease Activity Index (CDAI)

WORKSHEET

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

10.3.1. PATIENT DIARY CARD

Instructions:

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

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

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

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

Loperamide (Imodium)

Diphenoxylate (Lomotil, Lomocot)

Bismuth subsalicylate (Kaopectate, Pepto-Bismol)

Cholestyramine (Questran, Prevalite)

Codeine (Cocet, Tylenol with codeine, Vopac)

Eluxadoline (viberzi)

Other anti-diarrheal

Other opiate

10.4. Appendix 4: IMPACT-III Questionnaire

IMPACT-III

English-North America

A QUALITY OF LIFE QUESTIONNAIRE FOR CHILDREN WITH INFLAMMATORY BOWEL DISEASE

CCI

Contact: Dr. Anthony Otley impact@iwk.nshealth.ca Version: June 2013

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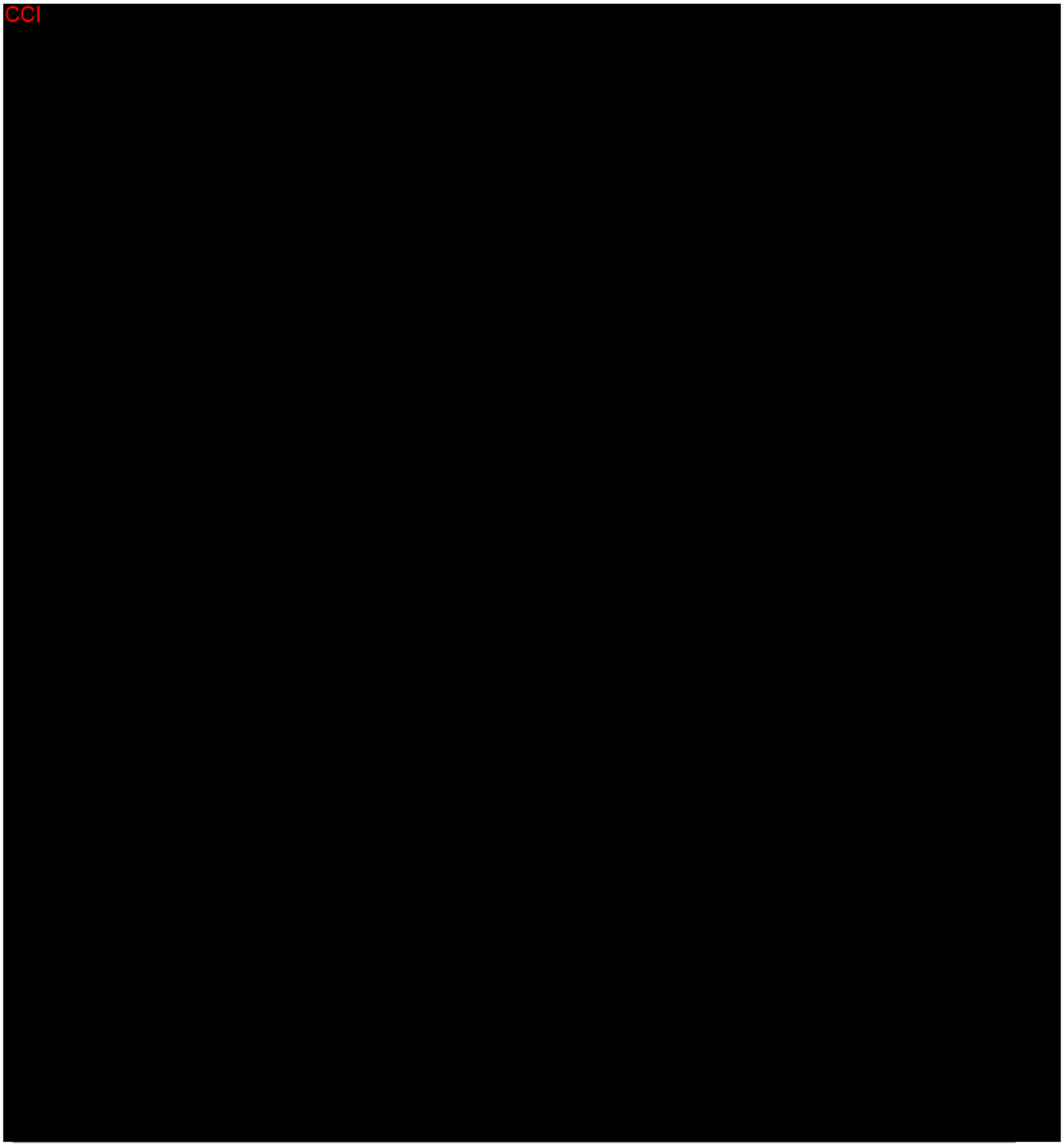
CCI



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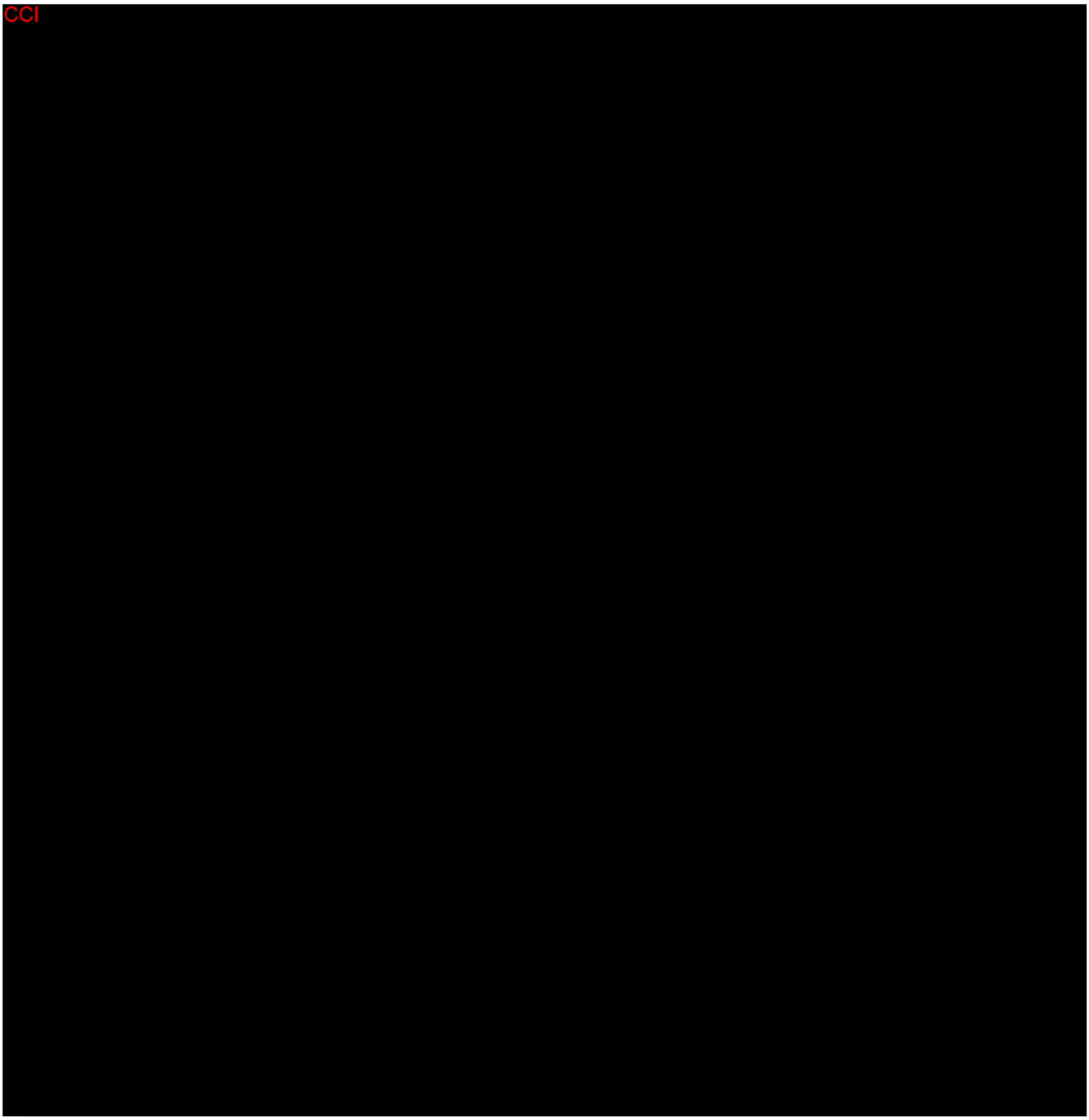

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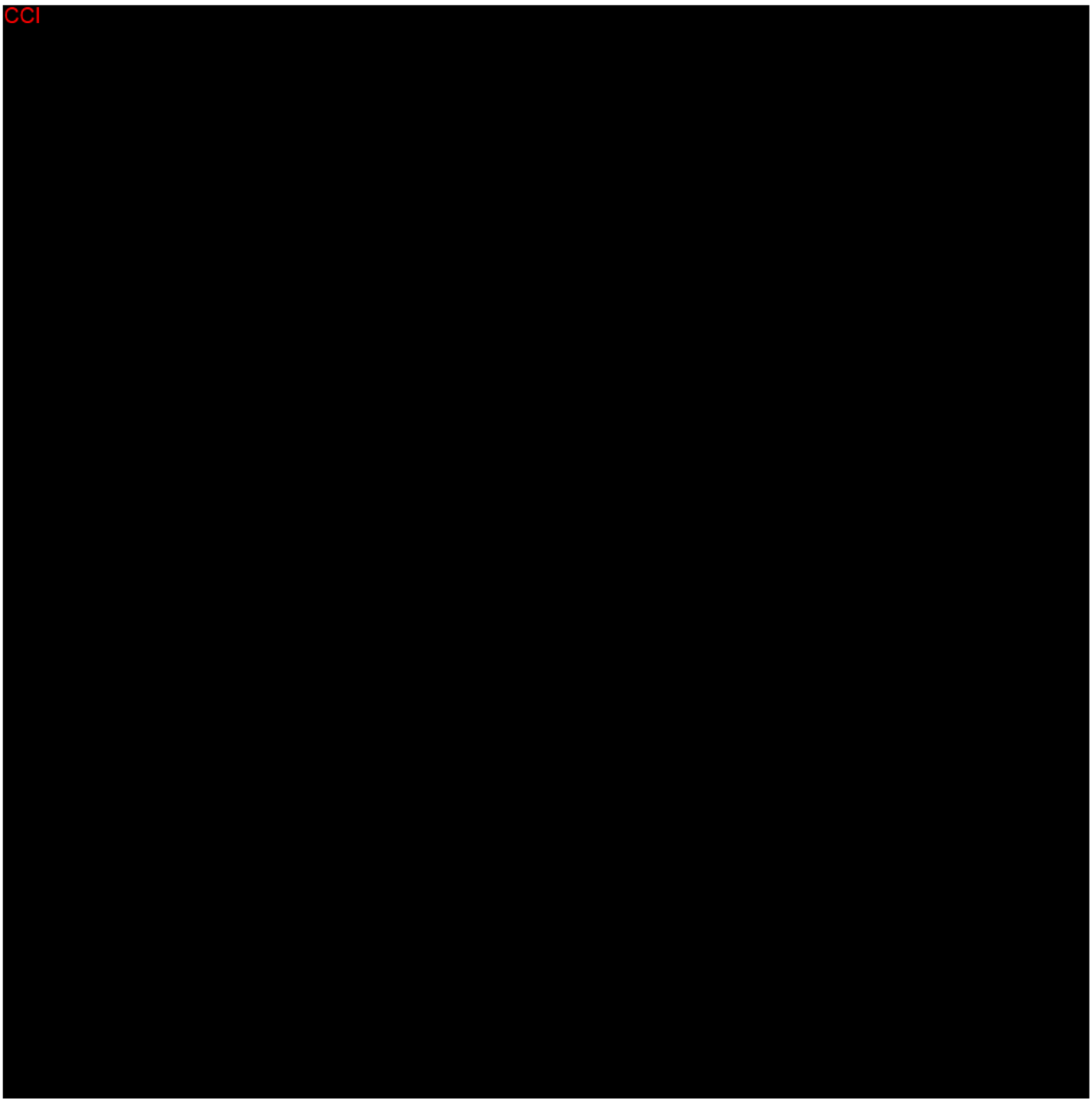

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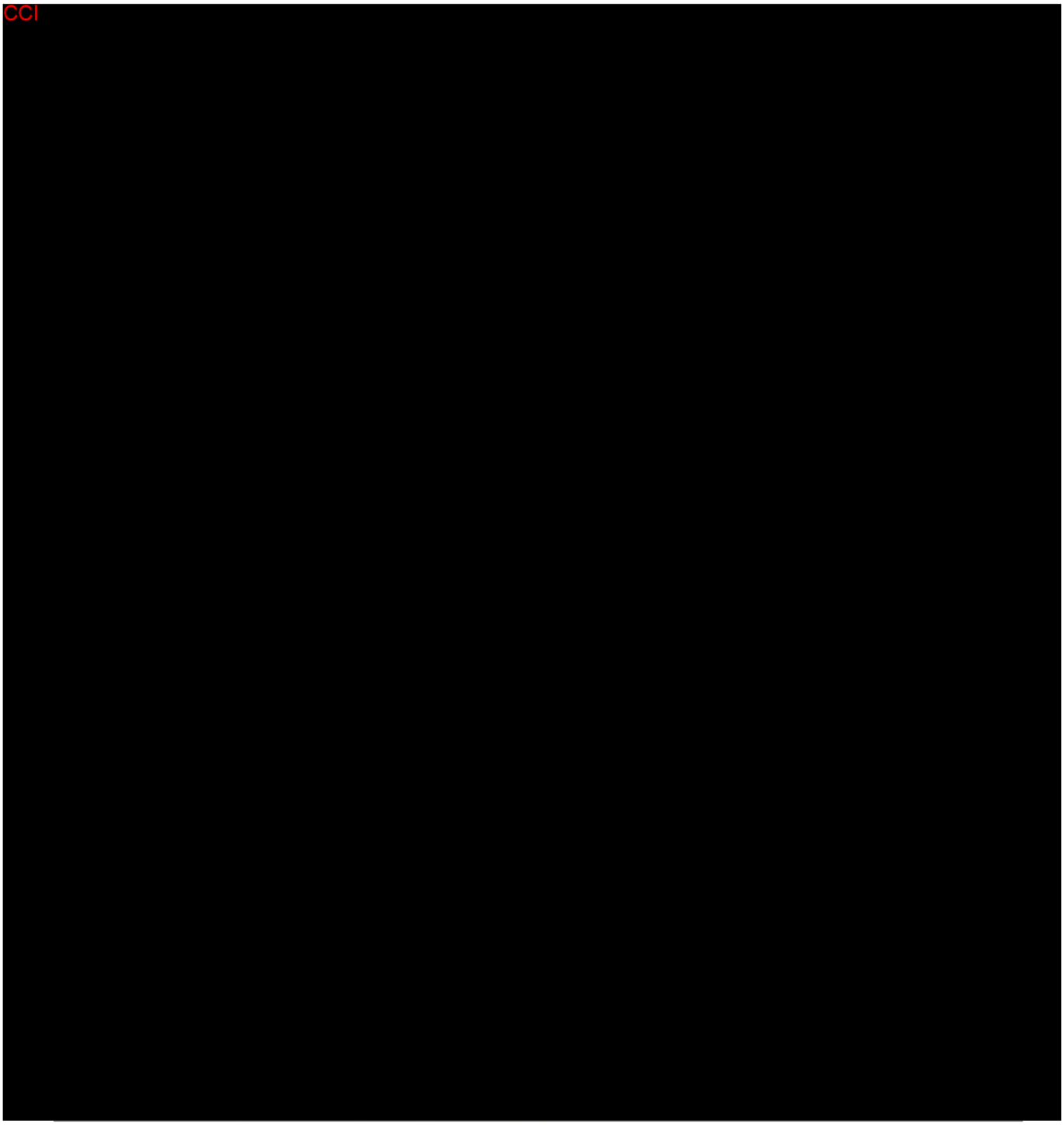

Version: June 13

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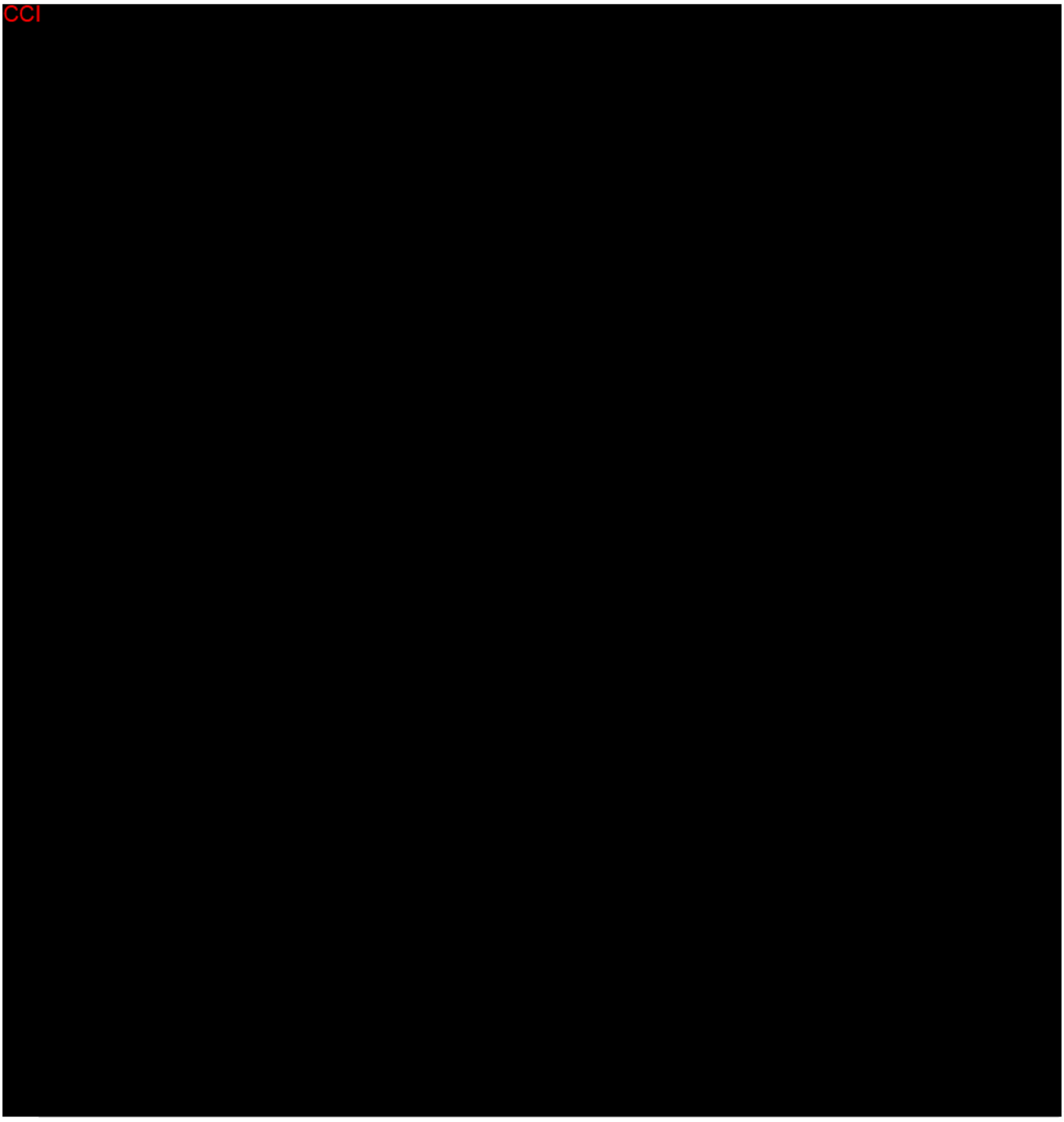

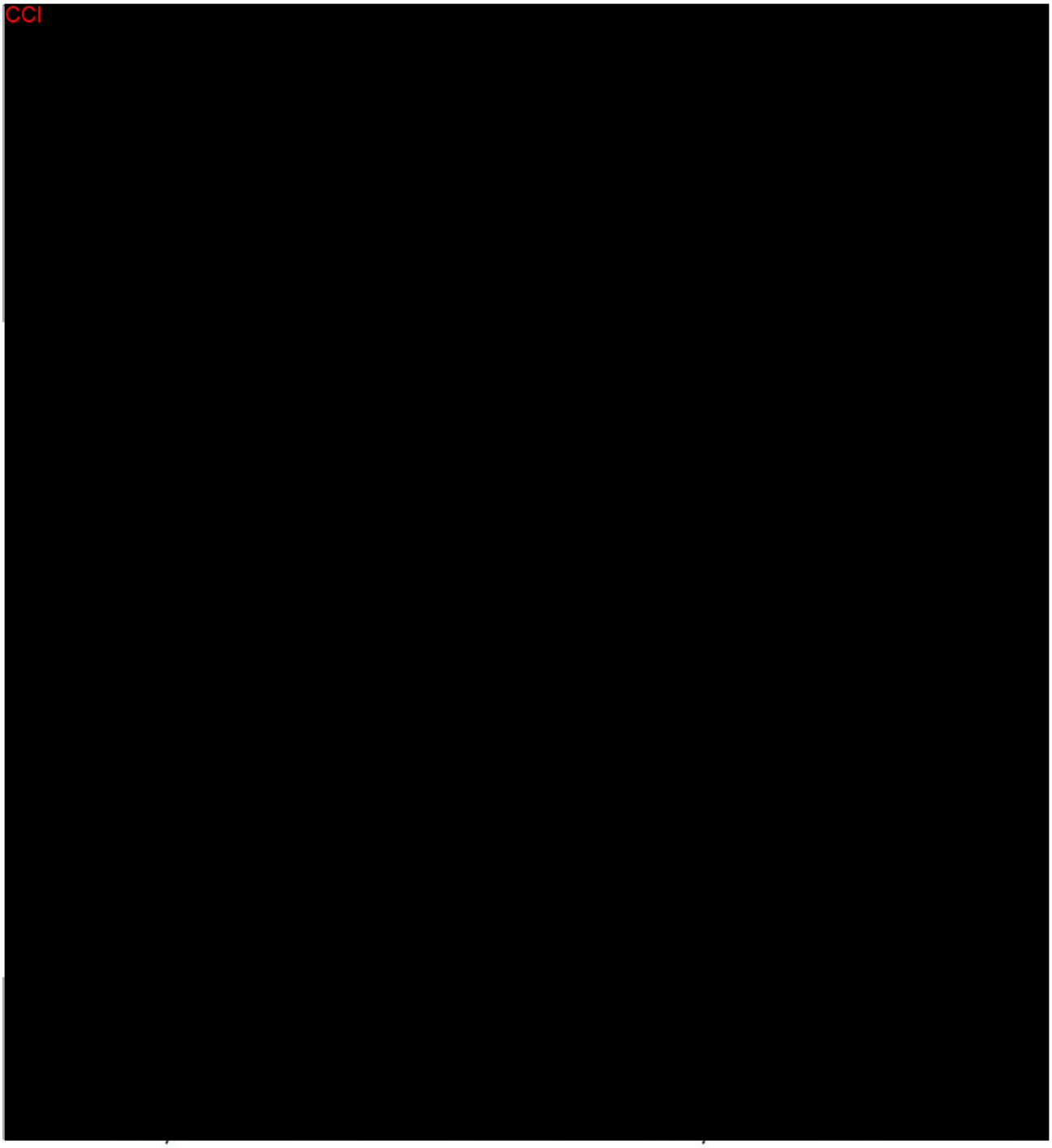

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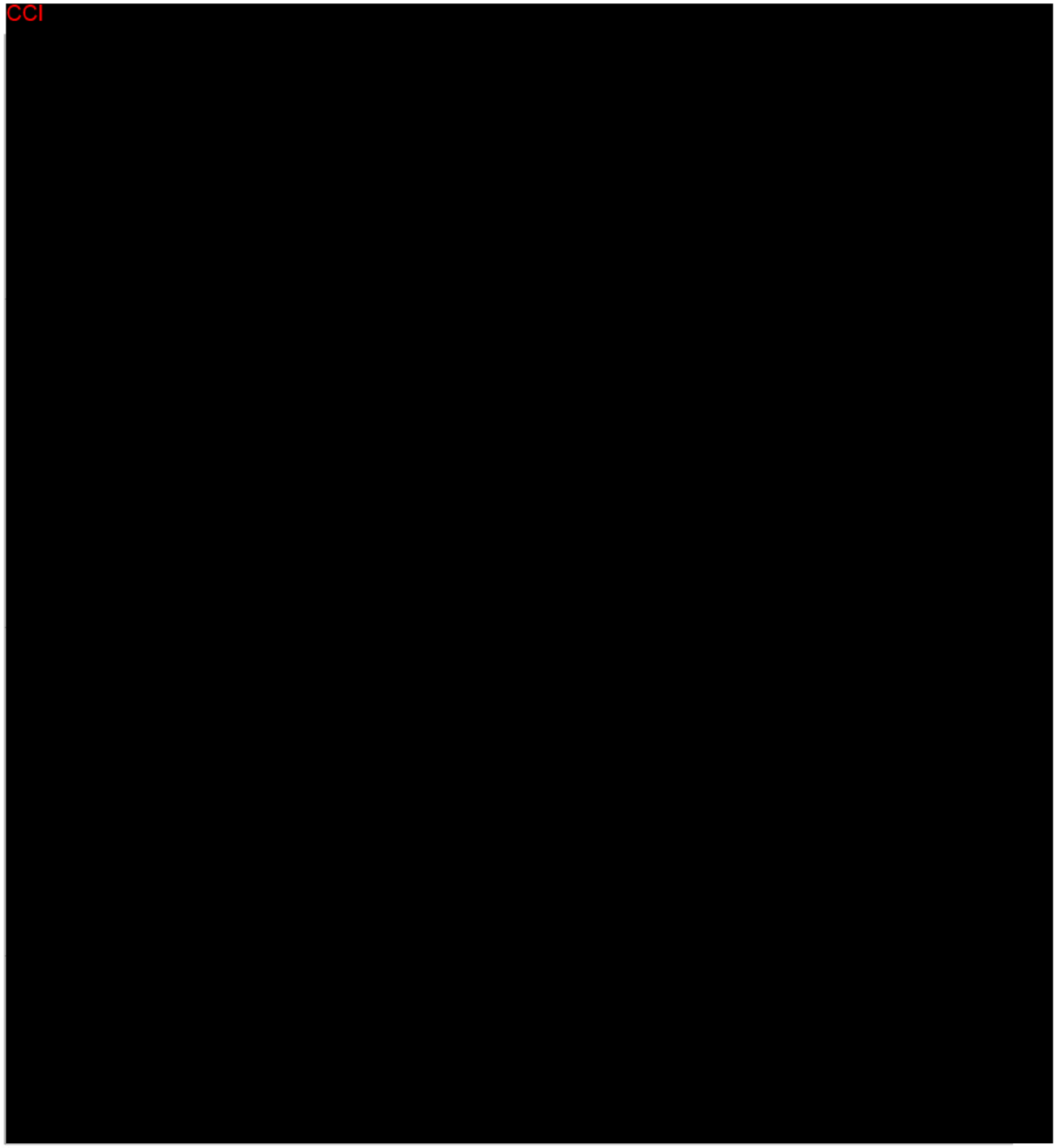

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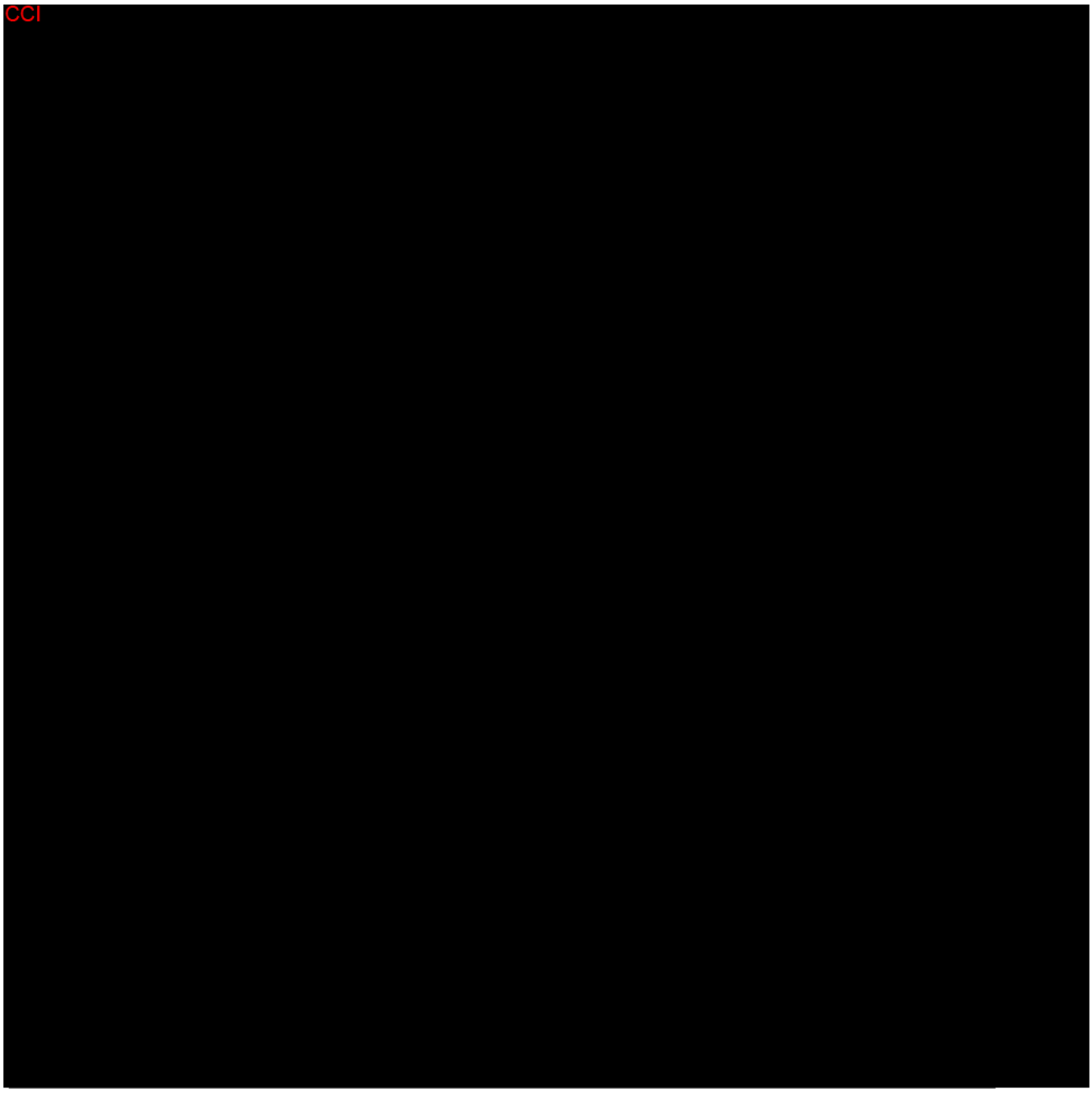


10.5. Appendix 5: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNFα Antagonist Therapies (Infliximab, Adalimumab, or Certolizumab Pegol) or Vedolizumab

The criteria for inadequate initial response, response followed by LOR, or intolerance to biologic therapy are described in items I, II, and III below.

I. Inadequate initial response to current or prior therapy with biologic therapy (primary nonresponder)

Eligible participants must satisfy criteria A, B, and C.

A. Have received induction doses of:

- Infliximab (≥6 years of age)

OR

- Adalimumab (≥17 kg body weight)

OR

Biologics considered standard of care (ie, infliximab <6 years of age, adalimumab <17 kg, certolizumab, or vedolizumab)

AND

B. Did not initially respond to induction doses of biologic therapy (ie, TNFα antagonist or vedolizumab) for Crohn's disease per approved labeling or standard of care as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of Crohn's disease, as assessed by a treating physician:

- Lack of improvement or worsening in stool frequency.
- Lack of improvement or worsening in daily abdominal pain.
- Occurrence, lack of improvement, or worsening of fever thought to be related to Crohn's disease.
- Lack of improvement or worsening in a draining fistula or development of a new draining fistula.
- Lack of improvement or worsening in rectal bleeding.
- Initiation or increase in antidiarrheal medication.

These signs and symptoms of Crohn's disease must have occurred ≥2 weeks after receiving the last induction dose of biologic therapy and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant

as having had an inadequate initial response to biologic therapy. This benchmark acknowledges that the PCDAI is not routinely recorded in clinical practice.

AND

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

- Provides the dates and doses of the failed biologic induction therapy.
- Documents that the participant had persistence of disease activity following biologic induction therapy.

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

II. Initial response followed by loss of response (ie, secondary nonresponse) to current or prior biologic therapy (secondary nonresponse)

Eligible participants must satisfy criteria A, B, C, and D.

A. Initially responded to induction therapy

AND

B. Have received at least 2 maintenance doses biologic therapy:

AND

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

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

These signs and symptoms of Crohn's disease must have occurred ≥2 weeks after receiving the last maintenance dose of biologic therapy and are offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having lost response to biologic therapy. This benchmark acknowledges that the PCDAI is not routinely recorded in clinical practice.

AND

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

- Provides the dates and doses of the failed biologic maintenance therapy.
- Documents that the participant had recurrence of disease activity despite biologic therapy.

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

III. Current or prior intolerance to biologic therapy

Eligible participants must satisfy criterion C in combination with criteria A or B.

A. Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (eg, delayed hypersensitivity or serum-sickness-like reaction); or 3) significant injection-site reaction. Definitions of these 3 criteria are provided below.

Adverse reactions must have followed ≥1 dose of biologic therapy and, in the treating physician's opinion, precluded continued use of the therapy.

1) A significant acute infusion/administration reaction is defined as an adverse reaction that was:

- Manifested through ≥1 of the following symptoms.
  a. Fever greater than 100°F (37.8°C).
  b. Chills or rigors.
  c. Itching.
  d. Rash.
  e. Flushing.
  f. Urticaria or angioedema.
  g. Breathing difficulties (eg, dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor).
  h. Clinical hypotension (pallor, diaphoresis, faintness, syncope), blood pressure less than 90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure of greater than 20 mm Hg.

AND

- Occurred ≤ 24 hours after infusion/administration of biologic therapy

AND

- Was considered related to the infusion/administration of biologic therapy

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

- Was manifested through 1 or more of the following symptoms:
  a. Myalgias
  b. Arthralgias
  c. Fever greater than 100°F (37.8°C)
  d. Malaise
  e. Rash

AND

- Occurred >24 hours and <15 days after infusion/administration of biologic therapy

AND

- Was considered related to the infusion/administration of biologic therapy

3) A significant injection-site reaction is defined as an adverse reaction that:

- Was manifested through 1 or more of the following symptoms:
  a. Significant bruising
  b. Erythema
  c. Hemorrhage
  d. Irritation
  e. Pain
  f. Pruritus
  g. "Injection-site reaction"

AND

- Occurred within 24 hours of an SC injection of biologic therapy

AND

- Was considered related to the injection.

B. Have had a severe psoriatic rash associated with the use of TNFα antagonist therapies (diagnosed by a dermatologist) that required discontinuation of anti-TNFα therapy.

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

- Provides the date of discontinuation of biologic therapy
- Documents that the participant had intolerance to biologic therapy.

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form). In the case of a rash associated with anti-TNFα therapy (B), must provide documentation of diagnosis from a consulting dermatologist.

10.6. Appendix 6: Half-life/Clearance for Various Biologic Therapies Used in Crohn's Disease

The sponsor requires a washout duration of ≥2 half-lives from the last administration of a prior biologic treatment prior to enrollment. A shorter washout duration is acceptable, if undetectable drug levels of the biologic can be demonstrated prior to I-0.

The table below lists the known half-life (T½) for each of the biologic agents which participants enrolled in this study may have had previous exposure.

BIOLOGIC AGENT	**HALF-LIFE (T½)**	**TIME TO WASHOUT (2 x half-lives)**
Infliximab	7.7 to 9.5 days	19 Days
Adalimumab	14 days	28 Days
Certolizumab pegol	14 days	28 Days
Vedolizumab	25 days	50 Days

10.7. Appendix 7: Definitions of Inadequate Response to or Intolerance of Corticosteroids or 6-MP/AZA/MTX and Corticosteroid Dependence

CORTICOSTEROIDS

Participants have failed to respond to corticosteroids if they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving at least 1.0 mg/kg/day or a maximum of 40 mg/day of prednisone (or corticosteroid equivalent, given orally or intravenously) for 2 weeks; or ≥9 mg/day of budesonide or ≥5 mg/day of beclomethasone dipropionate given orally for at least 4 weeks. Evidence of failure must be documented in the participant's source documentation.

Participants are intolerant of corticosteroids if:

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

OR

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

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

METHOTREXATE (MTX), 6-MERCAPTOPURINE (6-MP), OR AZATHIOPRINE (AZA)

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

- At least 3 months of therapy with ≥1 mg/kg/day of 6-MP, 2 mg/kg/day of AZA, or 10 mg/m^2 (up to 25 mg) weekly of MTX (intramuscular or SC).

OR

- At least 3 months at a lower dosage of 6-MP or AZA when country or local guidelines specify a different treatment regimen. (In such an event, the country or local guidelines needs to be included in the source document).

OR

- At least 3 months at a dosage of 6-MP or AZA confirmed to be therapeutic for the participant with whole blood thioguanine nucleotide levels >200 pmol/8 x 10^8 red blood cells.

OR

- At least 3 months at the highest tolerated dosage due to leukopenia, elevated liver enzymes, or nausea.

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

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

OR

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

10.8. Appendix 8: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.8.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to all AEs under Section 8.3.1, Time Period and Frequency for Collecting AEs and SAEs Information, for time of last adverse event recording).

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

Serious Adverse Event

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

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

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ustekinumab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

10.8.2. Attribution Definitions

Assessment of Causality

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

Related

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

Not Related

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

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

10.8.3. Severity Criteria

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

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

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

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

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

10.8.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a sponsor medicinal product (with or without patient exposure to the sponsor medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

Special reporting situations should be recorded in the case report form (CRF). Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

10.8.5. Procedures

All AEs

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

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

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

- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

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

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

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

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

The cause of death of a participant in a study within 20 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

10.8.6. Product Quality Complaint Handling

Definition

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

during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

All complaints related to ANY part of the Combination Product must be reported within 1 business day. In the event of public holiday, measures must be taken to ensure reporting no later than calendar day 3.

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

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel immediately but no later than 24 hours after being made aware of the event.

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

10.8.7. Contacting Sponsor Regarding Product Quality

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

10.9. Appendix 9: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or nonserious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

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

Reporting of Anticipated Events

All AEs will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described under all AEs in Section 8.3.1, Time Period and Frequency for Collecting adverse event and SAEs Information. Any anticipated event that meets SAEs criteria will be reported to the sponsor as described under SAEs in Section 8.3.1, Time Period and Frequency for Collecting adverse event and SAEs Information. These anticipated events are exempt from expedited reporting as individual single cases to health authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study intervention, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee

An Anticipated Event Review Committee (ARC) will be established to perform reviews of prespecified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

10.10. Appendix 10: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Participants should never be allowed to read their own tuberculin skin test results. If a participant fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a participant who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised participants, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the participants may not be immunocompromised at baseline.

In the US, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US, country-specific guidelines for immunocompromised participants should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised participants exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines for immunocompromised participants should be consulted for acceptable antituberculous treatment regimens. Patients with active or latent TB will not continue receiving treatment with study drug.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). *Tuberculosis, a comprehensive international approach*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

10.11. Appendix 11: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory, or by a local laboratory with approval from the sponsor:

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Protocol-Required Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet count
Hemoglobin
Hematocrit
Red blood cell count (At investigator request)
Erythrocyte sedimentation rate (ESR)*</td><td><u>Red Blood Cell (RBC) Indices:</u>
At investigator request</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td></td><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.

*ESR may be performed by a local lab</td></tr>
<tr><td>Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Blood urea nitrogen
Creatinine
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic</td><td>Total and direct bilirubin
Gamma-glutamyltransferase
Alkaline phosphatase
Calcium
Phosphate
Albumin
Total protein</td></tr>
<tr><td></td><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 13 Liver Safety.</td></tr>
<tr><td>Nutritional parameters</td><td colspan="3">• 25-hydroxy Vitamin D, MMA, and iron</td></tr>
<tr><td>Other Screening Tests</td><td colspan="3">• Highly sensitive urine pregnancy testing for females of childbearing potential only
• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], HBV antibody, anti-HBs, anti-HBc total, and hepatitis C virus antibody)
• QuantiFERON®-TB test or T-Spot®
• Serum (CRP)
• Stool samples (enteric pathogens including a stool culture and Clostridioides difficile test and additional testing [eg, ova and parasites or Escherichia coli 0157:H7 assessments]) and fecal calprotectin, fecal lactoferrin
• Colonic biopsy (RNA analysis, histology)</td></tr>
</table>

10.12. Appendix 12: Hepatitis B Virus Screening with HBV DNA Testing

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

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

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

These eligibility criteria based on HBV test results are also represented in the table below.

HEPATITIS B TEST RESULT			STATUS
Hepatitis B surface antigen (HBsAg)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	
negative	negative	negative	**Eligible**
negative	(+)	negative	
negative	(+)	(+)	
(+)	negative *or* (+)	negative *or* (+)	**Not eligible**
negative	negative	(+)	**(Require testing for presence of HBV DNA*)**

*If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.

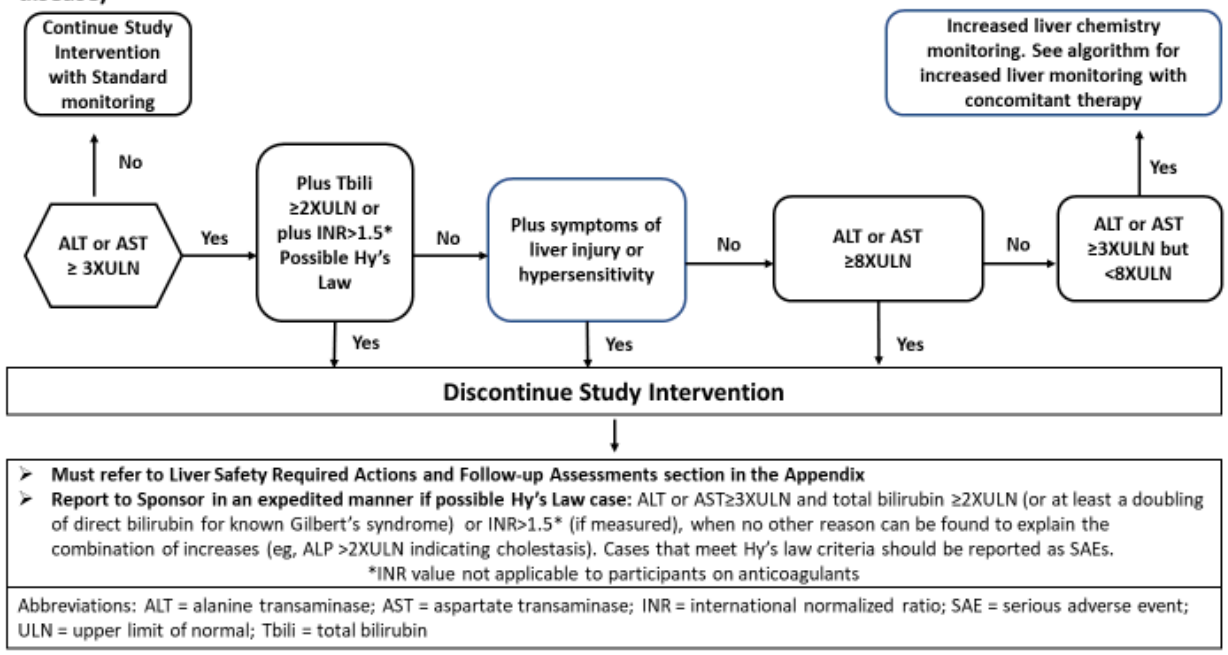
For participants who **are not eligible for this protocol due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

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

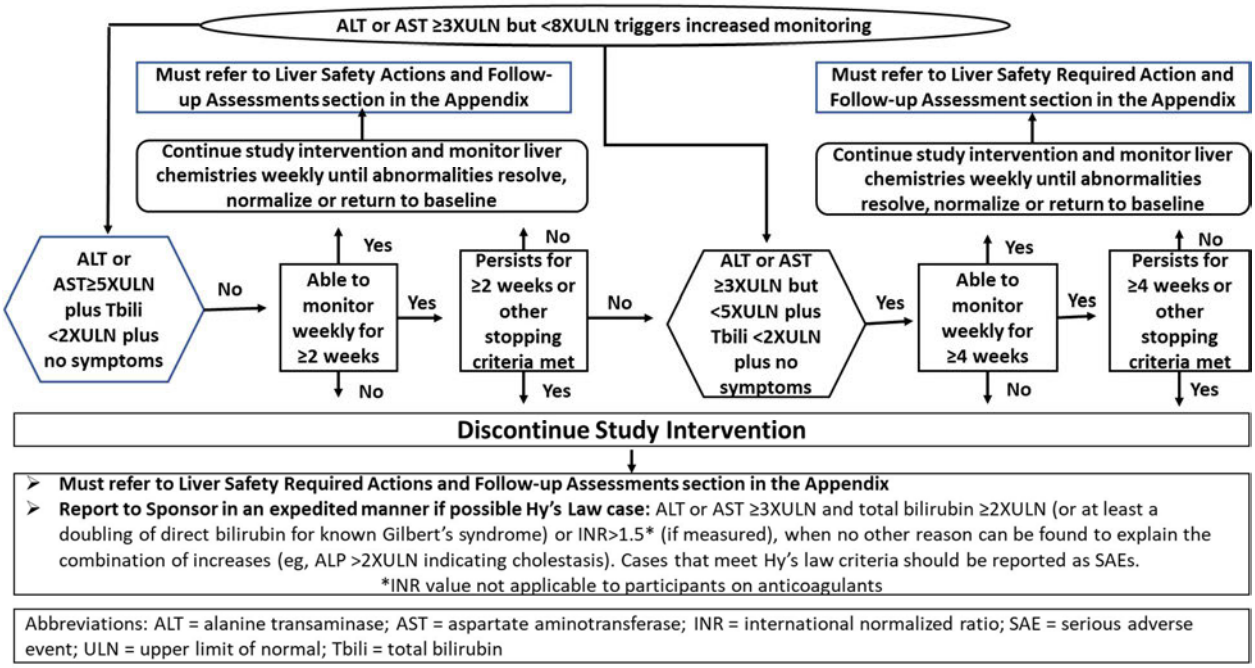
10.13.1. Stopping Algorithm

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Phase 3-4 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm (no preexisting liver disease)



Phase 3-4 Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT or AST ≥3xULN but <8xULN (no preexisting liver disease)



10.13.2. Follow-up Assessments

10.13.2.1. Phase 3-4 Liver Chemistry Stopping Criteria and Follow-up Assessments

Liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver Chemistry Stopping Criteria	
ALT/AST-absolute	ALT or AST ≥8 x ULN
ALT/AST Increase	ALT or AST ≥5 xULN but <8xULN persists for ≥2 weeks ALT or AST ≥3 x ULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT or AST ≥3 x ULN **and** total bilirubin ≥2xULN (>35% direct) or INR >1.5.
INR[2]	ALT or AST ≥3 x ULN **and** international normalized ratio (INR) >1.5, if INR measured
Cannot Monitor	ALT or AST ≥5 x ULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT or AST ≥3 x ULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT or AST ≥3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring, and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study intervention • Report the event to the sponsor within **24 hours** • Complete the liver event/expedited reporting form and complete an SAE CRF if the event also met the criteria for an SAE[2] • Perform follow-up assessments as described in the Follow-up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (See Monitoring) **MONITORING:** **<u>If ALT or AST ≥3×ULN AND total bilirubin ≥2×ULN (>35% direct) or INR >1.5 (if measured):</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin,	• Viral hepatitis serology[4] • Obtain blood sample for PK analysis within 1 week of the event of ALT or AST ≥3×ULN, if within the maximum blood volume allowed (Section 8.6) [5] • Obtain serum creatine phosphokinase, lactate dehydrogenase, gamma-glutamyltransferase, GDH, and serum albumin • Fractionate bilirubin, if total bilirubin ≥2×ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on liver event/expedited reporting form

and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **<u>For all other criteria</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention	• Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications) • Record alcohol use on the liver event alcohol intake form **<u>If ALT ≥3 x ULN AND total bilirubin ≥2 x ULN (>35% direct) or INR >1.5 (if measured)</u>** obtain the following in addition to the assessments listed above: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease; complete liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: – In participants when serology raises the possibility of autoimmune hepatitis – In participants when suspected drug-induced liver injury progresses or fails to resolve on withdrawal of study intervention – In participants with acute or chronic atypical presentation: hepatic vascular disorder, chronic hepatitis fibrosis, micro vesicular statosis • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, stop study intervention if ALT or AST ≥3 x ULN **and** total bilirubin ≥2 x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

2. All events of ALT or AST ≥3 x ULN **and** total bilirubin ≥2 x ULN (or at least a doubling of direct bilirubin for known Gilbert's syndrome) or ALT or AST ≥3 x ULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAgG and hepatis B core antibody (HBcAb); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Pharmacokinetics (PK) sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

References

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.
European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology 2019; 70 (6):1222-1261
Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

10.14. Appendix 14: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 8 (Section 10.8) Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Female of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Female Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile (for the purpose of this study)**
  - Permanent sterilization methods include hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
  - Has congenital abnormalities resulting in sterility.

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

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

Contraceptive (birth control) use by males or females should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

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

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

Pregnancy During the Study

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

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.15. Appendix 15: Regulatory, Ethical, and Study Oversight Considerations

10.15.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

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

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

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.2, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.2.

10.15.2. Financial Disclosure

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

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

10.15.3. Informed Consent Process and Assent Form

Each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), must give consent/assent according to local requirements, after the nature of the study has been fully explained. Assent is required of children capable of understanding the study, typically participants 7 years of age and older, depending on the institutional policies and national/local guidelines. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor or designee and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants, parents, or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. The ICF/assent will explain that placebo will be

used in this study for blinding purposes only, and not as a comparator. There will be no greater than a minor increase over the minimal risk of placebo injection. Participants will be informed that their participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF/assent the participant, parent(s)/legally authorized representative are authorizing such access. It also denotes that the participant and parent(s)/legally authorized representative agrees to allow participants study physician to recontact the participant for the purpose of obtaining consent/assent for additional safety evaluations, and subsequent disease-related treatments, if needed.

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

A participant may be rescreened. Participants who are rescreened and his/her parent(s)/legally acceptable representative are required to sign a new ICF/assent.

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

If the participant, parent(s) or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent/assent process (which includes reading and explaining all written information) and should personally date and sign the ICF/assent after the oral consent/assent of the participant or legally acceptable representative is obtained.

10.15.4. Data Protection

Privacy of Personal Data

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

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

The informed consent/assent obtained from the participant, parent(s), or his or her legally acceptable representative), includes information about, and where required per applicable regulations, explicit consent/assent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent/assent also provides information to address the lawful transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete, or make requests concerning his or her personal data in accordance with applicable data protection laws. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

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

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

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. The start of the storage period is defined as last participant last Week. Samples will only be used to understand ustekinumab, to understand pediatric Crohn's disease, to understand differential intervention responders, and to develop tests/assays related to ustekinumab and pediatric Crohn's disease. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent/assent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.15.6. Committees Structure

Data Monitoring Committee

An external DMC (consisting of at least one medical expert in the relevant therapeutic area and at least one statistician), will be established to monitor data on an ongoing basis until all participants reach the Week M-44 visit or terminate the study prior to the Week M-44 visit. In addition, for the PK interim analysis, an unblinded internal sponsor PK expert (independent of the study) will join the DMC to review the PK interim analysis results to evaluate the ustekinumab dosage for participants <40 kg (as measured at Week I-0).

10.15.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding ustekinumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

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

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

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will

be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

10.15.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring Weeks by the sponsor, and direct transmission of clinical laboratory data from a central laboratory, IWRS data to the sponsor's database, and direct transmission of participant-reported outcome (PRO) to the electronic participant-reported outcome (ePRO) vendor database and then into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor or designee will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the edata into the study database they will be verified for accuracy and consistency with the data sources.

10.15.9. Case Report Form Completion

Data from each study participant will be captured in an eCRF or ancillary data collection systems (DCS) such as the IWRS, PRO tablets, laboratory database, and imaging database. Electronic CRFs prepared by the sponsor are provided to the site for each participant. If the site is required to enter data directly into an ancillary DCS, the applicable system will be prepared by the ancillary data provider and provided to the site for each participant.

Study data will be transcribed by study-site personnel from the source documentation to the eCRF or the ancillary DCS, if applicable.

Worksheets may be used as source documentation to capture data and facilitate completion of the eCRF or entry of data into the applicable ancillary data system. Data entry in the applicable DCS must be completed as soon as possible after a participant Week, and the data should be available for review at the next scheduled monitoring visit.

Study-specific data from each source will be transmitted in a secure manner to the sponsor.

Necessary eCRF or ancillary data modifications can only be made/authorized by the investigator or appropriate site personnel using eCRF system functionality and/or ancillary data revision procedures. All data changes will be recorded in an audit trial. The investigator must verify that all data entries in the eCRF are accurate and correct by signing the eCRF using the eDC functionality.

10.15.10. Source Documents

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

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

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

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

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

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

Participant- and investigator-completed scales and assessments designated by the sponsor including PRO assessments (IMPACT-III and PCDAI) will be recorded into an electronic tablet device (ePRO) and/or patient handheld device at home before the visit or during the visit at the study site. These data will be considered electronic source documentation.

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

10.15.11. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor or designee will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these weeks, the monitor will compare the data entered into the applicable DCS component (as defined in the monitoring guidelines) with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the applicable DCS component are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.15.12. On-site Audits

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

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

10.15.13. Record Retention

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

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

10.15.14. Study and Site Start and Closure

First Act of Recruitment

The first participant screened is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

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

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

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.16. Appendix 16: Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study-site personnel being reassigned to critical tasks.

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

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

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

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

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

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

10.17. Appendix 17: Exposure Optimization Substudy

Introduction

In this optional substudy, induction responders and delayed responders who lose response during maintenance (including those who lose response after having been dose adjusted) and have a low steady-state, 8 weeks post-dose ustekinumab concentration will receive open-label q4w dosing under close surveillance. Nonresponders meeting Early Escape criteria, with a low steady-state, 8-week trough ustekinumab concentration at Week M-8 will also be eligible to enroll.

Study Design

Participants who lose response during Study CNTO1275CRD3004 and have an 8 weeks post-dose serum ustekinumab concentration of <1.4 µg/mL during the maintenance period (at the Week M-8 or Maintenance Week 32 [Week M-32] visit) will be eligible to enroll in this optional, open-label q4w substudy. Loss of response is defined in the main protocol. The Week M-8 and Week M-32 timepoints were selected to define participants with low exposure because ustekinumab trough concentration at these timepoints reflects an 8-week steady-state trough concentration for participants in both q8w and q12w dosing arms. Participants who fail to respond by Week M-8 (meeting Early Escape criteria) and have low exposure (steady-state 8-week ustekinumab trough concentration <1.4 µg/mL drawn at the Week M-8 visit) are also eligible to enroll in the substudy (see Table 5 and Table 6). In the case where a participant meets Early Escape criteria at Week M-8, but opts to await the Week M-8 trough concentration to determine substudy eligibility, the investigator may prescribe rescue medications if the investigator feels that this is in the participant's best interest.

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

During this substudy, ustekinumab will be administered subcutaneously q4w for a total duration of 16 weeks (5 doses) or through the Week M-40 visit, whichever is the longer duration of exposure. After entering the substudy, the frequency of study visits will be increased to q4w. Dose will be calculated the same way, only the dosing interval will change. Participants will continue to follow the study protocol Schedule of Activities, with the exception of Study Home Visits and at-Home Study Intervention. Substudy participants who regain clinical response may have Study Intervention Administration at Home and/or Study Site or Home visits. 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, an injection-site reaction evaluation carried out, AEs and concomitant medications reviewed, and a serum ustekinumab trough concentration and ESR and hematology/chemistry with CRP labs obtained. A highly sensitive urine pregnancy test will also be required before study intervention is administered. A PCDAI 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. The final data base lock for the substudy will occur after the last participant has completed

16 weeks in the study and completed a safety follow-up visit approximately 20 weeks after the last administration of study intervention.

The rationale for this study is that in adult ustekinumab trials, lower exposures were associated with lower response rates. In IM-UNITI, steady-state concentration cut-offs greater than 1.4 µg/mL were associated with greater clinical remission during maintenance. If a participant initially responded but subsequently lost response and has a ustekinumab trough level <1.4 µg/mL, this participant may benefit from a higher exposure.

In the IM-UNITI and UNIFI trials in adult Crohn's disease and UC respectively, the average ninety-fifth percentile of 8-week steady-state trough ustekinumab concentration was 7.2 µg/mL. Given that 1.3 µg/mL will be the highest 8-week ustekinumab trough concentrations in any enrolled participant, 4-week ustekinumab trough concentrations in this substudy are not expected to exceed those established for adults in the safety database.

In addition, in both the IM-UNITI and UNIFI, ustekinumab trough concentrations in the highest quartile were not associated with greater incidence of either serious adverse events or serious infections.[1,2]

The existing Phase 3 external independent DMC will monitor safety data of both the main CNTO1275CRD3004 study and the q4w substudy. 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 to evaluate the ustekinumab dosage for participants <40 kg (as measured at Week I-0).

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

Risk/Benefit

The benefit of this substudy is that it may optimize the chance for an individual participant who previously responded to ustekinumab to regain that response. It may also optimize the chance for an individual participant to achieve response following induction. Dosing of ustekinumab q4w in patients who lose response is common in pediatric IBD clinical practice. Thus, this substudy allows for rigorous safety monitoring that would not be possible if the participant were discontinued from the study and dosed at a higher frequency under clinical care. The risk is that there may be a higher

incidence of ustekinumab related AEs. However, this risk is considered low as a higher incidence of AEs was not associated with higher exposures in the adult ustekinumab UC or Crohn's disease studies.[1,2] In addition, PK will be monitored during the substudy to ensure that a participant's steady-state ustekinumab trough concentration does not exceed exposures seen in the adult IBD studies before entering the LTE. Of note, participants in the q12w arm with low 8-week ustekinumab trough exposure will be transitioned to q4w dosing interval in the substudy; this is done to ensure that participants are not being dose adjusted to subtherapeutic exposure.

Hypothesis

The primary research hypothesis is that achieving exposures similar to those in adult studies of ustekinumab in CD will lead to response in pediatric participants without a change to the safety profile.

Objectives

The primary objectives of this exploratory substudy are:

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

The secondary objective of this substudy is:

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

Endpoints

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

- 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).

Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Documented induction nonresponse at Week M-8, or LOR during the maintenance period
2. Trough ustekinumab concentration <1.4 ug/mL at Week M-8 or M-32 (8-week steady-state trough concentration)
3. Has not met any discontinuation criteria from the main study
4. Has not started an exclusionary medication or medical therapy
5. Signed informed consent/assent according to institutional requirements

Exclusion Criteria

1. Body weight less than 10 kg

Study Intervention

All participants will receive q4w open-label SC administration of ustekinumab. Dosing strength will be maintained based on weight, with a decrease in intervals between doses in the substudy to q4w.

Ustekinumab q4w: 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight.

Study Assessments and Procedures

Please refer to main protocol Schedule of Activities.

Statistical Considerations

Sample Size Determination

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

Statistical Analyses

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. Graphical data displays (eg, line plots) may also be used to summarize the data.

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 intercurrent event rules will be applied.

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 data will be labeled as such in the concentration data presentations or Statistical Analysis System datasets. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

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).

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 study: frequency and type of AEs, serious adverse events, reasonably related AEs as assessed by the investigator, AEs leading to discontinuation of study intervention, infections (including serious infections, and infections requiring oral or parenteral antimicrobial treatment), and injection-site reactions.

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

Table 5: Optional Exposure Optimization Substudy, CNTO1275CRD3004 (UNITI Jr): Possible Entry Points and Visit Schedules

Substudy Entry	*DB = Main Study Dosing, SS = Substudy Dosing*													
	M-8*	**M-12**	**M-16**	**M-20**	**M-24**	**M-28**	**M-32***	**M-36**	**M-40**	**M-44**	**M-48**	**M-52**	**M-56**	**M-60**
Option 1	DB	SS[1]	SS[2]	SS[3]	SS[4]	SS[5]	SS[6]	SS[7]	SS[8]					
Option 2	DB	DB	SS[1]	SS[2]	SS[3]	SS[4]	SS[5]	SS[6]	SS[7]					
Option 3	DB	DB	DB	SS[1]	SS[2]	SS[3]	SS[4]	SS[5]	SS[6]					
Option 4	DB	DB	DB		SS[1]	SS[2]	SS[3]	SS[4]	SS[5]					
Option 5	DB	DB	DB		DB	SS[1]	SS[2]	SS[3]	SS[4]	SS[5]				
Option 6	DB	DB	DB		DB		SS[1]	SS[2]	SS[3]	SS[4]	SS[5]			
Option 7	DB	DB	DB		DB		DB	SS[1]	SS[2]	SS[3]	SS[4]	SS[5]		
Option 8	DB	DB	DB		DB		DB	DB	SS[1]	SS[2]	SS[3]	SS[4]	SS[5]	
Option 9	DB	DB	DB		DB		DB	DB	DB	SS[1]	SS[2]	SS[3]	SS[4]	SS[5]

There are 9 possible entry points and 6 possible additional substudy visits/dosing timepoints
Depending on the participant's entry timepoint into the substudy, they could have 1 to 4 additional substudy/dose visits
The substudy is a minimum duration of 16 weeks (5 doses) and a participant can enter the substudy at any point *after* Week M-8 through Week M-44
[1-8] =Number of doses a participant will receive depending on when they enter the substudy

DB=Double-blind dosing visit during Maintenance Period q8w or q12w (active vs placebo)

* Trough concentration measurements from Week M-8 and Week M-32. Earliest possible substudy entry is Week M-12

SS=Substudy open-label dosing q4w for a minimum of 16 weeks (5 doses)

SS=Substudy open-label dosing q4w for >16 weeks (5 doses) if longer duration of exposure (discontinue if not in clinical response 16 weeks after substudy entry)

Light gray highlighted cells = possible extra substudy visits not reflected in protocol Schedule of Activities or Figure 2 of main protocol

Abbreviations: DB=double-blind; M=maintenance; q4w=every 4 weeks; q8w=every 8 weeks; q12w=every 12 weeks; SS=substudy dosing

Table 6: Optional Exposure Optimization Substudy, CNTO1275CRD3004 (UNITI Jr): Schedule of Activities for Substudy Visits

NOTE: All participants in the Exposure Optimization Substudy should continue to follow all main study assessments per Table 3: Maintenance Period Schedule of Activities.						
Additional Substudy Assessments	**M-20***	**M-28***	**M-48***	**M-52***	**M-56***	**M-60***
Informed consent	Prior to first substudy assessment	Prior to first substudy assessment				
Highly sensitive urine pregnancy test	X	X	X	X	X	X
Administer study intervention	X	X	X	X	X	X
Study intervention injection-site evaluation	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Height	X	X	X	X	X	X
AE review	X	X	X	X	X	X
PCDAI score	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X
Serum ustekinumab concentration	X	X	X	X	X	X
Hematology, chemistry	X	X	X	X	X	X
ESR	X	X	X	X	X	X
CRP	X	X	X	X	X	X
Physical examination			If final study visit	If final study visit	If final study visit	If final study visit
Stool sample (fecal calprotectin, fecal lactoferrin)			If final study visit	If final study visit	If final study visit	If final study visit
Antibodies to ustekinumab			If final study visit	If final study visit	If final study visit	If final study visit
* Not all visits will be incurred by all Exposure Optimization Substudy participants. The additional substudy visits will be dependent upon when the participant enters the substudy (see Table 5 for possible entry points and visit schedules for substudy participants).						
Abbreviations: AE=adverse events; CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; M=maintenance; PCDAI= Pediatric Crohn's Disease Activity Index; PK=pharmacokinetics						

10.18. Appendix 18: Exit Survey

Stelara Pediatric IBD Trials- Exit Questionnaire

Your answers to this survey are anonymous and cannot be traced back to you.

To answer each question, please think about your experiences as a clinical trial participant or a caregiver of a clinical trial participant over the past year. We are grateful to you and your child for participating in this survey, which we hope will improve future clinical trial programs.

* Required

1. **The person completing this form is**

*

- ◯ An adolescent participant in this clinical trial
- ◯ A caregiver of a participant in this clinical trial

2. **For how many years have you/your child had Inflammatory Bowel Disease (IBD) (years since diagnosis)?** *

3. **Why did you/your child participate in the study?** *

1/18/2022

4. **What is your overall level of satisfaction with the study in which you/your child participated?** *

- ◯ Very satisfied
- ◯ Satisfied
- ◯ Neither satisfied nor dissatisfied
- ◯ Dissatisfied
- ◯ Very dissatisfied

5. **What did you like about the study?**
If nothing, please write "nothing".

6. **What would you change about the study?**
If nothing, please write "nothing".

1/18/2022

7. **Have you/your child participated in any other research studies of investigational therapies/drugs?** *

- ◯ Yes
- ◯ No

8. **Were other therapies or studies offered to you/your child before you decided to participate in this trial?** *

- ◯ Yes
- ◯ No
- ◯ Not sure

9. **Did you think that participating in this trial was the only treatment option for you/your child?** *

- ◯ Yes
- ◯ No
- ◯ Not sure

10. **How important do you think this study is for children with IBD?** *

- ◯ Extremely important
- ◯ Somewhat important
- ◯ Neutral
- ◯ Somewhat not important
- ◯ Extremely not important

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11. **In general, how important do you think it is to evaluate new drugs in children by conducting clinical trials?** *

- ◯ Extremely important
- ◯ Somewhat important
- ◯ Neutral
- ◯ Somewhat not important
- ◯ Extremely not important

12. **Would you recommend this study to other families with a child who has IBD?** *

- ◯ Yes
- ◯ No
- ◯ Maybe

13. **In minutes, on average, approximately how long does it take for you to travel from your home to the study site?** *

14. **Would you consider home/telehealth visits if this was an option?** *

- ◯ Yes
- ◯ No
- ◯ Maybe

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15. **Why not?**

16. **What would you recommend that the Sponsor of this trial do differently, to make this study better for families/ patients? If nothing, please leave blank.**

17. **Would you like to receive the results of this study?** *

- ◯ Yes
- ◯ No
- ◯ Maybe

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18. **How important is it to you that you receive the overall results of the clinical trial?** *

- ◯ Extremely important
- ◯ Somewhat important
- ◯ Neutral
- ◯ Somewhat not important
- ◯ Extremely not important

19. **How important is it to you that you receive your own/your child's trial data results?** *

- ◯ Extremely important
- ◯ Somewhat important
- ◯ Neutral
- ◯ Somewhat not important
- ◯ Extremely not important

20. If you have other suggestions that you would like to communicate to the Sponsor of the trial to improve future programs, please describe them below.

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10.19. Appendix 19: Protocol Amendment History

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

Amendment 6 (25 May 2022)

Overall Rationale for the Amendment: The overall rationale for the current amendment is to increase operational efficiency and to decrease participant and study site burden.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3: Screening Period: Schedule of Activities, Ileocolonoscopy Section 5.1: Inclusion Criteria #5.2	Added text clarifying the screening ileonoscopy procedure in the Screening Period SoA and the corresponding inclusion criterion: **A video ileocolonoscopy recorded within 3 months prior to the Week I-0 visit may be used in case of rescreening of a participant who had an ileocolonoscopy but failed the initial screening for another reason, on a case-by-case basis, after consultation with the sponsor.**	Due to the invasiveness of the ileocolonoscopy procedure and participant burden in pediatric study participants, a video ileocolonoscopy obtained within 3 months of the I-0 visit may be acceptable, especially if the procedure established study eligibility (eg, presence of ulceration). A decision to allow the use of the video will be made after discussion with the sponsor and is dependent on the availability and quality of the video recording and if the recording can be transmitted, read and scored by the central readers (eg. anatomy is adequately visualized).
Section 1.3: Screening Period: Schedule of Activities, Ileocolonoscopy Maintenance Period: Schedule of Activities, Ileocolonoscopy	All study ileocolonoscopies ~~must~~ **should** be performed with study software to permit central review of the video of the ileocolonoscopy and scoring using the criteria of the SES-CD and the SEMA-CD (Section 8.1.7). (In case back-up software would need to be used, this should be recorded in the source documents.)	The rationale behind a possible exception is to be able to use back-up software in case of technical issues or failure of the study software.
Section 1.3: Induction Period: Schedule of Activities, Study Procedure – Induction Maintenance Period: Schedule of Activities, NOTES	A possible extension of the window for all visits in the induction and maintenance periods (except for the I-0 and M-0 visits) could be allowed in case a planned visit would coincide with a holiday. To that purpose, the following note was added to the corresponding SoAs: **If the first or the last day of a visit window coincides with a holiday, the window can be extended with 2 business days. This will not be considered a protocol deviation.**	It was clarified that a possible extension of the visit window due to a planned visit coinciding with a holiday would not be considered a protocol deviation.
Section 1.3: Screening Period: Schedule of Activities,	The following clarification has been added: **Note: In case Inclusion Criterion 5.2 is otherwise met, the fecal calprotectin assessment is not needed.**	The clarification was added to avoid an unnecessary fecal calprotectin assessment during screening in case Inclusion Criterion 5.2 is otherwise met.

Section Number and Name	Description of Change	Brief Rationale
Stool sample (fecal calprotectin)		
Section 1.3: Screening Period: Schedule of Activities, IGRA testing/Tuberculin skin test Induction Period: Schedule of Activities, TB evaluation / other infection assessment Maintenance Period: Schedule of Activities, TB evaluation / other infection assessment Section 5.1: Inclusion Criteria #14.1 Section 5.2: Exclusion Criteria #6.1, #16.1, #17.1 Section 7.1: Discontinuation of Study Intervention Section 8.3.6.1: Initial Tuberculosis Evaluation Section 8.3.6.2: Ongoing Tuberculosis Evaluation	• Both QuantiFERON-TB® and T-SPOT® are acceptable for TB testing. The tests are being referred to by using the more general terminology of "interferon gamma release assay (IGRA) testing". • There are no longer any inclusion criteria relating to TB. All eligibility criteria relating to TB are described as exclusion criteria. More extensive TB-related eligibility criteria have been added to the protocol. • It was clarified that investigators should consider tuberculin skin testing in addition to IGRA testing to screen for latent TB in participants less than 5 years old, if preferred by local health authorities, or if they believe based on their judgment that both tests are clinically indicated to evaluate a participant at high risk for latent TB. • It was clarified that study intervention must be withheld in case there is suspicion for a TB infection, or in case a participant had a close contact exposure to TB. If a diagnosis of active or latent TB is made, then study intervention must be permanently discontinued.	This update has been made due to a template change.
Section 1.3: Screening Period: Schedule of Activities, Highly Sensitive urine pregnancy test Induction Period: Schedule of Activities, Highly	The description of each urine pregnancy test has been updated to "highly sensitive urine pregnancy test".	Following the replacement of the serum pregnancy test by a urine pregnancy test (see Amendment 5), it was further specified that the urine pregnancy test needs to be highly sensitive.

Section Number and Name	Description of Change	Brief Rationale
Sensitive urine pregnancy test Maintenance Period: Schedule of Activities, Highly Sensitive urine pregnancy test Section 5.1: Inclusion Criteria #11.2 Section 5.3: Lifestyle Considerations #3.1 Section 8: Study Assessments and Procedures Section 8.2.4: Clinical Safety Laboratory Assessments Section 10.11: Appendix 11: Clinical Laboratory Tests, Other Screening Tests Section 10.16: Appendix 16: Guidance on Study Conduct During the COVID-19 Pandemic Section 10.17: Appendix 17: Exposure Optimization Substudy		
Section 1.3: Induction Period: Schedule of Activities, Nutritional parameters (25-hydroxyvitamin D, MMA, and iron)	Nutritional parameters should be collected at Week I-0 prior to the infusion. In children ~~<22~~ **<17** kg, these blood samples should be collected during the screening period. The results of the test will be sent to the investigator and recommendations will be provided for any follow-up treatment or retesting.	Following new recommendations for laboratory sample volumes and reduced blood testing, the body weight cutoff for recommended earlier sampling for nutritional parameters was lowered to <17 kg at Week I-0 and to <16 kg (<17 kg for participants in Japan) at Week M-44.

Section Number and Name	Description of Change	Brief Rationale
Maintenance Period: Schedule of Activities, Nutritional parameters (25-hydroxyvitamin D, MMA, and iron)	For children ~~<19~~ **<16** kg **(for participants in Japan: <17 kg)**, nutritional parameters may be collected prior to the Week M-44 visit.	
Section 1.3: Induction Period: Schedule of Activities, Serum ustekinumab concentration Maintenance Period: Schedule of Activities, Serum ustekinumab concentration	 At the induction infusion visit (Week I-0), blood samples for PK analysis should be collected before the start of the infusion and approximately 60 minutes after completion of the infusion. **At the other visits, blood samples for PK analysis should be collected prior to administering the study intervention.** The same blood draws can be used to collect serum samples for measuring ustekinumab concentration and antibodies to ustekinumab. **Blood samples for PK analysis should be collected prior to administering the study intervention.**	It has been clarified that blood samples for measurement of serum ustekinumab should be collected prior to administering the study intervention.
Section 1.3: Induction Period: Schedule of Activities, Serum biomarkers Section 8.4: Pharmacokinetics	**Participants who have received biologic therapy for the treatment of Crohn's disease prior to the I-0 visit and have had a biologic drug washout duration of <5 half-lives may have a blood test for the prior biologic drug level at Week I-8.** Serum samples will be used to evaluate the PK of ustekinumab. Serum collected for the analysis of serum concentrations of ustekinumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period **(eg, residue prior biologic level for participants who were enrolled with <5 half-lives washout of a prior biologic)** or for the evaluation of relevant biomarkers**.** Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.	It has been clarified that serum collected for the analysis of ustekinumab concentrations or biomarkers may also be used for determination of residual biologic level for participants who were enrolled with <5 half-lives washout of a prior biologic.
Section 1.3: Maintenance Period: Schedule of Activities, Stool for enteric pathogens Section 4.1.2: Loss of response during the maintenance period	Enteric pathogen testing has been added to the LOR visit assessments: **Stool studies for enteric pathogens will include a stool culture and *Clostridioides difficile* (formerly known as *Clostridium difficile*) test (*C. difficile* toxin/GDH with Reflex to PCR testing) and may be performed by a local laboratory. Additional testing (eg, ova and parasites or *Escherichia coli* 0157:H7 assessments) may be**	Enteric pathogen testing at the LOR visit has been included in order to rule out an enteric pathogen infection in case LOR is suspected.

Section Number and Name	Description of Change	Brief Rationale
	performed at the investigator's clinical discretion.	
Section 1.3: Maintenance Period: Schedule of Activities, PCDAI score	The following clarification was added to the PCDAI score assessment: **At the LOR visit, with the most recent laboratory results, including local laboratory results.**	Recent local lab results (obtained after the last study visit lab results) may be used for scoring the PCDAI to allow for flexibility and to reflect the most up-to-date clinical status of the patient and to better assess LOR status. In this case, the sponsor will have access to the local lab results.
Section 1.3: Maintenance Period: Schedule of Activities, Stool sample (fecal calprotectin, fecal lactoferrin)	It has been clarified that stool samples could be collected up to 4 days after a study-site visit in case a participant was not able to provide a sample prior to or during the visit.	This clarification has been added to allow for more flexibility in the collection of stool samples for fecal calprotectin and fecal lactoferrin.
Section 1.3: Maintenance Period: Schedule of Activities, ESR	An ESR assessment at the LOR visit has been added to the SoA. The ESR assessment at the safety follow-up visit has been deleted.	The ESR assessment at the LOR visit is needed to calculate the PCDAI score and was inadvertently omitted in the previous version of the protocol. Since no PCDAI score will be calculated at the safety follow-up visit, the ESR assessment is also not needed at that timepoint.
Section 1.3: Maintenance Period: Schedule of Activities, Exit survey Section 8.9: Exit Survey Section 10.18: Appendix 18: Exit Survey	An optional exit survey at the safety follow-up visit has been added to the SoA.	An optional exit survey will be conducted to elicit input from parents and participants (>12 years of age) on their experience in our trial and general views regarding pediatric research, elements of trial design, and receiving trial results. These data will be used to inform design of future trials.
Section 1.3: Maintenance Period: Schedule of Activities, footnote b Synopsis Section 4.1.2: Loss of Response During the Maintenance Period	The following clarification has been added: Participants who have LOR will be eligible for a dose adjustment**; those who have LOR and have documented low ustekinumab exposure will be eligible for the Exposure Optimization Substudy**.	It has been clarified that participants experiencing LOR will either be eligible for a dose adjustment or, in case they have documented low ustekinumab exposure, for enrollment in the Exposure Optimization Substudy.
Section 1.3: Schedule of Activities (SoA)	Minor edits have been made to the instructions in the SoA, mainly to provide guidance on review of the diaries and completion of the questionnaires.	Minor edits have been made to clarify site instructions.

Section Number and Name	Description of Change	Brief Rationale
Section 2.3.1: Risks for Study Participation	Risks Due to Study Intervention (Malignancy): The mitigation strategy has been changed to state that participants developing ANY malignancy will be discontinued from study intervention: Participants who develop a malignancy during the study ~~(with the exception of ≤2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease)~~ will be discontinued from study intervention (Section 7.1).	This had already been changed in Section 7.1 (Discontinuation of Study Intervention) at the time of Amendment 4 (02 February 2021). The corresponding update in Section 2.3.1 was inadvertently missed at that time.
Synopsis Section 2.3.3: Benefit-Risk Assessment for Study Participation Section 6.3: Measures to Minimize Bias: Randomization and Blinding Section 9.4.10: Other Analyses Section 9.5: Interim Analysis Section 9.6: Data Monitoring Committee Section 10.15.6: Committees Structure (Appendix 15) Section 10.17: Appendix 17: Exposure Optimization Substudy	A PK interim analysis has been added for this study: **When ~20 participants from both the CNTO1275CRD3004 and CNTO1275PUC3001 studies (combined) weighing <40 kg (as measured at Week I-0) complete the Week M-8 visit, a PK interim analysis to evaluate the ustekinumab dosage for participants <40 kg will be performed. The DMC members along with an unblinded internal sponsor PK expert (independent of the study) will review the results of this PK interim analysis.**	A PK interim analysis will be performed to evaluate the ustekinumab dosage for participants <40 kg (as measured at Week I-0).
Synopsis Section 3.1: Global Objectives, Endpoints and Hypothesis Section 3.2: US-specific Objectives, Endpoints and Hypothesis	The following changes have been made to the endpoints associated with the secondary objective to evaluate the efficacy of IV ustekinumab during the induction period: It has been clarified that clinical remission and clinical response at Week I-6 would be assessed by means of the sPCDAI score: • Clinical remission at Week I-6 **as assessed by sPCDAI.** • Clinical response at Week I-6 **as assessed by sPCDAI.**	Clarifications as to the parameters to be used.

Section Number and Name	Description of Change	Brief Rationale
Section 9.4.3.1: Global Secondary Endpoints Section 9.4.3.2: US-specific Secondary Endpoints	It has been clarified that endoscopic response at Week M-8 would be assessed by means of SES-CD: • Endoscopic response at Week M-8 **as assessed by SES-CD.**	
Synopsis Section 3.1: Global Objectives, Endpoints and Hypothesis Section 3.2: US-specific Objectives, Endpoints and Hypothesis Section 3.4: Endpoint Definitions Section 9.4.3.1: Global Secondary Endpoints Section 9.4.3.2: US-specific Secondary Endpoints	The following changes have been made to the endpoints associated with the secondary objective to evaluate the efficacy of SC ustekinumab during the maintenance period among participants who were in clinical response at Week I-8: Assessment of clinical remission at Week M-44 will be assessed overall as well as specifically from those participants who were in clinical remission at Week I-8. The following endpoint has been added: • **Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8.** Corticosteroid-free clinical response will no longer be assessed: • ~~Corticosteroid-free clinical response at Week M-44.~~ (The definition has been removed from Section 3.4: Endpoint Definitions.) Durable clinical remission will no longer be assessed: • ~~Durable clinical remission at Week M-44.~~	Changes were made in order to align with other studies (both adult and pediatric studies) in the STELARA® development program in the indications Crohn's disease and ulcerative colitis.
Synopsis Section 3.1: Global Objectives, Endpoints and Hypothesis Section 3.2: US-specific Objectives, Endpoints and Hypothesis Section 9.4.4: Tertiary/Exploratory Endpoints	Corticosteroid-free clinical remission at Week M-44 will be assessed overall (secondary endpoint) as well as specifically from those participants who received corticosteroids at Week I-0. The following endpoint has been added as a tertiary/exploratory endpoint: • **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.**	Changes were made in order to align with other studies (both adult and pediatric studies) in the STELARA® development program in the indications Crohn's disease and ulcerative colitis.
Synopsis Section 3.1: Global Objectives, Endpoints and Hypothesis	Body mass index has been added as an endpoint (both global and US-specific) to assess the effect of ustekinumab on growth.	Changes were made in order to align with other pediatric studies in the STELARA® development program in the indications Crohn's disease and ulcerative colitis.

Section Number and Name	Description of Change	Brief Rationale
Section 3.2: US-specific Objectives, Endpoints and Hypothesis Section 8.1: Efficacy Assessments Section 8.1.9: Height, Weight, and BMI z-Scores		
Section 3.1: Global Objectives, Endpoints and Hypothesis Section 3.2: US-specific Objectives, Endpoints and Hypothesis Section 3.4: Endpoint Definitions Section 8.1: Efficacy Assessments Section 8.1.8: Histology Section 9.4.4: Tertiary/Exploratory Endpoints	Histologic assessments have been updated to include the GHAS score, Geboes score, and RHI. Histologic assessment analyses are considered exploratory and will be summarized in separate technical reports.	Recent expert consensus opinions have recommended incorporation of standardized procedures for Crohn's disease clinical studies, aimed at addressing the need for improved definitions of histologic activity, and the establishment of widely acceptable definitions of histological response and remission. These consensus recommendations include incorporation of multiple assessments of histologic activity, including GHAS score, Geboes score, and RHI.
Section 3.3: Population Definitions	~~Delayed Responders: Induction nonresponders who are in clinical response at Week M-8 after a single SC dose of ustekinumab.~~ **All Responders: Induction and delayed responders combined. Delayed responders are defined as Induction nonresponders who are in clinical response at Week M-8 after a single SC dose of ustekinumab.**	The definition of delayed responders has been included in the overall definition of all responders.
Synopsis Section 4.1: Overall Design Section 9.2:	The study enrollment strategy has been updated: All participants entering maintenance will be randomized to one of two maintenance doses. The study will continue enrolling until at least 80 induction responders across the two	The changes have been made in order to reach a new randomization target.

Section Number and Name	Description of Change	Brief Rationale
Sample Size Determination	maintenance arms have been attained, with approximately 24 participants <40 kg including approximately 5 participants <30 kg enrolling in the study.	
Synopsis Section 4.1.1: Early Escape Criteria (Induction Nonresponders)	If a participant has not achieved response by Week M-8, and is documented to have low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit), the participant will be eligible for enrollment in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to q4w (See Appendix 17 Section 10.17). **If determined to be medically appropriate in the judgment of the investigator, participants who meet the Early Escape criteria may receive approved rescue therapies (Section 4.1.4) while they await the Week M-8 ustekinumab trough level result to determine eligibility for the Exposure Optimization Substudy.**	It was clarified that participants meeting the Early Escape criteria and enrolling in the Exposure Optimization Substudy may initiate treatment with rescue medication.
Synopsis Section 4.1.3: Dose Adjustment During the Maintenance Period Section 6.1.3.2: Maintenance Period	The following clarification has been added: **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.**	It has been clarified that participants who had a dose adjustment after having experienced LOR can be eligible for the Exposure Optimization Substudy if they experience a second LOR after having achieved response following the dose adjustment.
Section 4.2.2: Study-Specific Ethical Design Considerations	The following clarification has been added: **Written consent/assent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by applicable local regulations as well as study site and/or patient preferences.**	This update has been made due to a template change.
Section 5.1: Inclusion Criteria #6.1 Section 5.2: Exclusion Criteria #5.2 Section 10.6: Appendix 6: Half-life/Clearance for Various Biologic Therapies Used in Crohn's Disease	The required washout period prior to the first administration of study intervention for all biologic therapies received for Crohn's disease has been reduced to ≥2 half-lives.	This change has been made in order to align with clinical practice and in order to promote timely enrollment of subjects with active disease and reduce the potential need for escalation of corticosteroids as bridging therapy.
Section 5.2: Exclusion Criteria #14.2	Received, or are expected to receive, any live virus or bacterial vaccination within 4 weeks prior to the first administration of study intervention. ~~Receipt of a live SARS-CoV-2 vaccine (against the virus~~	This text has been deleted from Exclusion Criterion 14.2 since it is covered in Section 5.3, Lifestyle Considerations (#1.2).

Section Number and Name	Description of Change	Brief Rationale
	~~that causes Coronavirus Disease 2019 [COVID-19]) is not automatically an exclusion criterion and must be discussed with the medical monitor.~~	
Section 5.2: Exclusion Criteria #15.1	~~Have had a~~ **A** medical history of **or current** nontuberculous mycobacterial infection or **clinically significant** opportunistic infection (eg, ~~cytomegalovirus colitis, *Pneumocystis carinii*,~~ **pneumocystosis, invasive** aspergillosis, **progressive multifocal leukoencephalopathy**) at any time.	Cytomegalovirus colitis has been removed as an example of a clinically significant opportunistic infection, as it is not considered an opportunistic infection. "*Pneumocystis carinii*" was changed to "pneumocystosis", due to updates in medical terminology. Progressive multifocal leukoencephalopathy has been added as it is a known complication of other therapies for treatment of Crohn's disease.
Section 5.2: Exclusion Criteria #29.1	Are pregnant, nursing, or planning pregnancy ~~or fathering a child~~ **while enrolled in this study or within 16 weeks after the last dose of study intervention.**	This update has been made due to a template change.
Section 5.2: Exclusion Criteria #30.1	~~Are a~~ **A** child of an employee or a child who is a first-degree relative of an employee, or a child of the investigator who has direct involvement in the proposed study ~~or other studies under the direction of that investigator or study center~~, as well as the children of family members of the employees or the investigator~~.~~ **may not participate in the study at the study site at which the family member is employed. The child may participate in the study at a different study site that does not employ any first-degree family members.**	It has been clarified that a child that is a relative of an employee or investigator may participate in the study provided he/she is enrolled at a study site that does not employ any first-degree family members.
Section 5.2: Exclusion Criteria #31.1	During the 6 weeks prior to ~~baseline~~ **first administration of study intervention**, have had ANY of **the following (regardless of vaccination status):** (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features **of COVID-19** without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection:	This update has been made due to a template change.
Section 5.2: Exclusion Criteria #32	While previously included in Exclusion Criterion #29, planning to father a child is now added as a separate (additional) exclusion criterion: **Plans to father a child while enrolled in this study or within 16 weeks weeks after the last dose of study intervention.**	This update has been made due to a template change.
Section 5.3: Lifestyle Considerations #1.2	It is recommended that participants are up to date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. ~~For study participants who received~~ **It is strongly recommended that participants will have completed a** locally approved (including emergency-use-authorized) COVID-19 ~~vaccine(s) recently~~ **vaccination regimen at least 2 weeks**	This update has been made due to a template change.

Section Number and Name	Description of Change	Brief Rationale
	prior to ~~study entry,~~ **the first administration of study intervention**. Study participants should follow applicable local vaccine labeling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.8.3).	
Section 5.4: Screen failures	Rescreening Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened ~~1 time and~~ only after consultation with the sponsor. Participants who are rescreened will be assigned a new participant number, undergo the informed consent/assent process, and then start a new screening period. On a case-by-case basis after consultation with the sponsor, rescreening procedures may exceed the 6-week window and will not be considered protocol deviations.	A participant may be rescreened if it is expected that the specific enrollment criteria/criterion resulting in ineligibility may change to allow the participant to become eligible. The update has been made to allow for exceptions where a participant has more than 2 opportunities to screen for study.
Section 6.3: Measures to Minimize Bias: Randomization and Blinding Section 8.1.3: C-Reactive Protein Section 8.1.4: Fecal Calprotectin and Fecal Lactoferrin	The postbaseline results of CRP, fecal calprotectin, and fecal lactoferrin tests performed by the central laboratory will **not** be blinded to the investigative sites. ~~If an investigative site requests these data, they will be provided to the site after the Week M 44 analyses have been completed.~~ Results of CRP measurement will ~~not~~ be released to the investigators by the central laboratory. **Results of fecal calprotectin and fecal lactoferrin measurement will be released to the investigators by the central laboratory.**	The results from these tests are not needed to compute the primary efficacy outcomes. Conversely, these tests are frequently obtained during the course of clinical care. By allowing sites to assess these test results, the protocol is reducing the possibility of duplicate blood tests, thus decreasing participant burden.
Section 6.3: Measures to Minimize Bias: Randomization and Blinding	The following note has been added: **Notes:** • **If a participant has documented LOR and the investigator wishes to evaluate if the participant would be eligible for the Exposure Optimization Substudy, the site will be informed of the participant's exposure (ie, low [<1.4 µg/mL] or normal).** • **If a participant's ustekinumab trough concentration at the end of the Exposure Optimization Substudy (after at least 3 doses) is >7.2 µg/mL, the site will be informed and the participant will not be able to continue q4week dosing, but may continue q8w dosing in the LTE. (For details on the Exposure Optimization Substudy, refer to Appendix 17 [Section 10.17].)** **If an investigative site requests specific ustekinumab trough concentration data, they**	The note was added to clarify that exceptions to the blinding restrictions are allowed in specific cases, in order for the investigator: (i) to evaluate a participant's eligibility for the substudy, OR (ii) to evaluate the possibility for a participant to continue onto the LTE and hereby switch again to a less frequent dosing regimen (q8w) after having participated in the substudy (if the ustekinumab trough concentration at the end of the substudy [after at least 3 doses] is >7.2 µg/mL).

Section Number and Name	Description of Change	Brief Rationale
	will be provided to the site after the Week M-44 analyses have been completed.	
Section 6.6: Continued Access to Study Intervention After the End of the Study	Participants who **are <18 years of age at the end of the study and** do not discontinue prior to Week M-44 ~~are~~ **may be** eligible to enter into an LTE which will be described in a separate protocol. **If a participant has reached 18 years of age by the end of participation in the study and is not able to access ustekinumab commercially, the participant may be eligible for post-study access to ustekinumab via a country-specific mechanism. If post-study access is not possible, enrollment in the LTE may be permitted on a case-by-case basis.**	It has been clarified throughout the protocol that participants need to be <18 years in order to be eligible for the LTE. Continued access to ustekinumab for those ≥18 years without commercial access will also be possible via a country-specific mechanism, or by exceptional allowance in the LTE (on a case-by-case basis).
Section 8: Study Assessments and Procedures	The total blood volume to be collected from each participant will be approximately ~~141~~ **150** mL (or ~~158~~ **175** mL for participants in Japan).	Blood volumes were recalculated to reflect the blood sample collection associated with the assessments described in the current amendment.
Section 8.1: Efficacy assessments	For PROs: • The PRO instrument will be provided in the local language in accordance with local guidelines. • The PRO instrument ~~must~~ will be available for regulators and for IRB/IEC submissions, ~~therefore the PRO instrument or screen shots need to~~ and will be provided separately in a companion manual with the instruments that will be submitted with the protocol. • The PRO and AE data ~~and concomitant medication data may~~ will not be reconciled with one another.	This update has been made due to a template change.
Section 8.3.1: Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information Section 10.8.6: Product Quality Complaint Handling	It has been clarified that SAEs, as well as PQCs, need to be reported to the sponsor by study-site personnel immediately but not later than 24 hours: All SAEs, as well as PQCs, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel **immediately but no later than** ~~within~~ 24 hours of their knowledge of the event. All initial PQCs must be reported to the sponsor by the study-site personnel **immediately but no later than** ~~within~~ 24 hours after being made aware of the event.	This update has been made due to a template change.
Section 8.3.3: Follow-up of Adverse Events and Serious Adverse Events Section 10.8.4:	Participant pregnancy or participant partner(s) pregnancy will be considered a special reporting situation.	This update has been made due to a template change.

Section Number and Name	Description of Change	Brief Rationale
Special Reporting Situations (Appendix 8)		
Section 8.3.5: Pregnancy	All initial reports of pregnancy in females or partners of males must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy~~, preterm birth~~) are considered SAEs and must be reported using the SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention. Follow-up information regarding the outcome of the pregnancy **for female participants who become pregnant, or where the pregnancy was the result of male participant and his partner,** and any postnatal sequelae in the infant will be required.	This update has been made due to a template change.
Section 9.4.1: General Considerations	Data primarily will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, median, interquartile range, minimum and maximum, as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. **Unless otherwise specified, the Wilson Score method will be used to construct the 95% CI for binary endpoints where a proportion and the respective 95% CI are reported. Graphical data displays (eg, line plots) may also be used to summarize the data.** Unless otherwise specified, the endoscopic subscore as obtained during the central review of the video endoscopy will be used for all efficacy analyses involving ileocolonoscopy in this section. **Unless otherwise specified, all efficacy and safety analyses will be based on randomized study intervention.** **No multiplicity adjustments will be made in this study.**	It has been clarified that: • The Wilson Score method will be used to construct the 95% CI for binary endpoints. • All efficacy and safety analyses will be based on randomized study intervention. • No multiplicity adjustments will be made in this study.
Section 9.3: Populations for Analyses	The following analysis populations and their definitions have been added: All Enrolled Analysis Set, All Responder Analysis Set, PK All Responder Analysis Set, Immunogenicity Analysis Set, Immunogenicity Randomized Analysis Set, Immunogenicity Clinical Responder Analysis Set, Immunogenicity All Responder Analysis Set, and Substudy Analysis Set. Some minor clarifications have been added to the previously defined analysis populations.	Clarification and new analysis populations.

Section Number and Name	Description of Change	Brief Rationale
Section 9.4.6: Primary Endpoint Analysis	Details have been provided on the Global/US-specific primary estimand and the corresponding analysis.	Details on the primary estimand and corresponding analysis have been added following interaction with the health authorities.
Section 9.4.7: Secondary Endpoints Analysis	Details have been provided on the updated estimands for intercurrent event handling strategy.	Updates to the secondary endpoint analysis have been made, in order to be consistent with the updated Primary Estimands.
Section 9.4.9: Safety Analyses	Updates have been made to the planned summaries of clinical laboratory tests.	Clarification and new analysis.
Synopsis Section 9.4.10: Other Analyses	Details have been provided on the PK and immunogenicity analyses.	Clarifications to the analysis.
Section 10.5: Appendix 5: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNFα Antagonist Therapies (Infliximab, Adalimumab, or Certolizumab Pegol) or Vedolizumab	Psoriatic rash associated with the use of TNFα antagonist therapies was added to the list of criteria for current or prior intolerance to biologic therapy: **B. Have had a severe psoriatic rash associated with the use of TNFα antagonist therapies (diagnosed by a dermatologist) that required discontinuation of anti-TNFα therapy.**	Psoriatic rash associated with the use of TNFα antagonist therapies is not uncommon, and may be a reason that a physician/patient would desire to start ustekinumab.
Section 10.8.6: Product Quality Complaint Handling (Appendix 8)	The following clarification has been added: **All complaints related to <u>ANY part of the Combination Product</u> must be reported within 1 business day. In the event of public holiday, measures must be taken to ensure reporting no later than calendar day 3.**	This update has been made due to a template change.
Section 10.11: Appendix 11: Clinical Laboratory Tests	The following note has been added: **The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.**	This update has been made due to a template change.
Section 10.14: Appendix 14: Contraceptive and Barrier Guidance	EXAMPLES OF CONTRACEPTIVES ALLOWED **FOR FEMALE PARTICIPANTS** DURING THE STUDY INCLUDE:	It was clarified that the usage of contraceptives will only be allowed for female participants.
Section 10.14: Appendix 14: Contraceptive and Barrier Guidance	• Permanently sterile **(for the purpose of this study)** – Permanent sterilization methods include hysterectomy, bilateral salpingectomy, ~~bilateral tubal occlusion/ligation procedures, and~~ or bilateral oophorectomy. – **Has congenital abnormalities resulting in sterility.**	This update has been made due to a template change.

Section Number and Name	Description of Change	Brief Rationale
Section 10.15.3: Informed Consent Process and Assent Form (Appendix 15)	Each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), must give ~~written~~ consent/assent according to local requirements, after the nature of the study has been fully explained. Assent is required of children capable of understanding the study, typically participants 7 years of age and older, depending on the institutional policies and national/local guidelines. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor or designee and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.	This update has been made due to a template change.
Section 10.15.4: Data Protection (Appendix 15)	The informed consent/assent obtained from the participant, parent(s), or his or her legally acceptable representative~~),~~ includes **information about, and where required per applicable regulations,** explicit consent/assent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent/assent also **provides information to** address~~es~~ the **lawful** transfer of the data to other entities and to other countries. The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete**, or make requests concerning his or her personal data in accordance with applicable data protection laws**. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations. **In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection laws.** Exploratory biomarker, PK, and immunogenicity ~~tests are only for~~ research **is not conducted under standards appropriate for the return of data to participants**. ~~They will not be used for medical care of the participant or to make a diagnosis about~~	This update has been made due to a template change.

Section Number and Name	Description of Change	Brief Rationale
	~~the participant's health.~~ In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.	
Section 10.15.14: Study and Site Start and Closure (Appendix 15)	The first **participant screened** is considered the first act of recruitment and it becomes the study start date.	This update has been made due to a template change.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 5 (21 May 2021)

Overall Rationale for the Amendment: Participants will be required to be up to date with measles and varicella immunizations per local immunization guidelines for immunocompromised participants. Varicella and measles titers are no longer required in the absence of documented infection or immunization/vaccination. This approach is based on the following rationales: 1) the serology titers are not reliable predictors of protective immunity, especially in vaccinated individuals; 2) there is wide variability among laboratory procedures, results, and interpretation of antibody levels across the literature; 3) this approach follows current practice of bringing patients up to date with all vaccinations prior to initiating biologic therapy; and 4) the ustekinumab product label does not require determining the titers before dosing.

In addition, the serum pregnancy test was replaced with a urine pregnancy test to decrease participant burden; liver safety stopping algorithm/follow-up assessments and Coronavirus 2019 (COVID-19) language was updated; and tables were added to the optional Exposure Optimization Substudy, to clarify additional dosing and visit possibilities/activities.

Corrections reflecting these changes, together with other minor clarifications, have been made.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3: Screening Period: Schedule of Activities (SoA), Acceptable evidence of immunity to measles (as representative for MMR administration) and varicella	~~Screening for a~~**A**cceptable evidence of immunity to measles **(as representative for MMR administration) and varicella** **Confirm that the participant is up to date with all immunizations in agreement with current local immunization guidelines for immunosuppressed participants before Week I-0.** ~~Levels of IgG antibodies for measles (as representative for MMR administration) should only be tested if adequate documentation of complete vaccination schedule or HCP verification of previous infection is unavailable. In addition, the investigator must review that the participant is up to date with local vaccine schedule. Where only 1~~	Immunization status was updated to clarify that participants should be up to date with all immunizations per local guidelines. Varicella and measles titers are no longer required in the absence of documented infection or immunization/vaccination based on the following: 1) the serology titers are not reliable predictors of protective immunity, especially in vaccinated individuals; 2) there is wide variability among laboratory procedures, results, and interpretation of antibody levels across the literature; 3) this approach follows current practice

Section Number and Name	Description of Change	Brief Rationale
Section 5.1: Inclusion Criteria #15.2	~~vaccination dose has been given, the level should be checked (Section 5.1, Inclusion Criterion 15).~~ Deleted "Screening for acceptable evidence of immunity to varicella" row. ~~Levels of IgG antibodies for varicella should only be tested if adequate documentation of complete vaccination schedule or HCP verification of previous infection is unavailable. In addition, the investigator must review that the participant is up to date with local vaccine schedule. In regions where 2 varicella vaccines are required but only 1 varicella vaccination dose has been given, the antibody level should be checked (Section 5.1, Exclusion Criterion 15).~~ ~~Participants must have acceptable evidence of immunity to varicella and measles, mumps, and rubella:~~ ~~a. Health care provider (HCP) documentation of vaccination for:~~ ~~1) varicella that includes at least 1 or 2 doses based on country guidelines, AND~~ ~~2) measles, mumps and rubella that includes both doses of each vaccine~~ ~~(See note for participants who have not completed recommended vaccine doses).~~ ~~OR~~ ~~b. HCP documentation of past varicella and/or measles, mumps, and rubella.~~ ~~OR~~ ~~c. In the absence of (a) or (b) above for either immunization, must have positive protective antibody levels to varicella and/or measles prior to the first administration of study intervention. If antibody levels are checked and are negative, the participant must be excluded from the study until positive antibody levels have been demonstrated.~~ **Participants must be up to date with varicella and measles, mumps, and rubella in agreement**	of bringing patients up to date with all vaccinations prior to initiating biologic therapy; and 4) the ustekinumab product label does not require determining the titers before dosing.

Section Number and Name	Description of Change	Brief Rationale
	with current local immunization guidelines for immunosuppressed participants before Week I-0.	
Section 1.3: Screening Period: Schedule of Activities (SoA), Chest radiograph	Chest radiograph should be obtained during the screening period unless one was obtained **6 months prior to the first administration of study intervention** ~~within 6 months before screening~~ and the findings are recorded in the study source documents. Chest radiographs should be reviewed to assess for potential undiagnosed pulmonary pathologies that may include extraintestinal manifestations of IBD, malignancies, and prior or current infection.	Correction made to align with inclusion criteria.
Section 1.3: Screening Period: Schedule of Activities (SoA), Urine pregnancy test Section 5.1: Inclusion Criteria #11.1 Section 8: Study Assessments and Procedures Section 8.2.4: Clinical Safety Laboratory Assessments Section 10.11: Appendix 11: Clinical Laboratory Tests, Other Screening Tests	~~Serum~~ **Urine** pregnancy test Females of childbearing potential must have a negative ~~highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening, and then have a negative~~ urine pregnancy test **at screening and** at Week I-0 prior to study intervention administration. Additional ~~serum or~~ urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study; The total blood volume to be collected from each participant will be approximately ~~144~~**141** mL (or ~~164~~**158** mL for participants from Japan). Pregnancy testing: Females of childbearing potential will undergo ~~a serum β-human chorionic gonadotropin (β-HCG) pregnancy test at screening, and~~ a urine pregnancy test before all study intervention administration visits and at the Week M-44 and safety follow-up visit and, if applicable, at the LOR and early termination visits. ~~Serum (for screening) and u~~**U**rine pregnancy testing for females of childbearing potential only	The serum pregnancy test was replaced with a urine pregnancy test to reduce the volume of blood drawn from participants, to decrease participant burden, and to align with current standards of care.
Section 4.4: End of Study Definition	Participants who complete participation at Week M-44 or 16 weeks after dose adjustment (whichever is longer) will be eligible for inclusion into a separate LTE study**, unless they have reached 18 years of age.** *Long-Term Extension*	Clarification made to eligibility for the LTE study.

Section Number and Name	Description of Change	Brief Rationale
	Participants who complete Week M-44 and who may benefit from further treatment will be eligible to participate in an LTE study in order to continue to receive ustekinumab**, unless they have reached 18 years of age**.	
Section 5.3: Lifestyle Considerations #1.1 Section 5.5: Criteria for Temporarily Delaying Administration of Study Intervention Section 6.1: Study Interventions Administered Section 6.8.3: Vaccinations (Including COVID-19)	Refer to Section 6.8, Concomitant Therapy, for details regarding prohibited and restricted therapy during the study. **It is recommended that participants are up to date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. For study participants who received locally approved (including emergency-use-authorized) COVID-19 vaccine(s) recently prior to study entry, follow applicable local vaccine labeling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.8.3).** **Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.16.** **Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.16.** Added Section 6.8.3. **Vaccinations (Including COVID-19)** **Non-live vaccines are allowed to be administered during this study.** **When considering use of locally approved non-live vaccines (including emergency-use-authorized COVID-19 vaccines) in study participants, follow applicable local vaccine labeling, guidelines, and standards of care for participants receiving immune-targeted therapy.** **For study participants receiving a locally approved (including emergency-use-authorized) COVID-19 vaccine, in order to help identify acute reactions potentially related to the COVID-19 vaccine, it is recommended that, where possible, vaccine and study intervention be administered on different days, separated by as large an interval as is practical within the protocol.**	Information regarding the impact of COVID-19 on clinical studies updated to reflect current guidance.

Section Number and Name	Description of Change	Brief Rationale
Section 5.4: Screen Failures	Completion of screening and **enrollment** ~~randomization~~ procedures must occur within the specified screening window of 6 weeks.	Error corrected.
Section 7.1: Discontinuation of Study Intervention	• The participant is an induction nonresponder **who meets the Early Escape criteria and does not have low exposure or who does not wish to participate in the optional substudy**~~and does not have low exposure~~.	Criterion for discontinuation of study intervention revised per health authority feedback.
Section 7.1.1: Liver Chemistry Stopping Criteria Section 8.2.4: Clinical Safety Laboratory Assessments Section 10.13: Appendix 13: Liver Safety: Suggested Actions and Follow-up Assessments	**Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions in Appendix 13 (Section 10.13) Liver Safety: Suggested Actions and Follow-up Assessments, or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.** ~~The investigator has the discretion to discontinue a participant for any reason, including abnormal liver tests when a participant meets one of the conditions outlined in Appendix 13 (Section 10.13) or for abnormal liver tests that do not meet prespecified stopping criteria if the investigator believes that it is in best interest of the participant.~~ Abnormal liver tests: If laboratory testing for a participant who is enrolled in the study and receiving study intervention reveals an increase of serum aminotransferases (ALT or AST) to ≥~~>~~3 x upper limit of normal (ULN) and an increase of bilirubin to ≥~~>~~2 x ULN, study intervention should be suspended immediately. The liver safety stopping algorithm and follow-up assessments were replaced with updated versions (see Section 10.13).	The liver safety stopping algorithm and follow-up assessments were updated for clarification.
Section 9.3: Populations for Analyses, Table 4, "Population" Column	Full Analysis Set ~~Induction~~ (FAS~~I~~) Full Randomized Analysis Set ~~Maintenance~~ (FASR~~M~~) Full Clinical Responders Analysis Set (FASCR~~M~~) Safety Analysis Set ~~Induction~~ Safety **Randomized Analysis Set** ~~Analysis Set Maintenance~~ Safety **Clinical** Responder Analysis Set ~~Maintenance~~ PK Analysis Set ~~Induction~~ PK **Randomized** Analysis Set ~~Maintenance~~	Edits made to the analysis set definitions to align with the Statistical Analysis Plan.

Section Number and Name	Description of Change	Brief Rationale
	PK **Clinical** Responder Analysis Set ~~Maintenance~~	
Section 9.4.5: Population for Efficacy Analysis	Unless otherwise noted, efficacy analyses will be based on the Full Analysis Set ~~Induction~~ (FAS~~I~~) for induction endpoints through Week I-8 and Full Clinical Responders Analysis Set (FASCR~~M~~) for maintenance endpoints from Weeks M-0 through M-44 (refer to Section 9.3 for definition). For the FASCR~~M~~, participants will be analyzed according to the intervention group to which they were randomized regardless of the intervention they actually received. For selected endpoints beyond Week I-8, analyses will also be conducted based on the FAS~~I~~. Details will be provided in the SAP.	
Section 9.4.6.1: Global Primary Analysis	The global primary analysis population includes all participants who received an administration of study intervention at Week I-0 (FAS~~I~~).	
Section 9.4.6.2: US-Specific Primary Analysis	The US-specific primary analysis population includes all participants who were randomized into the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and received at least 1 administration of study intervention during maintenance (FASCR~~M~~).	
Section 9.4.7: Secondary Endpoints Analyses	The analysis population for secondary endpoints through Week I-8 includes all participants who received one administration of study ~~administration~~**intervention** at Week I-0 (FAS~~I~~). The analysis population for secondary endpoints after Week M-0 includes all participants who were randomized in the maintenance period of the study and were in clinical response to ustekinumab induction therapy at Week I-8 and received at least one administration of study intervention during maintenance (FASCR~~M~~). Secondary endpoints beyond Week I-8 will also be conducted based on the FAS~~I~~.	
Section 9.4.7.1: Additional US-Specific Secondary Endpoint Analyses	Other secondary endpoints during maintenance for all randomized participants who were clinical responders at Week I-8 and who were treated with ustekinumab (combined treatment group) in maintenance (FASCR~~M~~), will be descriptively compared with the proportion (and 95% CI) of adult participants who meet the endpoint at Week M-44 in the CNTO1275CRD3003 study among participants who are clinical responders at Week I-8 (90 mg q8w treatment group).	
Section 9.4.9: Safety Analyses	All safety analyses will be performed using the Safety Analysis Set ~~Induction~~ population for the induction period and the Safety **Randomized**	

Section Number and Name	Description of Change	Brief Rationale
	Analysis Set ~~Maintenance~~ population for the maintenance period (refer to Section 9.3 for definitions).	
Section 10.11: Appendix 11: Clinical Laboratory Tests, Other Screening Tests	• Stool samples (enteric pathogens **including a stool culture and *Clostridioides difficile* test and additional testing [eg, ova and parasites or *Escherichia coli* 0157:H7 assessments]) and** ~~at screening,~~ fecal calprotectin, fecal lactoferrin~~)~~	Updated to allow for local stool testing with sponsor approval.
Section 10.17: Appendix 17: Exposure Optimization Substudy	Study Design Participants who fail to respond by Week M-8 and have low exposure (steady-state 8-week ustekinumab trough concentration <1.4 µg/mL drawn at the Week M-8 visit) are also eligible to enroll in the substudy **(see Table 5 and Table 6)**. During these additional visits, weight and height will be obtained for BSA dosing, vital signs assessed, **an injection-site reaction evaluation carried out,** AEs and concomitant medications reviewed, and a serum ustekinumab trough concentration and **ESR and hematology/chemistry with CRP**~~safety~~ labs obtained. **A urine pregnancy test will also be required before study intervention is administered.** **Table 5** added to the optional Exposure Optimization Substudy to clarify possible participant entry points and visit schedules. **Table 6** added to the optional Exposure Optimization Substudy to provide a Schedule of Activities for substudy visits.	Clarifications made to the additional dosing and visit possibilities and activities required for substudy participants.
Section 5.1: Inclusion Criteria #7.2	Inclusion criterion numbering updated from 7.1 to 7.2.	This criterion was modified in Amendment 4 and the changes were noted in the Amendment 4 Summary of Changes Table; however, the numbering of the criterion was not updated. The numbering was updated here for consistency.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 4 (02 February 2021)

Overall Rationale for the Amendment: An optional Exposure Optimization Substudy for induction nonresponders who have a low steady-state, 8 weeks post-dose ustekinumab concentration, and for induction responders and delayed responders who lose response during

maintenance and have a low steady-state, 8 weeks post-dose ustekinumab concentration has been added.

Section Number And Name	Description of Change	Brief Rationale
Synopsis	Early Escape Criteria **(Induction Nonresponders)** At Week M-8, the following early escape criterion applies: • **Induction nonresponders who do not achieve clinical response based on the PCDAI by Week M-8 (ie, a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30) will have 1 of 2 options:** **1. Must be discontinued from blinded study intervention and then complete a safety follow-up visit approximately 20 weeks after the last administration of study intervention and discontinue the study** **OR** **2. Wait to determine if they have low exposure and would like to participate in the optional substudy:** • **If a participant has not achieved response by Week M-8, and is documented to have low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit), the participant will be eligible for enrollment in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to q4w (See Appendix 17 Section 10.17).** • Induction nonresponders who do not achieve clinical response based on the PCDAI by Week M-8 (ie, a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30) **and do not have low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit)** must be discontinued from study intervention and complete a safety follow-up visit **approximately** 20 weeks after the last administration of study intervention. **Dose Adjustment Criteria:** Beginning at Week M-8 for induction responders and **beginning** at Week M-16 for delayed	Clarification for future treatment options for participants who are considered responders, delayed responders, and/or induction nonresponders have been made.

Section Number And Name	Description of Change	Brief Rationale
	responders (induction nonresponders who are in clinical response at Week M-8), participants who experience LOR ~~will~~ **may** be eligible for a~~n immediate~~ dose adjustment as follows: **Exposure Optimization Substudy** **If a participant has not achieved response by Week M-8, and is documented to have low exposure (defined as an ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit), the participant will be eligible to be enrolled in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to q4w (Appendix 17, Section 10.17).** **If a participant has achieved response by Week M-8 and in the maintenance phase has loss of response at any time after Week M-8 and has low exposure*, he/she may be enrolled in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to q4w (Appendix 17, Section 10.17) (*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).** ~~Participants who lose response and have low ustekinumab exposure can be withdrawn from study participation at the discretion of the investigator~~	
Section 1.2: Schema	***Nonresponders at Week M-8:** **1. If Week M-8 ustekinumab trough concentration is low, option to enter substudy.** • **If choose not to enter substudy, must withdraw study intervention with approximately 20 week safety follow-up.** **2. If Week M-8 ustekinumab trough concentration is not low, must withdraw study intervention with approximately 20 week safety follow-up.** ~~Early escape criterion apply: Induction nonresponders who do not achieve clinical response must be discontinued from study intervention.~~	
Section 1.3: Maintenance Period: Schedule of Activities (SoA)	~~Evaluation for~~ **Assessment for** Early Escape **Criteria and Induction Nonresponders status** ~~At Week M-8, p~~**P**articipants who were not in	

Section Number And Name	Description of Change	Brief Rationale
	clinical response at Week I-8 will be evaluated for clinical response (see Section 4.1.1). ~~Participants who do not achieve clinical response at Week M-8 will discontinue study intervention and have a safety follow-up approximately 20 weeks after their last dose of study intervention.~~ Assessment for Early Escape Criteria and Induction Nonresponders status added to Week M-12.	
Section 2.3.1: Risks for Study Participation	Participants **may be** ~~will~~ discontinue**d from** study intervention if not in clinical response by Week M-8 (Section 7.1) or **if they** need to initiate protocol-prohibited medications (Sections 6.8.2 and 7.1). **Participants not in clinical response with low exposure may be eligible for the optional substudy and eligible for dose adjustment q4w.**	
Section 3.3: Population Definitions	**Exposure Optimization Substudy Participants: Participants who are eligible for and enroll in the Exposure Optimization Substudy with adjustment to q4w interval dosing, including induction nonresponders with low steady-state ustekinumab trough exposure, and participants with LOR and low steady-state trough exposure.**	
Section 4.1: Overall Design	A database lock (DBL) will occur at Week M-44 after all participants have either completed their Week M-44 visit or terminated study participation prior to Week M-44. A second DBL will occur when all participants who are not participating in the LTE have completed their final safety visit (20 weeks after the last administration of study intervention). **A third DBL will be conducted after all participants have completed the Exposure Optimization Substudy, including their final safety visit.** Additional DBLs other than the ones specified above may be performed. No interim analyses are planned.	
Section 4.1.1: Early Escape Criteria (Induction Nonresponders)	Early Escape Criteria **(Induction Nonresponders)** At Week M-8, the following early escape criterion applies: • Induction nonresponder**s** who do~~es~~ not achieve clinical response based on the PCDAI by Week M-8 (ie, a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30) ~~must be discontinued from study intervention (Section 7.1) and complete a safety follow-up visit 20 weeks after the last administration of study medication.~~ **will have 1 of 2 options:**	

Section Number And Name	Description of Change	Brief Rationale
Section 4.1.2: Loss of Response During the Maintenance Period	**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 substudy:** • **If a participant has not achieved response by Week M-8, and is documented to have low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit), the participant will be eligible for enrollment in an optional open-label Exposure Optimization Substudy of minimum 16 weeks duration, with dose interval adjustment to q4w (See Appendix 17 Section 10.17).** • **Induction nonresponders who do not achieve clinical response based on the PCDAI by Week M-8 (ie, a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30) and do not have low exposure (defined as a ustekinumab trough level <1.4 µg/mL from blood sample drawn at the Week M-8 visit) must be discontinued from study intervention and complete a safety follow-up visit approximately 20 weeks after the last administration of study intervention.** **Exposure Optimization Substudy (**Loss of Response and Low Exposure During the Maintenance Period**)** ~~Participants who lose response and have low ustekinumab exposure can be withdrawn from study participation at the discretion of the investigator.~~ **Participants who lose response during the maintenance period of the main study and have a trough serum ustekinumab concentration of <1.4 µg/mL during the maintenance period (M-8 or M-32) will be eligible to enroll in this optional, open-label q4w substudy (Appendix 17 Section 10.17). Loss of response is defined in the main protocol. All eligible participants must sign**	

Section Number And Name	Description of Change	Brief Rationale
	informed consent/assent (based on intuitional requirements) prior to entry into the substudy. Added note to Figure 2: **The following participants are eligible for enrolling in the Exposure Optimization Substudy:** **-Induction nonresponders at Week M-8 with low 8-week steady-state ustekinumab trough concentration.** **-Those with LOR at Week M-8 or later with low 8-week steady-state ustekinumab trough concentration (at Week M-8 or M-32).**	
Section 4.1.3: Dose Adjustment During the Maintenance Period	Beginning at Week M-8 for induction responders and beginning at Week M-16 for delayed responders (induction nonresponders who are in clinical response at Week M-8), participants who experience LOR (Section 4.1.2 and Figure 2) may be eligible for ~~an immediate~~ **a** dose adjustment as follows. 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 the LOR occurs between their scheduled study intervention injections in order to maintain study blinding. Participants who experience LOR will proceed to visits every 4 weeks until clinical response or sPCDAI clinical response is achieved. The ~~first~~ LOR visit **and all subsequent visits after LOR** must be **conducted** at the study site~~, and subsequent LOR visits may be conducted at the study clinic or remotely, at the investigator's clinical discretion~~. Participants who ~~lose response~~ **experience LOR** and have low ustekinumab exposure ~~can~~ **may** be **eligible to participate in an optional substudy (see Appendix 17 Section 10.17) or** be withdrawn from study participation at the discretion of the investigator.	
Section 4.1.4: Rescue Medication	If determined to be medically appropriate in the judgment of the investigator, dose adjustment **or entry into q4w substudy** should precede institution	

Section Number And Name	Description of Change	Brief Rationale
Section 4.1.5: Long-Term Extension Section 4.2: Scientific Rationale for Study Design	of Crohn's disease-specific therapies in participants meeting study-specific LOR criteria. **If in response, P**~~P~~participants ~~who complete participation at Week M-44 may be eligible to enter an LTE and continue to receive SC ustekinumab at the dose they were receiving on completion of the maintenance period~~ **may be eligible to enter an LTE trial after completion of the M-44 visit, or completion of 16 weeks of follow-up post LOR dose adjustment or substudy entry (whichever is longer).** Details **of the LTE** will be provided in a separate protocol, including separate parental consent and child assent form(s). ***Maintenance Phase*** Participants who qualify for early escape~~will discontinue both study intervention and placebo~~ **at Week M-8 have the option to be discontinued from study intervention and complete a safety follow-up visit approximately 20 weeks after the last administration of study intervention.** **Alternatively, participants may remain in the study until the results from the M-8 ustekinumab trough concentration level become available.** ***Exposure Optimization Substudy*** **Blinding is not applicable in the optional Exposure Optimization Substudy.** • **If the ustekinumab trough concentration is <1.4 µg/mL, the participant will be eligible to enroll in the optional q4w Exposure Optimization Substudy (Appendix 17; Section 10.17)** **Participants who choose not to enroll in the q4w Exposure Optimization Substudy must be discontinued from study intervention (Section 7.1) and complete a safety follow-up visit approximately 20 weeks after the last administration of the intervention.** Participants who experience LOR will no longer receive placebo injections but will continue to receive active study intervention q8w. **Participants who experience LOR with low exposure opting to participate in the Exposure Optimization Substudy will no longer receive placebo injections but will continue to receive active study intervention q4w.**	

Section Number And Name	Description of Change	Brief Rationale
Section 4.2.2: Study-Specific Ethical Design Considerations	Further, dose adjustment from q12w to q8w **(or q4w with low exposure for the Exposure Optimization Substudy)** ~~has~~ also **has to** be integrated for any participants with LOR.	
Section 4.4: End of Study Definition	The end of study is considered as the last scheduled study assessment as shown in the Schedule of Activities for the last participant in the study. The expected duration of the study is 74 weeks. This includes 6 weeks of screening, 48 weeks of treatment (8 weeks in the induction period followed by 40 weeks in the maintenance period) with study intervention and 20 weeks of safety follow-up after the last study intervention administration. Participants who complete participation at Week M-44 **or 16 weeks after dose adjustment (whichever is longer)** will be eligible for inclusion into a separate LTE study. If participants do not participate in the LTE study, they will continue safety follow-up for approximately 20 weeks after the last administration of study intervention. The study will end when the last participant has either completed Week M-44 **or 16 weeks after dose adjustment (whichever is longer)** and transitioned into the LTE study or completed their final safety visit (approximately 20 weeks after the last administration of study intervention), or terminated study participation, whichever is later. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.	
Section 6.1.3.2: Maintenance Period	Further information on the study interventions is provided in Section 6.1.2. Ustekinumab doses from Week M-0 through Week M-40 will be based on the participants' weight and height obtained at each visit or based on participant weight and height at the last on-site study 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 (see Section 7.1). **For induction nonresponders who do not achieve clinical response based on the PCDAI by Week M-8 (ie, a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30), the Week M-8 ustekinumab trough concentration will determine eligibility for the Exposure Optimization Substudy (Appendix 17,**	

Section Number And Name	Description of Change	Brief Rationale
Section 7.1: Discontinuation of Study Intervention Section 9.4.4: Tertiary/Exploratory Endpoints Section 9.4.6: Primary Endpoint Analysis Section 9.4.7: Secondary Endpoints Analyses	**Section 10.17), or requirement for study withdrawal.** Beginning at Week M-8 for induction responders and beginning at Week M-16 for delayed responders (induction nonresponders who are in clinical response at Week M-8), participants who experience LOR (Section 4.1.2) will be ~~immediately~~ eligible for dose adjustment as follows: ~~Participants who lose response and have low ustekinumab exposure can be withdrawn from study participation at the discretion of the investigator.~~ **Participants who lose response and have low ustekinumab exposure may be eligible to participate in an optional substudy (see Appendix 17 Section 10.17) or be withdrawn from study participation at the discretion of the investigator**. **The participant is an induction nonresponder and does not have low exposure.** ~~Induction nonresponders who meet the Early Escape criteria.~~ ~~A~~ **The** participant ~~who~~ experiences LOR during the maintenance period of the study ~~who~~ **and does not achieve clinical response** after 16 weeks from dose adjustment.~~ does not achieve clinical response.~~ **The participant experiences LOR and low exposure leading to substudy entry and does not achieve clinical response after 16 weeks after substudy entry.** Change from baseline in IMPACT-III values ~~over time through~~ **at** Week M-44. In addition, during the maintenance period, participants who use rescue medication (initiation or increase above baseline) for treatment of LOR**, including those who enter the Exposure Optimization Substudy,** will also be considered a treatment failure. Participants who have dose adjustment are considered treatment failures. In addition, participants who do not return for evaluation or have insufficient data to calculate their PCDAI score at Week I-8 will be considered to not have achieved clinical remission (based on the PCDAI score) at Week I-8.	

Section Number And Name	Description of Change	Brief Rationale
	Treatment failure rules will be applied as specified for the primary endpoint analysis. Participants who use rescue medication (initiation or increase above baseline) for a LOR **or LOR and low exposure during maintenance** after Week I-8 will also be considered a treatment failure ~~for~~ **at Week M-44** ~~endpoints after Week I-8~~ (detailed in the SAP). In addition, participants who dose adjust during maintenance **or enter the Exposure Optimization Substudy** will be considered treatment failures.	
Section 1.3: Screening Period: Schedule of Activities (SoA) Section 5.1: Inclusion criteria #17.1	Stool for enteric pathogens Stool studies for enteric pathogens including a stool culture and ~~*Clostridium difficile*~~ ***Clostridioides difficile*** **(formerly known as *Clostridium difficile*)** test (*C. difficile* toxin/GDH with Reflex to PCR testing) will be performed by the central laboratory. Have negative stool results for enteric pathogens. Stool studies must include a stool culture and ~~*Clostridium difficile*~~ ***Clostridioides difficile*** **(formerly known as *Clostridium difficile*)** toxin assay (*C. difficile* toxin/**glutamate dehydrogenase [**GDH**]** with Reflex to polymerase chain reaction testing).	Clarification on the name of the toxin has been made.
Section 1.3: Screening Period: Schedule of Activities (SoA)	Confirmation of Crohn's disease diagnosis Confirmation of Crohn's disease or fistulizing Crohn's disease ~~of at least 3 months duration,~~ with active colitis, ileitis, or ileocolitis, confirmed at any time in the past by endoscopy and histology.	Modified to align with change to inclusion criterion.
Section 1.3: Induction Period: Schedule of Activities (SoA)	Study Procedure-Induction ~~If discontinuation of study participation occurs before or at Week I-8, early termination visit assessments should be completed.~~	Clarification of Study Procedure-Induction has been made.
Section 1.3: Maintenance Period: Schedule of Activities (SoA)	Notes for Study Week Name ~~Visit dates are based on the participant's Week I-0 visit date; except for Week M-0, during the maintenance period visit windows are ±10 days.~~ **Maintenance visit dates are based on the participant's M-0 visit date ±10 days.** **Footnote "c" added to Study Week M-0:** **c. Week M-0 assessments should be completed at Week I-8 visit; participants may be able to**	Clarification of visit window has been made.

Section Number And Name	Description of Change	Brief Rationale
Section 6.4: Study Intervention Compliance	**complete the Week M-0 assessments within 4 days after Week I-8. At the investigator's discretion, the window may be extended up to 8 days to allow appropriate treatment of and/or recovery from nonserious infections. All other maintenance period visit windows are ±10 days.** From Week I-3 through Week I-8, all visits will occur within a range of ±4 days of the scheduled visit. From Week M-4 through Week M-44, it is expected that all visits will occur within a range of ±10 days of the scheduled visit (Section 1.3). Any visits outside of these ranges should be discussed with the sponsor. If a **maintenance** study visit occurs outside the specified visit window, the participant should then resume his or her normal dose schedule relative to the Week ~~I~~**M**-0 visit as soon as possible. After Week M-44, the follow-up safety visit should occur approximately 20 weeks after the last administration of study intervention (within ±10 days of the scheduled visit). Any out of range visit should be documented in the eCRF.	
Section 1.3: Maintenance Period Schedule of Activities (SoA)	Notes for Study Visit Location **Home visits may occur at home at the discretion of the primary investigator (PI), caregiver, or participant, and upon completion of training. If it is determined by the PI, caregiver, or participant that they will not participate in home visits, the caregiver and participant will come to the clinic study site to complete the visit.** ~~**Study intervention administration may occur at home or at the Study Site at the discretion of the PI.**~~	Clarification of Study Visit Location has been made.
Section 1.3: Maintenance Period: Schedule of Activities (SoA)	Study Procedure – Maintenance If discontinuation of study intervention administration occurs after Week M-0 but before or at Week M-8, the ~~Week M-8~~ **early termination visit** assessments should be completed, and a safety follow-up visit should be scheduled approximately 20 weeks ±10 days after the last study intervention administration. ~~Participants who are entering the LTE at Week M-44 should complete the Week M-44 activities in this table and then follow the LTE study protocol Schedule of Activities for continued study intervention administration and other protocol requirements.~~ Participants who do not enter the LTE ~~at Week M-44~~ should complete a safety follow-up	Clarification of Study Procedure – Maintenance has been made.

Section Number And Name	Description of Change	Brief Rationale
	visit approximately 20 weeks after their last study intervention administration.	
Section 1.3: Maintenance Period: Schedule of Activities (SoA)	Urine pregnancy test added to Loss of Response.	Clarification has been made that urine pregnancy test should be carried out prior to administration of study intervention during a loss of response visit.
Section 2.2: Background	In the maintenance study of adult participants with Crohn's disease (IM-UNITI [CNTO1275CRD3003]), following maintenance treatment with ustekinumab 90 mg SC q8w or q12w, steady state was reached at approximately 8 weeks for participants receiving ustekinumab q8w, or at 12 weeks for participants receiving ustekinumab q12w maintenance doses. Median steady-state trough serum ustekinumab concentrations over time in the ustekinumab q8w group (1.97 µg/mL to 2.24 µg/mL) were approximately 3-fold the concentrations in the ustekinumab q12w group (0.61 µg/mL to 0.76 µg/mL). Following maintenance doses of ustekinumab 90 mg SC q8w or q12w, serum ustekinumab concentrations were sustained through Week 44 in almost all participants, with a smaller proportion of participants with undetectable **ustekinumab** trough concentrations over time in the 90 mg q8w group (3.2% to 4.9%) compared with those in the 90 mg q12w group (11.1% to 19.1%). The median ustekinumab concentration in participants in the placebo group was below detectable levels by Week 16.	Clarification of trough concentration has been made throughout protocol.
Section 3.1: Global Objectives, Endpoints, and Hypothesis Section 3.2: US-specific Objectives, Endpoints, and Hypothesis Section 8.1.5: IMPACT-III	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. 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. 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~~, I-8,~~ and M-44.	Discrepancy regarding IMPACT-III assessment timing corrected to provide consistency with Schedule of Activities.
Section 5.1: Inclusion Criteria Criterion #4.1 Criterion #5.1	Have Crohn's disease or fistulizing Crohn's disease ~~of at least 3 months duration,~~ with active colitis, ileitis, or ileocolitis, confirmed at any time in the past by endoscopy and histology.	For Inclusion Criterion #4, the requirement for a minimum disease duration since diagnosis prior to randomization has been removed to facilitate enrollment. Criterion #5 was modified to include a score-based endoscopy-based inclusion

Section Number And Name	Description of Change	Brief Rationale
	i. Must have moderately to severely active Crohn's disease (as defined by a baseline PCDAI score >30)**.** ~~AND at least one of the following:~~ **ii. Have ileocolonoscopy with evidence of active Crohn's disease defined as presence of ulceration (which is equal to SES-CD score ≥3) during screening into this study*** ***If unable to evaluate ulceration due to stricture or inadequate bowel preparation, at least one of the following criteria may instead be applied:** a. An abnormal CRP (>0.3 mg/dL or 3.0 mg/L at screening) OR b. Fecal calprotectin of ≥250 mg/kg or ≥250 µg/g at screening ~~OR~~ ~~c. Ileocolonoscopy with evidence of active Crohn's disease (defined as ulcerations in the ileum and/or colon) during screening into this study including at the baseline visit.~~	criterion. Minor clarifications were made to additional inclusion criteria.
Criterion #7.1d	If receiving oral ~~or rectal~~ 5-ASA compounds, the dose must have been stable for at least 2 weeks prior to Week I-0.	
Criterion #7.1h	If receiving a single antibiotic as a primary treatment of Crohn's disease, the dos**age of the medication/antibiotic** must have been stable for at least 2 weeks prior to Week I-0. **Participants cannot be receiving more than one antibiotic for the primary treatment of Crohn's disease.**	
Section 5.2: Exclusion Criteria Criterion #14.1	Received, or are expected to receive, any live virus or bacterial vaccination within 4 weeks prior to the first administration of study intervention. **Receipt of a live SARS-CoV-2 vaccine (against the virus that causes Coronavirus Disease 2019 [COVID-19]) is *not* automatically an exclusion criterion and must be discussed with the medical monitor.**	Clarifications to exclusion criteria have been made.
Criterion #28.1	Received an investigational intervention including any investigational vaccines or used an invasive investigational medical device within 3 months before the planned first dose of study intervention	

Section Number And Name	Description of Change	Brief Rationale
	or is currently enrolled in an investigational study. **Receipt of an investigational vaccine for COVID-19 is not an automatic exclusion criterion; discuss with medical monitor.**	
Section 6.1: Study Interventions Administered	Intravenous study intervention (including the flush) should be administered over a period of not less than 1 hour, and not more than 2 hours. The infusion (including the flush) should be completed within ~~6~~ **8** hours of preparation of the study ~~medication~~ **intervention**.	Edited for consistency with Instructions for Use document.
Section 7.1: Discontinuation of Study Intervention	The participant ~~has~~ **experiences** a serious adverse **event**~~reaction that is~~ related to **either** an injection **or infusion**~~, during or within one hour of infusion,~~ including **severe hypersensitivity reactions.** ~~an injection site reaction or infusion reaction, resulting in bronchospasm with wheezing and/or dyspnea that requires ventilatory support, OR that results in symptomatic hypotension with a decrease in systolic blood pressure <90 mm Hg for children >10 years old or decrease in baseline systolic blood pressure of 30% for children <10 years of age.~~ **Discontinuation of ustekinumab administration must also be considered for participants who develop a nonserious but severe infusion or injection-site reaction.** The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) ~~occurring 1 to 14 days~~ after an injection of study intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache. The participant has a malignancy including squamous cell skin cancer. ~~Consideration may be given to allowing participants who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study intervention.~~	Clarifications made to Discontinuation of Study Intervention criteria.
Section 8: Study Assessments and Procedures	For at-home visits, blood draws for serum concentration and antibodies to ustekinumab and clinical laboratory tests will be performed by a home health care aide, study-site personnel, or other designate. **The study sites will arrange for transfer of blood samples to the study site's laboratory for further processing and shipping to the central laboratory. Study sample handling and processing instructions will be provided in a home study visit guidance document.**	More detail has been provided regarding collection and handling of samples per the FDA's request.

Section Number And Name	Description of Change	Brief Rationale
Section 8: Study Assessments and Procedures	~~Electronic Data Capture (eDC) Manual~~	Repetitive bullet deleted.
Section 8: Study Assessments and Procedures	~~National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5 for laboratory assessments~~	Item deleted from supply list.
Section 8.1.8: Global Histology Activity Score	The GHAS described by D'Haens et al[9] is a numerical histologic disease activity index which consists of 8 items that assess the following: epithelial damage, architectural changes, infiltration of neutrophils and mononuclear cells in the lamina propria, neutrophils in the epithelium, erosions/ulcers, granulomas, and the number of biopsy specimens affected. The GHAS is simplified for use in clinical trials and accounts for bowel segments, which is necessary to measure global response to therapy in Crohn's disease. **At the discretion of the PI if an additional endoscope and biopsy is required this will be reviewed and approved by the medical monitor on a case-by-case basis.**	Clarification has been made regarding additional endoscope and biopsy.
Appendix 10.13	Figure in Appendix 10.13 updated. 1. **Contact the medical monitor.** Cascading numbers in section updated accordingly.	Clarifications have been made to figure to provide additional instructions for clinicians.
Appendix 10.17	An exploratory Exposure Optimization Substudy has been added.	An optional Exposure Optimization Substudy for those that lose response during the maintenance phase has been added.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (21 October 2020)

Overall Rationale for the Amendment: The study design was changed per Food and Drug Administration's (FDA) recommendation. For participants ≥40 kg, dosing will be based on a weight-tiered induction dose which is the same as the approved adult dosing regimen. For participants <40 kg, dosing will be body surface area (BSA)-adjusted.

Section number and Name	Description of Change	Brief Rationale
Section 4.3: Justification for Dose	~~Results from the studies of biologics such as anti-TNFα monoclonal antibodies (mAbs, eg, infliximab, golimumab, adalimumab), ustekinumab, and vedolizumab in Crohn's disease have shown that the PK (after appropriate adjustment for body size differences) and exposure response relationships of these agents are similar between pediatric and adult patients.~~ Previous studies of the anti-tumor necrosis factor (TNF) monoclonal antibodies (mAbs) infliximab, golimumab, and adalimumab, and the anti-interleukin (IL)12/IL23	The revisions of these paragraphs were inadvertently omitted in Amendment 2

Section number and Name	Description of Change	Brief Rationale
	mAb ustekinumab in pediatric participants with Crohn's disease have demonstrated similar exposure-response (E-R) relationships in children and adults. The PK and exposure-response relationship of ustekinumab in adult participants with Crohn's disease have been characterized using data from several late phase clinical studies including 2 Phase 3 induction (CNTO1275CRD3001 and CNTO1275CRD3002) and 1 maintenance (CNTO1275CRD3003) clinical ~~studies~~ **study**. Based on the data from these studies, a posology consisting of a weight-tiered induction dose approximating 6 mg/kg ustekinumab IV (ie, 260 mg [weight ≤55 kg], or 390 mg [weight >55 kg and ≤85 kg], or 520 mg [weight >85 kg]), followed by a maintenance dose of 90 mg SC given every 8 weeks (or every 12 weeks in some regions) **has been shown to be effective for the treatment of Crohn's disease in adult participants and** is approved for the treatment of Crohn's disease in adult patients. For induction treatment in this Phase 3 pediatric Crohn's disease study, a single dose of either ~~390 mg IV ustekinumab for pediatric participants with body weight ≥40 kg or BSA-adjusted dose of 250 mg/m^2 in pediatric participants with body weight <40 kg will be evaluated~~ **a BSA-adjusted dose of 250 mg/m^2 in pediatric participants with body weight <40 kg, 260 mg IV for participants with ≥40 to ≤55 kg body weight, 390 mg IV for participants with >55 to ≤85 kg body weight, or 520 mg IV for participants with >85 kg body weight, will be evaluated.** The choice of a single induction dose is supported by the positive E-R relationships and higher magnitude of benefit with the weight-ranged based ~6 mg/kg dose relative to the lower fixed 130 mg dose in adult Crohn's disease in the absence of a dose-related safety signal. ~~Of note, while body weight range based IV induction doses (260 mg for body weight ≤55 kg, 390 mg for body weight >55 to ≤85 kg, and 520 mg for body weight >85 kg) are approved in Crohn's disease, only the 390 mg dose was selected for pediatric participants in the present study in order to ensure exposure matching when ustekinumab exposure in pediatric participants is compared with those in the typical adult, with the knowledge that the dose in the typical adult with Crohn's disease corresponds to the 390 mg IV induction dose. In addition, the choice of the 390 mg dose as a~~	

Section number and Name	Description of Change	Brief Rationale
	~~reference target simplifies the posology of ustekinumab in pediatric patients, especially considering that the tiered body weight range based dosing in adults does not lead to uniform ustekinumab exposure across the adult body weight range. Specifically, the systemic ustekinumab exposure in adult patients with Crohn's disease receiving the 260 mg IV dose with body weight <55 kg was lower than those in patients receiving the ustekinumab 390 mg with body weights 55 to <85 kg, or 520 mg with body weight >85 kg. In addition, based on data from the adult Crohn's disease induction studies, increased efficacy with the 520 mg IV dose is not anticipated in pediatric participants >85 kg. Furthermore, no pediatric participant in the CNTO1275CRD1001 study had a body weight >85 kg (the highest body weight was approximately 70 kg). Based on these reasons, the sponsor considers the choice of a fixed 390 mg induction dose in pediatric participants ≥40 kg (instead of the body weight range based doses in adults) reasonable for evaluation in this Phase 3 pediatric Crohn's disease study.~~	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 2 14 October 2020

Overall Rationale for the Amendment: The study design was changed per Food and Drug Administration's (FDA) recommendation. For participants ≥40 kg, dosing will be based on a weight-tiered induction dose which is the same as the approved adult dosing regimen. For participants <40 kg, dosing will be body surface area (BSA)-adjusted.

Section number and Name	Description of Change	Brief Rationale
Synopsis: Intervention Groups and Duration Section 4.1: Overall Design Section 4.3: Justification of Dose Section 6.1.3.1: Induction Period	**All participants will receive a single open-label IV administration of ustekinumab at Week I-0. For participants ≥40 kg, dosing will be based on a weight-tiered induction dose which is the same as the approved adult dosing regimen. For participants <40 kg, dosing will be body surface area (BSA)-adjusted.** **For participants with body weight <40 kg:** • **250 mg/m^2 IV** **For participants with body weight ≥40 kg:** • **260 mg IV for participants with ≥40 kg to ≤55 kg body weight** • **390 mg IV for participants with >55 kg to ≤85 kg body weight**	Changes were made to the dosing regimen for participants with body weight ≥40 kg, to match the posology in Study CNTO1275UCO3001 (adult UC study) per FDA recommendations.

Section number and Name	Description of Change	Brief Rationale
Section 6.7: Treatment of Overdose	• **520 mg IV for participants with >85 kg body weight** For this study, any dose of ustekinumab greater than the highest dose at a single dosing visit **(**~~exceeding 390 mg IV for participants with ≥40 kg body weight or 250 mg/m^2 IV for participants with <40 kg body weight or exceeding 90 mg SC for participants with ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight~~ **exceeding 250 mg/m^2 IV for participants with <40 kg body weight, 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, and 520 mg IV for participants with >85 kg body weight or exceeding 90 mg SC for participants with ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight)** will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.	
Footnote in Figure 1	~~Intravenous Ustekinumab: 390 mg for participants with body weight≥40 kg; 250 mg/m2 for participants with <40 kg body weight~~ **Intravenous ustekinumab: 250 mg/m^2 IV for participants with <40 kg body weight; 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.**	
Figures 3 and 4	Figures updated	
Schedule of Activities: Table 3 (Collect and review CDAI electronic diary)	Diary tools will be provided to all participants to complete for the 7 days prior to Weeks M-8, ~~M-16~~, and M-44 and for LOR and early termination visits. Diary completion is not mandatory for unscheduled LOR and early termination participants.	Week M-16 was erroneously listed.
Schedule of Activities: Table 3 (sPCDAI score)	The sPCDAI may be used if laboratory test values are not available including for those participants who lose response. ~~An abdominal examination will not be conducted during home visits. The sPCDAI score will be computed without the abdominal exam item. The sPCDAI may be used if laboratory test values are not available including for those participants who lose response~~. During home visits an abdominal examination will not be conducted and will be computed without the abdominal examination item.	Clarification of abdominal examinations during home visits has been made.

Section number and Name	Description of Change	Brief Rationale
Section 3.1: Global Objectives, Endpoints and Hypothesis: Global Objectives (Other) Section 9.4.4: Tertiary/Exploratory Endpoints (#5)	25-hydroxyvitamin D, methylmalonic acid (MMA), and iron **at Weeks M-4 and M-44.** The change from baseline in 25-hydroxyvitamin D, MMA, and iron at Weeks M-4 and ~~M-40~~ **M-44**.	Clarification of time points of evaluation have been made.
Synopsis Section 4.1.2: Loss of Response During the Maintenance Period Section 4.1.3: Dose Adjustment During the Maintenance Period Section 6.1.3.2: Maintenance Period Figure 2	**Participants who lose response and have low ustekinumab exposure can be withdrawn from study participation at the discretion of the investigator** Participants who have a loss of response at or any time after M-8 (induction responders) or M-16 (delayed responders) ~~will~~ **may** move to a q8w schedule without placebo injections.	Clarification for future treatment options for participants who are considered nonresponders and/or delayed responders have been made.
Section 1.3: Table 1 Schedule of Activities: QuantiFERON®-TB test (or T-Spot®)/Tuberculin skin test Section 5.1: Inclusion criterion #14d	All participants will undergo QuantiFERON®-TB testing. The results of the local T-Spot® test will be acceptable in place of the QuantiFERON-TB test in regions where the T-Spot test is ~~mandated~~ **considered standard of care recommended** by local health authorities. TB skin testing (Appendix 10, Section 10.10) will be required in countries where the QuantiFERON-TB test is not registered/approved or if the tuberculin skin test is mandated by local health authorities. **Tuberculosis ~~Screening and Vaccination~~ and Immunization History** Within 6 weeks prior to the first administration of study intervention, have a negative QuantiFERON®-TB (or T-Spot®) test result. Within 6 weeks, a negative tuberculin skin test prior to the first administration of study intervention is additionally required if the QuantiFERON-TB (or T-Spot) test is not approved or registered in that country or the alternative test is mandated by local health authorities (Appendix 10 [Section 10.10]). The results of the T-Spot test will be acceptable in place of the QuantiFERON-TB test in regions where the T-Spot is ~~mandated~~ **considered standard of care recommended** by local health authorities.	Clarification regarding the use of T-Spot TB test instead of the QuantiFERON®-TB test has been made.

Section number and Name	Description of Change	Brief Rationale
Section 1.3: Schedule of Activities (Screening): Table 1 Ileocolonoscopy	Ileocolonoscopy should be performed within ~~2~~ **approximately 3 weeks prior to** the administration of study intervention at Week I-0. A SES-CD **and a SEMA-CD** score will be assessed by **a central endoscopist** ~~the investigator (ie, local endoscopist)~~. All study ileocolonoscopies must be performed with study software to permit central review of the video of the ileocolonoscopy and scoring using the criteria of the SES-CD and the SEMA-CD (Section 8.1.7).	The timing for ileocolonoscopy and biopsy samples has been changed to within approximately 3 weeks before the Weeks I-0, M-8, and M-44 visits so the preparation of the bowel and recovery of the participant of this procedure does not interfere with the CDAI and PCDAI results.
Schedule of Activities: (Screening): Table 1 Ileocolonic Biopsy (RNA, histology)	The screening biopsy samples for histology and RNA analyses will be collected during the screening ileocolonoscopy performed within ~~2~~ **approximately 3** weeks before the first study intervention administration.	
Schedule of Activities (maintenance) Table 3 Ileocolonoscopy	Ileocolonoscopy should be performed within ~~2~~ **approximately 3 weeks prior** to the Week M-8 visit and within ~~2~~ **approximately 3** weeks **prior to** the Week M-44 visit. For participants in early termination prior to Week M-44, an ileocolonoscopy is recommended but not required.	
Section 8.1.7: Ileocolonoscopy	To explore the potential utility of endoscopic improvement endpoints in children, 3 ileocolonoscopies will be performed, one at screening, another at Week M-8, and one at Week M-44 ~~within 2~~ **approximately 3** weeks **prior** ~~of~~ **to** these timepoints per the Schedule of Activities.	
Schedule of Activities: (Screening): Table 1 Study Procedure	Screening should occur within 6 weeks before the Week I-0 visit. Blood sampling in participants with a body weight ≤20 kg must be divided between visits during the screening period and other visits as required for **countries** outside of Japan. Blood sampling in participants in Japan weighing <~~25~~ **26** kg must be divided between visits during the screening period and other visits as required. Contact the sponsor for details of the recommended sampling sequence.	The weight has been updated due to a correction of blood volume taken at screening.
Section 1.1: Synopsis	**Loss of Response** All participants randomized into the maintenance period will be assessed for loss of response (LOR) based on PCDAI or short	Clarification of the definition of delayed responders.

Section number and Name	Description of Change	Brief Rationale
Section 4.1.2: Loss of Response During the Maintenance Period Section 6.8.1: Crohn's Disease-Specific Allowed Medications/Therapies	pediatric Crohn's Disease Activity Index (sPCDAI) score. For the purpose of this protocol, participants in the maintenance period who meet the following criteria will be considered to have LOR: 1. An increase in the PCDAI >12.5 above the reference PCDAI score, or an increase in the sPCDAI ≥10 above the reference sPCDAI score, at 2 consecutive visits at least 7 days apart. The reference PCDAI is Week M-0 for induction responders and Week M-8 for delayed **induction** responders. For participants receiving 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 **induction** responders as follows.	
Section 2: Introduction	Ustekinumab (subcutaneous [SC] formulation) has been approved for the treatment of psoriasis in adults, adolescents, ~~and children ≥6 years of age~~ **and pediatric patients 6 years and older with moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy,** and for psoriatic arthritis (PsA) in adults. Ustekinumab has also been approved for the treatment of Crohn's disease and ulcerative colitis in adults using intravenous (IV) induction dosing followed by SC maintenance dosing.	Clarification of the age and state of psoriasis in pediatric patients have been made.
Section 5.1 Inclusion Criteria #10	Not sexually active, practicing abstinence, or using a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until ~~6 months~~ **16 weeks** after the last dose – the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in	The use of contraception has been changed from 6 months to 16 weeks to align the washout period with 5 x half-life for the study intervention.

Section number and Name	Description of Change	Brief Rationale
#12 #13 Section 5.3 Lifestyles Considerations #4 #6	Appendix 14 Contraceptive and Barrier Guidance (Section 10.14). Females of childbearing potential must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a minimum of ~~6 months~~ **16 weeks** after receiving the last dose of study intervention. During the study and for a minimum of ~~6 months~~ **16 weeks** after receiving the last dose of study intervention, a male: a. Who is sexually active with a female of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) b. Who is sexually active with a female who is pregnant must use a condom c. Must agree not to donate sperm. If sexually active, females must remain on a highly effective method of birth control during the study and for ~~6 months~~ **16 weeks** after receiving the last administration of study intervention. Must agree not to plan a pregnancy or father a child within ~~6 months~~ **16 weeks** following the last administration of study intervention.	
Section 5.1: Inclusion Criteria #3a	Medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel including liver enzymes, other specific tests, ~~blood coagulation~~, or hematology are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and acknowledged by the investigator.	
Section 5.1: Inclusion Criteria #7b	If receiving oral corticosteroids other than budesonide or beclomethasone dipropionate, the dose must be ≤1.5 mg/kg/day prednisone (or its equivalent) up to 40 mg/day prednisone and	Clarifications on the use of prednisone have been made.

Section number and Name	Description of Change	Brief Rationale
#7c	must have been stable **or discontinued** for at least 2 weeks prior to Week I-0. If ~~oral,~~ IV, or rectal corticosteroids have recently been discontinued, they must have been stopped for at least 2 weeks prior to Week I-0.	
Section 6.1.2.1: Induction Period	**For participants with body weight ≥40 kg:** ~~3~~ **multiple** vials ~~(ie, 390 mg)~~ of ustekinumab 5 mg/mL LIV, described above, will be diluted to an appropriate concentration using an appropriate diluent for IV administration.	~~Clarification on the formulation has been made.~~ Clarification on the supply of study intervention for participants with body weight ≥40 kg has been made.
Section 8: Study Assessments and Procedures (Overview) Section 8.4.1: Evaluations	The total blood volume to be collected from each participant will be approximately ~~140~~ **144** mL (or ~~158~~ **164** mL for participants in Japan). Venous blood samples of approximately ~~65~~ **70** mL over the course of the study, will be collected for measurement of serum concentrations of ustekinumab and analytes at the time points indicated in the Schedule of Activities	The total blood volume to be collected from each participant has been updated to correctly reflect the most current blood sampling schedule.
Section 9.4.6: Primary Endpoint Analysis	In addition, during the maintenance period, participants who use rescue medication (initiation or increase above baseline) for treatment of LOR will also be considered a treatment failure. Participants who have dose adjustment are considered treatment failures. **In addition, participants who do not return for evaluation or have insufficient data to calculate their PCDAI score at Week I-8 will be considered to not have achieved clinical remission (based on the PCDAI score) at Week I-8.**	Clarification of definition of clinical remission has been made.
Section 9.6: Data Monitoring Committee ~~or Other Review Board~~	The same DMC, consisting of at least one medical expert in the relevant therapeutic area and at least one statistician, will be used for ~~this ustekinumab pediatric Crohn's disease study and other ustekinumab studies in pediatric participants~~ **studies CNTO1275PUC3001 and CNTO1275CRD3004** and will monitor safety data on an ongoing basis.	The Title of the Section has been revised. Clarifications regarding the studies to be monitored by the DMC have been made.
Section 10.3 Appendix 3: Crohn's Disease Activity Index (CDAI)	Appendix 3 has been replaced with an updated version	An updated version of the CDAI to be used in the study has been included.
Section 10.11: Appendix 11 Clinical Laboratory	**Erythrocyte sedimentation rate (ESR)*** ***ESR may be performed by a local lab**	An ESR evaluation has been added to the laboratory

Section number and Name	Description of Change	Brief Rationale
		assessments that may be performed at a local laboratory
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (26 June 2020)

Overall Rationale for the Amendment

The study design was changed per United States (US) Food and Drug Administration's (FDA) recommendation; all study participants, not only clinical responders, will be randomized at the beginning of the Maintenance Period (Week M-0). Furthermore, the study objectives, endpoints, and hypotheses were expanded to include both US-specific and global objectives, endpoints, and hypotheses per FDA feedback and to maintain alignment with the approved pediatric investigation plan (PIP) in the EU.

In addition, information from interviews with primary investigators, pediatric patients with Crohn's disease, and their caregivers were used to modify the study design. The number and duration of study-site visits are now reduced, and the timepoint for the Week I-8 colonoscopy was moved to Week M-8 to allow for more time for onset of endoscopic response.

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study. In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of COVID-19-related disruption to the conduct of the study.

Additionally, text defining the combination product was added, and updates to the template were incorporated.

Section Number and Name	Description of Change	Brief Rationale
Title Page	UNITI Jr Study name was added.	Aligned ustekinumab pediatric Crohn's disease study name with that for ustekinumab adult Crohn's disease
Synopsis Objectives and Endpoints, Statistical Methods; 3 Objectives and Endpoints; 9.4.2 Primary Endpoint; 9.4.3 Secondary Endpoints; 9.4.6 Primary Endpoint Analysis; 9.4.7 Secondary Endpoints Analysis	Objectives and Endpoints were updated to be global and US-specific.	Objectives and Endpoints updated to address health authority feedback. Global and US-specific objectives and endpoints created to maintain alignment with the approved PIP in the EU. Statistical methods text added.
Synopsis Hypothesis; Statistical Methods; 3 Objectives and Endpoints; 9.1 Statistical Hypothesis	Hypothesis was redefined to a global hypothesis and US-specific hypothesis.	Hypothesis modified to address FDA's recommendation for an intent-to-treat study design and to align with the approved PIP in the EU.

Section Number and Name	Description of Change	Brief Rationale
Synopsis Overall Design; Section 4.1; 5 Study Population	Text was modified to correct prior medication history.	Text corrected to indicate that participants must have demonstrated an inadequate response and/or intolerance to biologic therapy.
Synopsis Intervention Groups and Duration	Update was made that all participants who complete the Week I-8 visit will be randomized at Week M-0. Early escape, loss of response, and dose adjustment criteria were also provided.	Study design modified to align with FDA's recommendation for an intent-to-treat study design
Synopsis Efficacy Evaluations	The Simple Endoscopic Mucosal Assessment-Crohn's Disease (SEMA-CD) was added.	SEMA-CD allows for an additional evaluation of mucosal improvement using a novel outcome.
Synopsis Statistical Methods *Biomarker Analyses*	Update was made to text to explain how biomarker data will be analyzed.	The new text describes how biomarker data will be analyzed.
1.2 Schema	Figure 1 updated to show that all study participants will be randomized at Week M-0.	The revised figure addresses FDA's recommendation for an intent-to-treat study design
1.3 Schedule of Activities, Table 1, Screening Period	Updates were provided for the timing and types of assessments to be performed as well as the availability of supporting information and whether local or central laboratories would be used.	Updates were made to ensure patient safety; the weight restrictions were updated to reflect most current blood sampling schedule and the allowable volume of blood that may be drawn during the screening period.
1.3 Schedule of Activities, Table 2, Study Procedure-Induction Period	Updates were provided for the timing of assessments to be performed.	Clarification provided that participant-reported outcome (PRO) assessments and vital sign measurement should be performed prior to study intervention administration.
1.3 Schedule of Activities, Table 3, Study Procedure-Maintenance Period; 8 Study Assessments and Procedures 8.2.6 Infusion and Injection-site Reactions	Updates were provided for the option of home visits, including training for at-home study intervention administration, at-home monitoring of injection-site reactions, and remote collection of blood and stool samples. In addition, updates to the timing of assessments, use of the Crohn's Disease Activity Index (CDAI) electronic diary, and addition of the SEMA-CD assessment were made.	Based on Participant Input Into Study Design (Section 4.2.1) and the interest in having fewer study-site visits, updates made that certain study visits can be home visits.

Section Number and Name	Description of Change	Brief Rationale
2.3.1 Risks for Study Participation	Update was provided for monitoring Hypersensitivity reactions for study intervention administrations that will be performed at home. Steroid tapering text under Immunosuppression was removed.	Based on Participant Input Into Study Design (Section 4.2.1) and the interest in having fewer study-site visits, updates made that certain study visits can be home visits. Steroid tapering text was removed because it was described in Section 6.8.1.
4 Study Design; 6.1.3.2 Maintenance Period	Study design for the maintenance period was modified so that all participants will be randomized at Week M-0. Early escape criterion was added. Loss of response and dose adjustment were clarified, particularly in regard to at-home visits. Clarification was provided on the use of rescue medication, and the long-term extension was described.	Study design modified to align with FDA's recommendation for an intent-to-treat study design and to accommodate home visits.
4.2.1 Participant Input into Study Design	Section updated to incorporate feedback from patients with inflammatory bowel disease (IBD) and their caregivers about the study design. As a result, the Week I-8 ileocolonoscopy exam was moved to Week M-8. Also, certain study visits can be home visits, electronic diaries and questionnaires will be used, and placebo injections will be minimized.	Patients with IBD and their caregivers from a pediatric gastrointestinal practice were interviewed about the clinical study process. This information was used to inform elements of the study design.
4.2.3 Rationale for Target Population	Section updated to provide rationale for including participants <6 years of age in \to the study.	Clarification was added regarding prior use of biologics in children, particularly under the age of 6 years.
5.1 Inclusion Criteria Inclusion Criterion #9	Inclusion Criterion was deleted.	The risk of ileocolonic cancer is low in patients with Crohn's disease.
5.1 Inclusion Criteria Inclusion Criterion #15	Clarification provided for acceptable evidence of immunity to varicella, and measles, mumps, and rubella.	Clarification was provided on acceptable documentation for vaccination or prior disease history.
5.1 Inclusion Criteria Inclusion Criterion #16	Clarification that participants who have received a live vaccine must wait at least 4 weeks to receive study intervention.	Clarification was provided on guidelines for live vaccines.

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria Exclusion Criterion #5	Exclusion Criterion 5b regarding fecal transplants was deleted. Addition of Exclusion Criteria 5o, 5p, and 5q that participants who are on rectal therapy with either 5-ASA medications or corticosteroids, on IV steroids, or on more than one antibiotic prescribed for the treatment of Crohn's disease will be excluded from the study.	Clarification was provided on prior use of fecal transplants and 3 additional exclusionary concomitant medications were added.
5.2 Exclusion Criteria Exclusion Criterion #14; 5.3 Lifestyle Considerations, Criterion #7; 6.8.2 Prohibited Concomitant Medications	Text regarding administration of live vaccines was updated.	Guidance was added for use of live vaccines during and after the study.
5.2 Exclusion Criteria Exclusion Criterion #31; 8 Study Assessments and Procedures 10.16 Appendix 16: Guidance on Study Conduct during the COVID-19 Pandemic	A new exclusion criterion related to COVID-19 was added, and guidance on COVID-19 was added as Appendix 16.	An exclusion criterion was added and information about study conduct due to COVID-19 pandemic as added.
5.5 Criteria for Temporarily Delaying Administration of Study Intervention (new Section)	New text was added allowing for delayed administration of study intervention between Week I-8 and Week M-0).	This update made due to template change.
Section 6.1.1 Combination Product (new Section)	The prefilled syringe (PFS) assembled with an UltraSafe Plus™ Passive Needle Guard (PFS-U) containing 90 mg of ustekinumab was described.	This update made due to template change.
6.1.4 Optional Home Study Intervention Administration (New Section)	A description of how home study administration would be performed was added.	Based on survey results described in Participant Input Into Study Design (Section 4.2.1), of participants and caregivers have an interest in having fewer study-site visits. Therefore, certain study visits can be home visits.
6.2 Preparation/Handling/ Storage/ Accountability	Text was added describing accountability of study intervention for at-home administration.	Based on survey results described in Participant Input Into Study Design (Section 4.2.1), of participants and caregivers have an interest in having fewer study-site visits. Therefore, certain study visits can be home visits.

Section Number and Name	Description of Change	Brief Rationale
6.3 Measures to Minimize Bias: Randomization and Blinding (Section 6.2 in original protocol)	Modification made that all participants will be randomized at Week M-0.	Updates made to address health authority feedback.
6.4 Study Intervention Compliance (Section 6.3 in original protocol)	Text was added describing study intervention compliance for at-home administration.	Based on survey results described in Participant Input Into Study Design (Section 4.2.1), of participants and caregivers have an interest in having fewer study-site visits. Therefore, certain study visits can be home visits.
6.7 Treatment of Overdose (formerly Section 8.4 in the template)	Updates regarding treatment of overdose were added.	Section was moved and new text added to comply with template change
6.8 Concomitant Therapy (Section 6.4 in original protocol)	Updates regarding allowed and prohibited concomitant therapy were made.	Greater clarification was provided.
7.1 Discontinuation of Study Intervention	Updates regarding discontinuation of study intervention were made.	Greater clarification was provided.
7.1.1 Liver Chemistry Stopping Criteria (new Section in template)	Updates regarding the discontinuation due to abnormal liver tests at the discretion of the investigator were provided.	The sponsor's protocol template was updated.
8 Study Assessments and Procedures 8.1 Efficacy Assessments, 8.1.7 Ileocolonoscopy	Addition of SEMA-CD assessment and inclusion of new PRO text per the protocol template update were made.	SEMA-CD allows for an additional evaluation of mucosal improvement using a novel outcome.

Section Number and Name	Description of Change	Brief Rationale
8.2.4 Clinical Safety Laboratory Assessments	Updates were provided for handling of hematology and serum chemistry samples that will not be collected at the study site and for pregnancy testing when study intervention is administered at home.	Clarification provided for collection of hematology and chemistry samples and pregnancy test for at-home study visits since certain home visits will be permitted per Participant Input Into Study Design (Section 4.2.1).
8.3 Adverse Events, Serious Adverse Events, and other Safety Reporting; 8.3.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information	Updates were provided regarding combination products included in most recent protocol template as well adverse event (AE)/serious adverse event (SAE) reporting during home visits.	The sponsor's protocol template was updated. Based on Participant Input Into Study Design (Section 4.2.1) and the interest in having fewer study-site visits, updates made that certain study visits can be home visits.
8.3.3 Follow-up of Adverse Events and Serious Adverse Events	Updates were made per the template.	The sponsor's protocol template was updated.
8.4 Treatment of Overdose (now Section 6.7 Treatment of Overdose)	Section was moved, and clarification on overdose definition was made based on participant weight.	The sponsor's protocol template was updated.
8.4 Pharmacokinetics; 8.4.1 Evaluations (formerly Section 8.5/8.5.1)	Missing text was added to this section.	Clarification provided for collection of PK samples.
8.4 Pharmacokinetics; 8.4.3 Pharmacokinetic Parameters and Evaluations Parameters (formerly Section 8.5/8.5.3)	Missing text was added to this section. A population PK analysis approach will be used to characterize the PK of ustekinumab in pediatric participants with Crohn's disease and to evaluate the effect of potential covariates that influence the PK of ustekinumab.	Clarification provided for evaluation of PK samples.
9.2 Sample Size Determination	Updates made for the sample size determination for the global and US-specific primary endpoints.	Clarification provided that sample size is sufficient to determine efficacy under the extrapolation concept.
9.3 Populations for Analyses	The populations for analyses were updated.	Updates made to address change to intent-to-treat study design.
9.4.10 Other Analyses	Pharmacokinetic and biomarker analyses were updated.	Clarification provided on how PK and biomarker analyses will be handled.

Section Number and Name	Description of Change	Brief Rationale
9.6 Data Monitoring Committee or Other Review Board	Updates were made to Data Monitoring Committee (DMC) membership.	Clarification made to broaden definition of DMC membership.
10.8 Appendix 8: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Text was added regarding AEs and SAEs for a combination product with a device component and product quality complaint handling.	Appendix 8 has been updated per the updates in the protocol template.
10.11 Appendix 11: Clinical Laboratory Tests	Statement added that testing can be performed at a local laboratory. Clarification provided for liver enzyme tests, and serum C-reactive protein, stool sample, and colonic biopsy added as screening tests.	Testing at local laboratory permitted for remote visits.
10.14 Appendix 14: Contraceptive and Barrier Guidance	Updates were made to the text.	Appendix has been updated per the updates in the protocol template.
10.15 Appendix 15: Regulatory, Ethical, and Study Site Considerations	Updates made to sections on Country Selection, Informed Consent Process and Assent Form, and Source Documents	Appendix has been updated per the updates in the protocol template.
10.17 Appendix 17: Protocol Amendment History	The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).	Appendix has been updated per protocol template instructions.
Throughout the protocol	Updates were made to the protocol based on template language changes.	The sponsor's protocol template was updated.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD , MD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	09-Mar-2023 13:52:58 (GMT)	Document Approval