26 February 2026
EMADOC-1700519818-2358864
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Stelara

International non-proprietary name: Ustekinumab

Procedure No. EMA/VR/0000290099

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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## List of abbreviations

BMI Body Mass Index

CD Crohn's disease

CDAI' Crohn's Disease Activity Index

CI confidence interval

CRP C-reactive protein

CSR clinical study report

CTD common technical dossier

CWRES absolute population weighted residuals

DBL database lock

EMA European Medicines Agency

ERAS EMA Randomized Analysis Set

EOS Exposure Optimisation Substudy

EU European Union

FAS Full analysis set

FASCR Full Randomised Analysis Set

FASRES All Responder Analysis Set

GCP Good Clinical Practices

GHAS Global Histology Activity Score

GOF Goodness-of-Fit

HRQoL health-related quality of life

IBD inflammatory bowel disease

ICE Intercurrent Current Event

ICF Informed Consent Form

IgG1k immunoglobulin G1 kappa

IL interleukin

IPRED individual predictions

IQ Interquartile

IV intravenous/ly

IWRS interactive web response system

LIV liquid in vial

LOR loss of response

LTE Long Term Extension

Nabs Neutralising Antibodies

OR odds ratio

PCDAI Paediatric Crohn’s Disease Activity Index

PD pharmacodynamic(s)

PFS prefilled syringe

PIP paediatric investigation plan

PK pharmacokinetic(s)

PRED population predictions

RHI Robarts Histopathology Index

SAE serious adverse event

SAP Statistical Analysis Plan

SC subcutaneous

SD Standard Deviation

SEMA-CD simplified endoscopic mucosal assessment for Crohn’s disease

SES-CD simple endoscopic score for Crohn’s disease

sPCDAI short Paediatric Crohn’s Disease Activity Index

TB tuberculosis

Th1 T-helper cell 1

Th17 T-helper cell 17

TNF tumour necrosis factor

UC Ulcerative Colitis

ULN Upper Limit of Normal

VPC Visual Predictive Check

# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen Cilag International submitted to the European Medicines Agency on 30 July 2025 an application for a variation.

The following changes were proposed:

| Variation(s) requested | | Type |
|---|---|---|
| C.I.6.a | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II |

Extension of indication to include treatment of moderately to severely active Crohn's disease in paediatric patients from the age of 2 years and older, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy, for STELARA, based on final results from the Phase 3 open-label CNTO1275CRD3004 study and the supportive results from the Phase 1 PK CNTO1275CRD1001 study. Study CNTO1275CRD3004 is a Phase 3 study of the efficacy, safety, and pharmacokinetics of ustekinumab as open-label intravenous induction treatment followed by randomised double-blind subcutaneous ustekinumab maintenance in paediatric participants 2 to <18 years of age with moderately to severely active Crohn's disease. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are being updated. The Package Leaflet is updated accordingly. The RMP version 32.1 has also been submitted. In addition, the MAH took the opportunity to introduce editorial, formatting and administrative changes to the PI, bringing it in line with the latest QRD template. In addition, the MAH updated the list of local representatives in the Package Leaflet.

The requested variation(s) proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0341/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0341/2023 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## *Similarity*

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Derogation(s) of market exclusivity*

NA

## *Scientific advice*

The MAH received Scientific Advice from the CHMP on 23 July 2020 on the use of RWE in regulatory decision making supporting the approval of ustekinumab for the treatment of paediatric patients with Crohn's disease (EMEA/H/SA/563/7/2020/PED/II).

## *1.1. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Finbarr Leacy Co-Rapporteur: Thalia Marie Estrup Blicher

| Timetable | Actual dates |
|---|---|
| Submission date | 30 July 2025 |
| Start of procedure: | 16 August 2025 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 10 October 2025 |
| PRAC Rapporteur's preliminary assessment report circulated on: | 10 October 2025 |
| CHMP CoRapporteur's preliminary assessment report circulated on:> | 25 October 2025 |
| Joint Rapporteur's updated assessment report circulated on: | 6 November 2025 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 13 November 2025 |
| MAH's responses submitted to the CHMP on: | 22 December 2025 |
| CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 2 February 2026 |
| Joint Rapporteur's updated assessment report on the MAH's responses circulated on: | 19 February 2026 |
| CHMP opinion: | 26 February 2026 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. About the product

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human IL-12/23p40 that binds with high affinity to human interleukins IL-12 and IL-23. Ustekinumab prevents IL-12 and IL-23 bioactivity by preventing their interaction with their cell surface IL-12Rβ1 receptor protein. Through this mechanism of action, ustekinumab effectively neutralises ll IL-12 (Th1)- and IL-23 (Th17)-mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases, including IBD, and binding the IL-12/23p40 subunit may provide effective therapy in paediatric Crohn's disease.

Since its first approval in the EU in January 2009, STELARA (ustekinumab) has been approved for the following indications:

- Paediatric (6 years and older) and adult patients with moderate to severe PsO
- Adult patients with active PsA
- Paediatric (≥ 40 kg) and adult patients with moderately to severely active Crohn's Disease
- Adult patients with moderately to severely active UC

In the US, STELARA (ustekinumab) has also been approved for paediatric (6 years and older) patients with PsA.

The applied for therapeutic indication in this procedure is:

*Paediatric Crohn's disease*

*STELARA is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients from the age of 2 years and older, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.*

### 2.1.2. The development programme/scientific advice

Per ICH guideline E11A on paediatric extrapolation and ICH E11(R1), paediatric extrapolation is defined as "an approach to providing evidence in support of effective and safe use of drugs in the paediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the paediatric (target) and reference [adult] population." paediatric extrapolation can extend what is known about the reference population (e.g., efficacy, safety, and dosing) to the target population based on an assessment of the relevant similarities of disease and response to therapy of the 2 populations. Paediatric extrapolation is a well-accepted approach that was also used to facilitate approval of the other available biologics for paediatric Crohn's disease (i.e., adalimumab and infliximab).

In the applicant's current extrapolation concept, the reference population is adults with moderately to severely active CD, 18 years of age or older. The target population is paediatric participants (2 to <18 years of age) with moderately to severely active CD.

On 23 July 2020 the Applicant received EMA scientific advice on the use of RWE in regulatory decision

making supporting the approval of ustekinumab for the treatment of paediatric patients with Crohn's disease (EMEA/H/SA/563/7/2020/PED/II). This scientific advice was generally followed.

## *2.2. Quality aspects*

There are no changes to the manufacturing process to accommodate the treatment of paediatric patients. The only quality changes provided are updated compatibility studies as the final concentration of Stelara within the infusion bag will be higher than the highest concentration in the existing compatibility study. As such, an updated compatibility study has been provided to support the paediatric use.

## *2.3. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

### 2.3.1. Ecotoxicity/environmental risk assessment

Ustekinumab is a fully human IgG1κ mAb comprised of natural amino acids. It is not excreted unchanged but is completely metabolised to non-pharmacologically active simple molecules and does not give rise to biologically active metabolites. Due to the nature of the active substance, ustekinumab is not considered to pose a risk to the environment and no ERA studies are required.

### 2.3.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of ustekinumab.

Considering the above data, ustekinumab is not expected to pose a risk to the environment.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

The development programme consists of the Phase 1 PK Study CNTO1275CRD1001 (UNISTAR; hereafter referred to as CRD1001), and its LTE phase, and Phase 3 open label Study CRD3004 (UNITI Jr.).

Supportive data will be presented from an observational RWE Study CNTO1275CRD3010 (REALITI; hereafter referred to as CRD3010), and Study C0168Z02 (DEVELOP), which is a REMICADE (infliximab) PASS that includes ustekinumab-treated paediatric participants with Crohn's disease.

**Table 1: Clinical development programme in support of the application**

| Study ID, Type, Status | Study Duration | Treatment Group/Analysis Sets (n) | Objectives |
|---|---|---|---|
| **Phase 1** | | | |
| CNTO1275CRD1001 (UNISTAR), pediatric, completed | Induction- Week 0 to Week 8<br>Maintenance- Week 8 to Week 16<br>LTE- At Week 16, all participants who received benefit from ustekinumab maintenance therapy as determined by the investigator, were eligible to enter the LTE of the study, whichever occurs first. Transitioned to CNTO1275ISD3001 for Week 16 to Week 240<br><br>Participants entering the LTE period received SC ustekinumab q8w beginning at Week 16 and continued through the end of the LTE period. | Total population (randomized and treated; n=44)<br>• Randomized, Double-blind Period Week 0 to Week 16 (n=44)<br>• LTE Period (Week 16 to Week 240) (n=34)<br>• Transitioned to CNTO1275ISD3001 for LTE (n=6) | • To evaluate the PK of ustekinumab in participants from 2 to <18 years and determine if it is similar to that observed in adults with moderately to severely active Crohn's disease<br>• To evaluate the safety and immunogenicity of ustekinumab in this population<br>• To assess the efficacy of ustekinumab in the treatment of moderately to severely active Crohn's disease, including assessment of improvement in the endoscopic appearance of the mucosa |
| **Phase 3** | | | |
| CNTO1275CRD3004 (UNITI Jr), pediatric, completed | Induction- Week 0 to Week 8<br>Maintenance- Week 8 to Week 44<br>LTE- Transitioned to CNTO1275ISD3001 for Week 44 to Week 240 | Total population (n=48)<br>• q12w (n=25)<br>• q8w (n=23)<br>• Transitioned to CNTO1275ISD3001 for LTE (n=59) | • To evaluate the efficacy of ustekinumab dosing in inducing clinical remission in pediatric participants with moderately to severely active Crohn's disease<br>• To evaluate the efficacy of IV ustekinumab during the induction period<br>• To evaluate the efficacy of SC ustekinumab during the maintenance period among participants who were in clinical response in induction<br>• To evaluate the safety profile of ustekinumab in pediatric participants with moderately to severely active Crohn's disease<br>• To evaluate ustekinumab exposure (PK) |

| **Efficacy and Safety Non-interventional Clinical Studies: Crohn's Disease** | | | | | |
|---|---|---|---|---|---|
| CNTO1275CRD3010<br>REALITI<br>Non-interventional real-world study<br>NA<br>Synopsis<br>Start of data collection 21 March 2022 (start of chart reviews).<br>End of data collection 22 May 2023 (Database lock). | USA: 51 | Phase 3<br>Retrospective, single arm, non-interventional, observational, real-world evidence study<br><br>Pediatric subjects (ages ≥2 to <18) and young adults (ages 18 to <26) with moderately to severely active Crohn's disease.<br><br>Evaluate the effectiveness of ustekinumab in achieving clinical remission in pediatric patients (≥2 to <18 years and weight ≥40 kg at baseline) | Enrolled: 479 | Ustekinumab | Cohort 1 (Pediatric Patients [Primary Cohort]): 114<br><br>Cohort 2: 31<br><br>Cohort 3:145<br><br>Cohort 4: 204<br><br>Cohort 5:56<br><br>Cohort 6: 348<br><br>Cohort 7 (Young Adults [Reference]): 51<br><br>Cohort 8: 91<br><br>Cohort 9: 131 |

| Safety Uncontrolled Clinical Studies: Inflammatory Bowel Disease | | | | |
|---|---|---|---|---|
| C0168Z02 (North America)<br>DEVELOP™<br>NA<br>Start of data collection<br>31 May 2007 (first patient dosed with ustekinumab on 17 December 2010<br>End of data collection<br><br>Ongoing.<br><br>Data cutoff for this report 30 June 2022 | BEL, CAN, DEU, DNK, FRA, GBR, ITA, NLD, USA: 82 | Registry<br>Multicenter, prospective, observational registry<br><br>Pediatric patients with a confirmed diagnosis of IBD (ie, Crohn's disease, UC, or IC) for at least 2 months who are less than 17 years of age in North America and ≥6 to < 17 years of age in the EU at the time of enrollment.<br><br>The objective of this registry is to obtain long-term safety and clinical status information on pediatric patients with IBD (ie, CD, UC, or IC). | Ustekinumab = 119 (only those patients who were <18 years of age and weighed ≥40 kg upon initial ustekinumab treatment. | Infliximab<br>Ustekinumab |

## GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

## Clinical pharmacology

### 2.4.2. Pharmacokinetics

**Summary of biopharmaceutic and analytical methods**

This SBAAM presents a summary of the ustekinumab formulations and devices, and the bioanalytical methodologies, including relevant method updates for PK and immunogenicity analyses of ustekinumab in clinical studies in support of the application for the treatment of paediatric patients with moderately to severely active CD.

Studies CNTO1275CRD3004 and CNTO1275CRD1001 used liquid in vial (LIV 45 mg/0.5 mL or 90 mg/mL or 130 mg/26 mL [5 mg/mL]) and PFS (45 mg/0.5 mL or 90 mg/mL) presentations of ustekinumab.

Both the LIV (45 mg/0.5 mL or 90 mg/mL or 130 mg/26 mL [5 mg/mL]) and the PFS (45 mg/0.5 mL or 90 mg/mL) products of ustekinumab have been approved for adult use. Methodologies and validations of the bioanalytical methods used to determine serum ustekinumab concentrations, and ADAs and NAbs to ustekinumab have previously been submitted. The following updates are included in this summary:

- The method used for detection of serum ustekinumab concentrations has been partially validated for selectivity in different matrices and selectivity in the presence of other drugs. Validation addenda documenting incurred sample reproducibility, parallelism, and incurred sample reanalysis are presented.

- The method used for detection of serum antibodies to ustekinumab has been partially validated to meet regulatory authority guidance requirements and to assess assay interference with other drugs.
- The method used for detection of NAbs to ustekinumab in human serum has been validated for revision of acceptance criteria for assay control, partially validated for combination therapy with different drugs and for assessing the cutpoint in serum samples of different patients. The method has also been cross-validated from the Janssen Spring House Laboratory to Frontage Laboratories.

Cross Validation for addition of Janssen Spring House Laboratory to Frontage Laboratories.

An electrochemiluminescence-based immunoassay to detect neutralizing antibodies (NAbs) to Ustekinumab (CNTO 1275) in human serum samples was developed and fully validated by Janssen Research & Development and was successfully transferred to Frontage Satellite Lab (FSL). The experiments were carried out to demonstrate the performance comparability between Janssen Spring House (SH) and FSL through assay sensitivity, drug tolerance, and analysis of 8 mock samples.

**Table 2: Results of the cross-validation study**

| | |
|---|---|
| Validation Period | 19Jul2024 to 25Sep2024 |
| NAb SOP | Janssen TV-SOP-07840 (V5.0): Electrochemiluminescence-based Immunoassay to Detect Neutralizing Antibodies to ustekinumab (CNTO 1275) in Human Serum. |
| Sensitivity: | Acceptable<br>SH: 261.70 ng/mL in neat human serum<br>FSL: 188.37 ng/mL in neat human serum |
| Drug Tolerance: | Acceptable<br>SH: 550 ng/mL of CNTO 1438 was detectable in the presence of up to 1.32 µg/mL exogeneous CNTO 1275 in neat human serum.<br>FSL: 550 ng/mL of CNTO 1438 was detectable in the presence of up to 2.36 µg/mL exogeneous CNTO 1275 in neat human serum. |
| NAb Classification of Mock Samples | Acceptable<br>SH: 5 out of 5 NAb positive mock samples and 2 out of 3 NAb negative mock samples were correctly classified.<br>FSL: 5 out of 5 NAb positive mock samples and 3 out of 3 NAb negative mock samples were correctly classified. |

The PK and ER data presented for this submission builds on the previous paediatric submission for patients ≥40 kg to support the extension of the indication to include paediatric patients <40 kg.

**Study CRD1001:** Phase 1 CD study in paediatric participants (≥2 years) has been assessed in the extension of indication EMEA/H/C/000958/II/0108 and no new data were presented in the current submission.

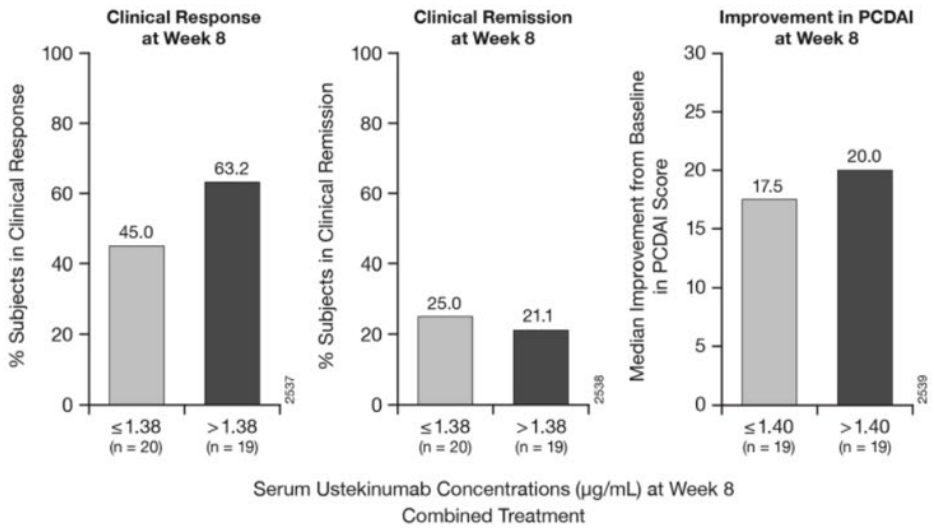
**Pharmacokinetic/Pharmacodynamic Relationships**

To assess the relationship of clinical efficacy with exposure to ustekinumab, the association between efficacy measures at Week 8 and at Week 16, with serum ustekinumab concentrations at Week 8 and at Week 16, respectively, were evaluated. Serum ustekinumab concentrations from all ustekinumab-treated subjects were categorised into 2 groups based on the median serum concentration (≤median, >median) at Week 8 and at Week 16.

In general, in the combined ustekinumab group, greater proportions of subjects achieved clinical response and improvement from baseline in the PCDAI score at Week 8 with increasing ustekinumab concentration, while a positive exposure-response (E-R) relationship was not observed for clinical remission at Week 8 (Figure 1). This pattern was also observed at Week 16.

In the combined ustekinumab group, subjects in the higher ustekinumab concentration category had lower median SES-CD score at Week 16 compared with those in the lower ustekinumab concentration category.

**Figure 1: Bar chart of clinical response, clinical remission, and median improvement from baseline in the PCDAI score at week 8 by median serum ustekinumab concentrations (micrograms/mL) at week 8 (combined treatment); PK analysis set (Study CNTO1275CRD1001)**




Higher serum ustekinumab concentrations at Week 8 generally corresponded to lower CRP levels at Week 8. A similar pattern was observed at Week 16 where CRP levels were lower among subjects in the higher serum ustekinumab concentration group. Consistent with the above results, in the combined ustekinumab group, a greater proportion of subjects achieved normalised CRP at Week 8 in the higher serum concentration group (35.7% [5 subjects] versus 13.3% [2 subjects]). A similar pattern was observed at Week 16.

Higher serum ustekinumab concentrations at Week 8 generally corresponded to lower faecal calprotectin levels at Week 8. A similar pattern was observed at Week 16. Consistent with the above results, in the combined ustekinumab group, a greater proportion of subjects achieved normalised faecal calprotectin at Week 8 in the higher serum concentration group (18.8% [3 subjects] versus 0% [no subjects]). A similar pattern was observed at Week 16.

Higher serum ustekinumab concentrations at Week 16 generally corresponded to lower faecal lactoferrin levels at Week 16. This pattern was not observed at Week 8. Consistent with the above results, in the combined ustekinumab group, a greater proportion of subjects achieved normalised faecal lactoferrin at Week 16 in the higher serum concentration group (17.6% [3 subjects] versus 5.6% [1 subject]). At Week 8, both groups had 5.0% of subjects (1 subject in each group) who achieved normalised faecal lactoferrin.

Serum ustekinumab concentrations at Week 48 from ustekinumab-treated subjects were categorised into 2 groups based on the median serum concentration (≤median, >median) at Week 48. Taking into account the small sample sizes involved in these analyses, no clear exposure-response relationship was evident between these clinical efficacy endpoints and serum ustekinumab concentrations at Week 48.

**Study CRN3004: Phase 3 CD study in paediatric participants (≥2 Years)**

This was a Phase 3, multicentre interventional study consisting of an open-label induction period with a single IV ustekinumab induction dose followed by a maintenance period with a randomised, double-blind,

parallel-group 2-arm design in paediatric participants (2 to <18 years of age) who had a diagnosis of moderately to severely active CD.

*Induction period*

All participants received a single IV dose of ustekinumab at induction Week 0 (Week I-0).

For participants with body weight <40 kg: 250 mg/$m^2$ IV

For participants with body weight ≥40 kg (approved adult dose regimen):

- 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*

All participants who completed the Week I-8 visit were randomised at maintenance Week 0 (Week M-0) to receive 1 of 2 SC dose regimens, stratified by response status (induction responders/induction nonresponders) and weight (<40 kg, ≥40 kg):

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

Participants who experienced loss of response (LOR) were eligible for a dose adjustment as follows (unless they had documented low ustekinumab exposure at Week M-8):

- Participants who were randomised to ustekinumab q12w and had LOR were eligible for a dose adjustment to ustekinumab q8w.
- Participants who were randomised to ustekinumab q8w and who experienced a LOR remained on ustekinumab q8w (a sham adjustment).

Participants who had a confirmed LOR and had documented low exposure (defined as steady-state ustekinumab Ctrough <1.4 µg/mL at either Week M-8 or Week M-32) were eligible to participate in the optional Exposure Optimisation Substudy and received q4w dosing.

***Results***

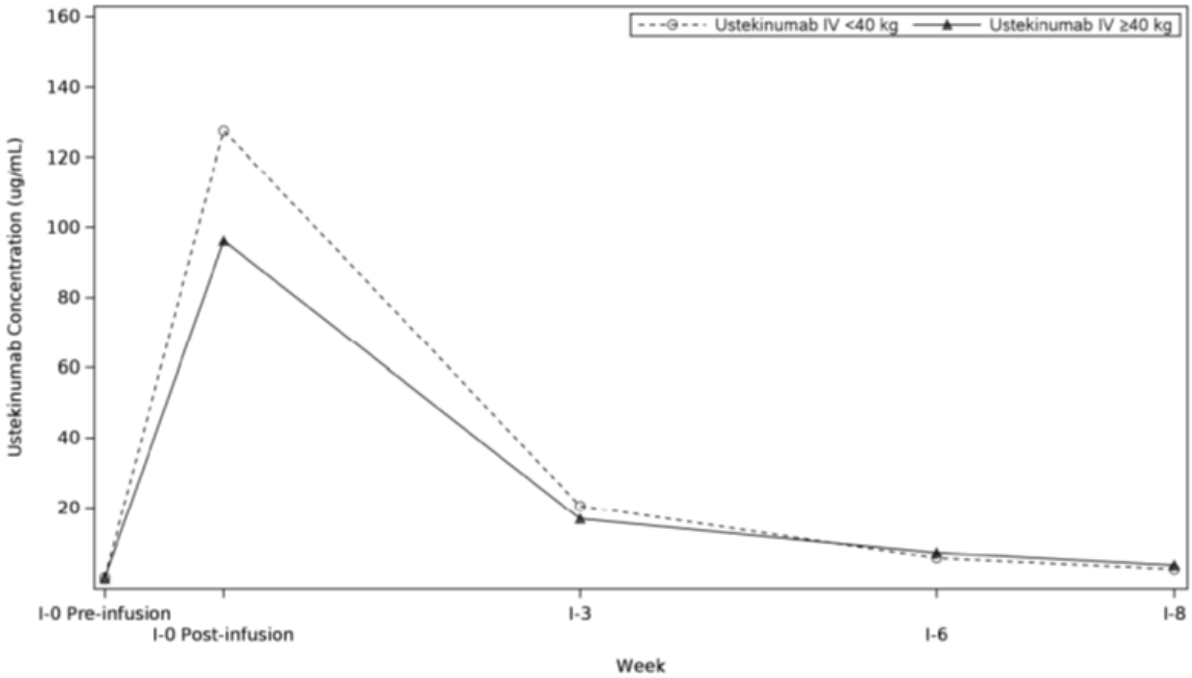
A total of 101 participants (59.4% male, 87.1% White) with a median body weight of 47.2 kg (range: 13 to 88 kg) and a median age of 14.0 years (range: 2 to 17 years) were randomised. There were 29 (28.7%) participants <40 kg and 72 (71.3%) participants ≥40 kg.

*Serum Ustekinumab Concentrations through Week I-8*

Median (mean) peak serum ustekinumab concentrations observed 1 hour after the end of the infusion at Week 0 was 106.0 µg/mL (107.9 µg/mL). At Week 8, the time of the main efficacy assessment, median (mean) serum ustekinumab concentration was 2.90 µg/mL (4.08 µg/mL).

Serum ustekinumab concentrations through Week I-8 were generally comparable between participants with body weight <40 kg and those ≥40 kg (Figure 2). At Week I-0, 1-hour post infusion, median (mean) serum ustekinumab concentrations appeared slightly higher among participants with body weight <30 kg (148.0 [143.2] µg/mL) and participants at ≥30 to <40 kg (123.7 [117.6] µg/mL), compared with those ≥40 kg (96.2 [99.8] µg/mL). Conversely at Week I-8, median (mean) serum ustekinumab concentrations were 1.64 (2.00) µg/mL, 2.93 (3.76) µg/mL, and 3.43 (4.53) µg/mL among participants with body weight <30 kg, ≥30 to <40 kg, and >40 kg, respectively.

**Figure 2: Line plot of median serum ustekinumab concentrations (micrograms/mL) through Week I-8 (linear scale) by baseline body weight; PK analysis set (Study CNTO1275CRD3004)**




*Serum Ustekinumab Concentrations from Week M-0 through Week M-44*

Before administration of the first maintenance dose at M-0, median (mean) serum ustekinumab concentrations were 2.87 (3.81) and 2.91 (4.58) µg/mL in the ustekinumab q12w and q8w groups, respectively. Participants randomised to q8w or q12w had sustained serum ustekinumab concentrations through Week M-44.

Steady-state concentrations were reached at approximately 8 weeks (M-8 or 16 weeks after IV induction) for participants receiving ustekinumab 90 mg q8w, or at 12 weeks (M-12 or 20 weeks after IV induction) for participants receiving ustekinumab 90 mg q12w maintenance doses. There was no apparent accumulation in ustekinumab concentration over time when given SC q8w or q12w.

In the q8w group, median (mean) pre-administration serum ustekinumab concentrations (at Weeks M-8, M-16, M-24, M-32) were consistent through Week M-44 ranging from 1.47 (2.17) µg/mL to 1.79 (2.56) µg/mL. The average steady-state trough serum ustekinumab concentrations were comparable between the <40 kg and ≥40 kg subgroups (Table 6).

In the q12w group, median (mean) pre-administration serum ustekinumab concentrations (at Weeks M-12, M-24, and M-36) were also consistent through Week M-44, ranging from 0.41 (0.58) µg/mL to 0.63 (0.64) µg/mL. average steady-state trough serum ustekinumab concentrations were lower in the <40 kg subgroup compared with the ≥40 kg group (Table 6).

**Table 3: Summary of paediatric by baseline body weight vs adult average steady state trough serum ustekinumab concentrations (micrograms/mL); PK clinical responder analysis set (Study CNTO1275CRD3004)**

| | Ustekinumab | | | | | |
|---|---|---|---|---|---|---|
| | Pediatric | | | | | |
| | <40 kg | | ≥ 40 kg | | Adult | |
| | q12w | q8w | q12w | q8w | q12w | q8w |
| Analysis set | 10 | 11 | 34 | 30 | 129 | 127 |
| Average steady state trough concentration | | | | | | |
| N | 9 | 8 | 26 | 20 | 95 | 93 |
| Mean (SD) | 0.27 (0.261) | 3.09 (3.212) | 0.74 (0.585) | 2.29 (1.791) | 0.87 (0.908) | 2.50 (1.897) |
| Median | 0.29 | 1.70 | 0.69 | 1.64 | 0.62 | 2.14 |
| Range | (0.0; 0.7) | (0.6; 8.7) | (0.0; 1.9) | (0.3; 7.7) | (0.0; 5.9) | (0.0; 9.4) |
| IQ range | (0.00; 0.41) | (1.04; 5.00) | (0.25; 1.20) | (1.18; 2.66) | (0.26; 1.20) | (1.18; 3.22) |

Key: SD=standard deviation, IQ=interquartile
Note: Concentrations below the lowest quantifiable concentration are treated as zero in calculating the summary statistics.
Note: Trough serum ustekinumab at Weeks M-24 and M-36 in case of Q12W; Weeks M-24 and M-32 in case of Q8W for pediatric CRD3004 are averaged.
Note: Trough serum ustekinumab at Weeks M-24 and M-36 in case of Q12W; Weeks M-24, M-32 and M-40 in case of Q8W for adult study are averaged.

Steady-state trough ustekinumab concentrations in participants who received ustekinumab 90 mg q8w were approximately 3-fold higher than those in paediatric participants who received ustekinumab 90 mg q12w.

At Week M-44 (i.e., 4 weeks and 8 weeks from the previous dose for the q8w group and the q12w group, respectively), where key maintenance efficacy endpoints (e.g., clinical remission) were assessed in this study, median (mean) serum ustekinumab concentrations were 6.00 (6.37) µg/mL in the q8w group and 1.88 (1.84) µg/mL in the q12w group.

The sample size of participants who had a dose adjustment in the main study (n=5) was too small, hence no conclusion could be reached on the impact of dose adjustment on ustekinumab concentrations. A total of 5 (5.2%) of 97 randomised participants dose-adjusted from ustekinumab through Week M-44 (2 participants who dose adjusted to q8w and 3 participants who received a sham dose adjustment).

*Exposure Optimising Substudy*

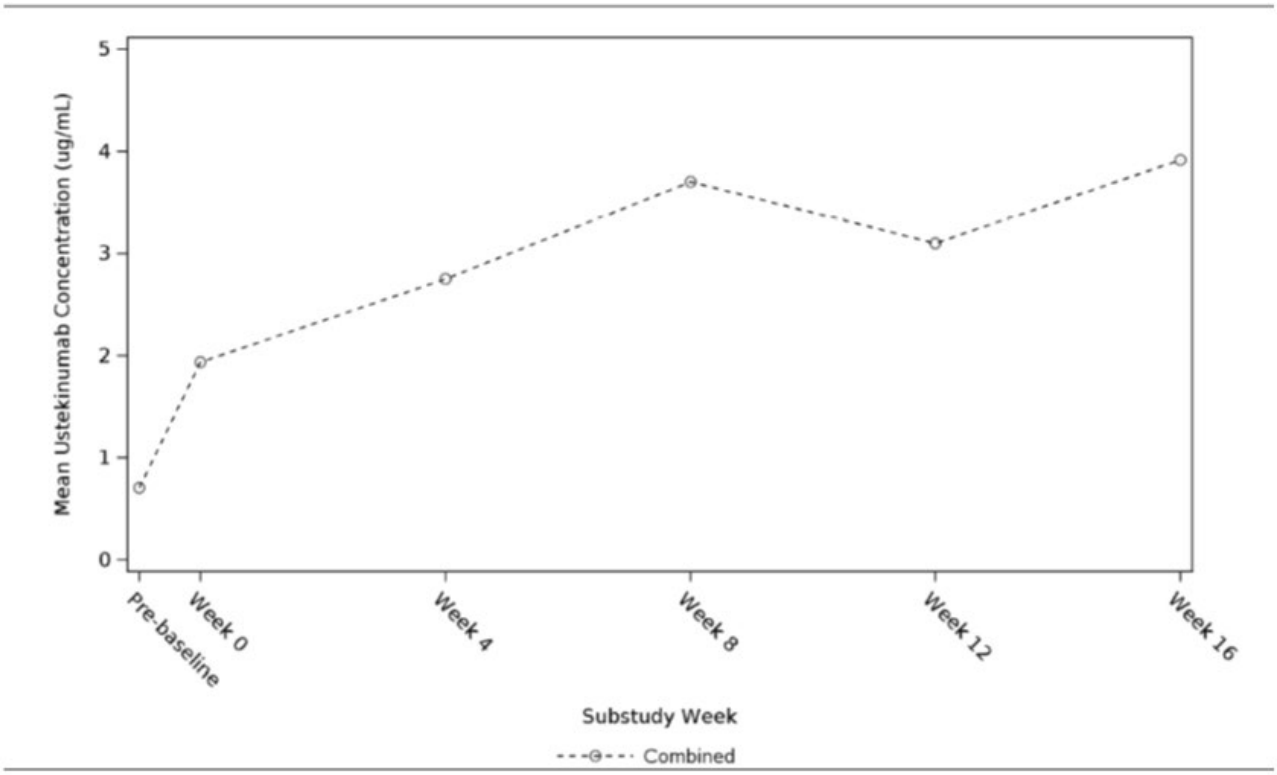
Twenty-six participants (11 on the q12w regimen and 15 on the q8w regimen) entered the Exposure Optimising Substudy. These participants had induction nonresponse or LOR and low ustekinumab exposure (defined as an 8-week, steady-state ustekinumab trough concentration of <1.4 µg/mL) at Week M-8 and/or Week M-32. During this substudy, ustekinumab was administered SC q4w for a total duration of 16 weeks (5 doses) or through the Week M-40 visit, whichever was the longer duration of exposure. Any participant who was not in clinical response 16 weeks after entry into the substudy was discontinued from the study intervention.

Before the first dose of ustekinumab q4w at Substudy Week 0, the median (mean) serum ustekinumab concentration was 1.74 (1.94) µg/mL in the combined treatment group (0.30 [1.87] µg/mL in the q12w→q4w treatment group and 1.85 [1.98] in the q8w→q4w treatment group). Following administration of the q4w regimen, ustekinumab concentrations in paediatric participants increased, reaching levels within the range of the concentrations observed in the adult CD study (Figure 3). For example, serum trough ustekinumab concentrations ranged between 1.57 µg/mL to 5.05 µg/mL at substudy Week 12, when the concentration data were anticipated to be at approximate steady state. By comparison, in adult participants with CD who received the q8w regimen, steady state trough ustekinumab concentration

ranged between 0.00 µg/mL and 15.9 µg/mL at Week M-8, the first steady state timepoint in the adult study CRD3003.

Of the 26 participants who entered the EOS, 21 (80.8%) completed a minimum of 16 weeks of substudy treatment. The reasons for the 5 (19.2%) participants who discontinued the EOS treatment included an AE of worsening of Crohn's disease, participant initiated prohibited medication, lack of efficacy, other (high ustekinumab trough concentration of >7.2 ug/mL, so the participant was not able to proceed on the q4w dose regimen), and withdrawal by parent or guardian (this participant also discontinued participation in the study prior to Week M44).

**Figure 3: Line plot of mean serum ustekinumab concentrations (microgram/mL) over time up to 16 weeks after entering the substudy; PK analysis set (Study CNTO1275CRD3004)**



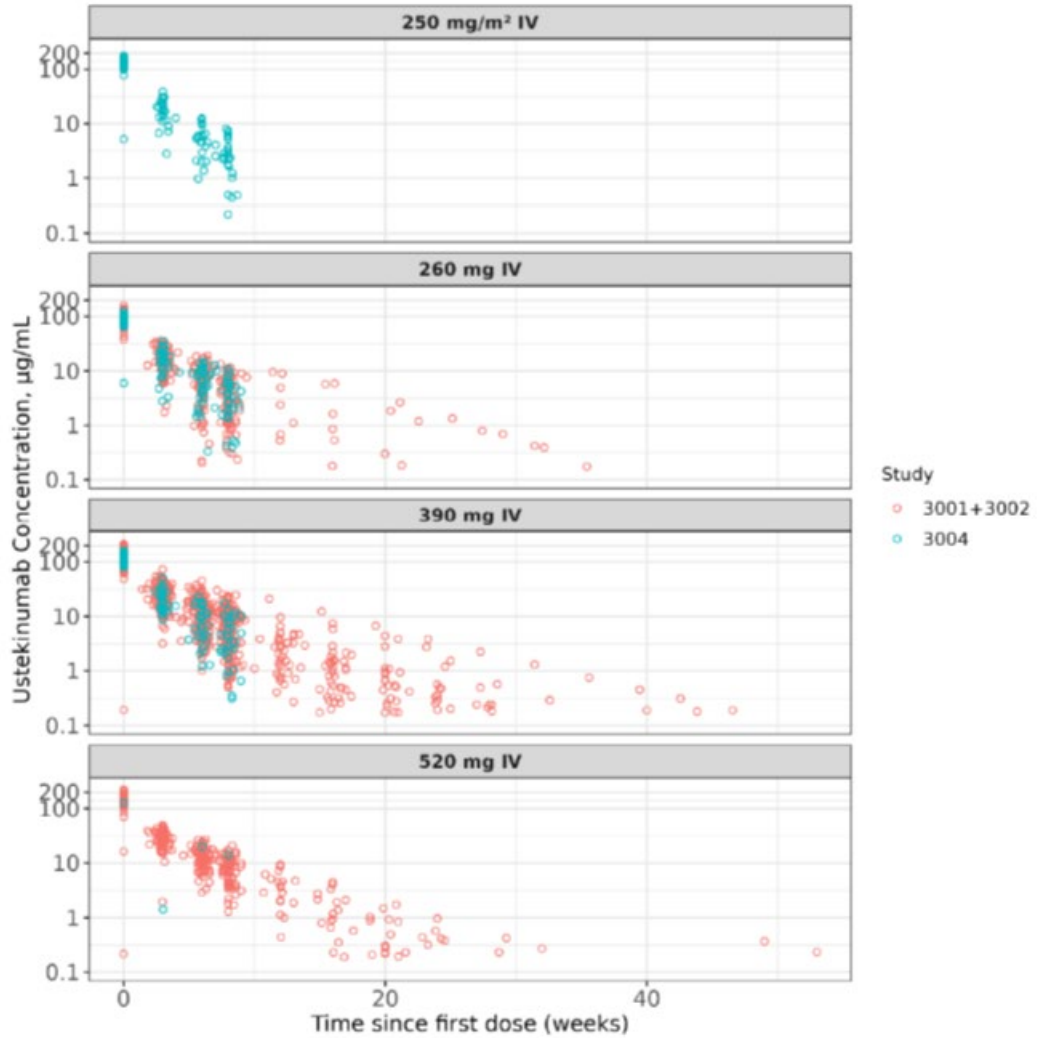

Note: Reter to table TSSPKCONC01.

***Comparison of observed serum ustekinumab concentrations between paediatric study CRD3004 and adult studies CRD3001, CRD3002, and CRD3003***

*Induction*

Through Week I-8, median or mean serum ustekinumab concentrations were generally comparable between the paediatric CD population and adult participants with CD who received the same induction dose (Figure 4).

**Figure 4: Scatterplot of ustekinumab serum concentrations versus time in paediatric participants from CNTO1275CRD3004 and in adult participants from CNTO1275CRD3001 and CNTO1275CRD3002 following 250 mg/m² or ~6 mg/kg IV Induction**

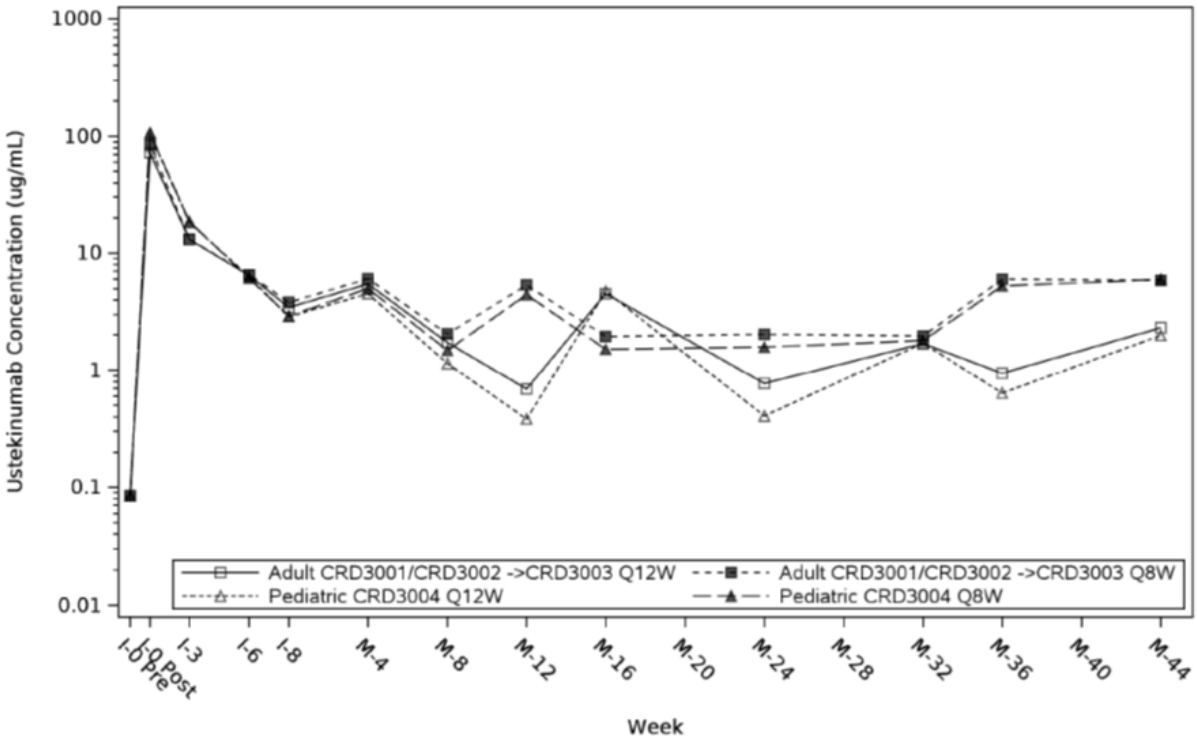



Abbreviations: 3001=CNTO1275CRD3001; 3002=CNTO1275CRD3002; 3004=CNTO1275CRD3004; IV=intravenous.

Following the 260 mg IV induction dose, median (mean) serum ustekinumab concentration at post-infusion Week I-0 was 91.15 (90.59) µg/mL among paediatric participants (body weight ≥40 to ≤55 kg) compared with 101.31 (100.74) µg/mL among adult participants (6 mg/kg for participants with body weight ≤55 kg). Likewise, at Week I-8, the median (mean) serum ustekinumab concentration was 2.68 (3.49) µg/mL among paediatric participants compared with 4.08 (4.39) µg/mL among adult participants. A similar pattern was observed among paediatric and adult participants who received the 390 mg induction dose.*Maintenance*

A line plot of median serum ustekinumab concentrations through Week M-44 for paediatric and adult participants with CD is provided in Figure 5.

**Figure 5: Line plot of paediatric vs adult median serum ustekinumab concentrations (micrograms/mL) semi-log scale through week M-44 for subjects who received ustekinumab in CNTO1275CRD3001 and CNTO1275CRD3002, CNTO1275CRD3003 and CNTO1275CRD3004; PK analysis set (Study CNTO1275CRD3004)**




Following the respective induction and maintenance dose regimens, median serum ustekinumab concentrations were comparable between the overall paediatric and adult participants with CD.

A comparison of average steady-state serum ustekinumab concentrations between paediatric and adult participants is provided in Table 4.

**Table 4: Summary of paediatric (by baseline body weight) versus adult average steady state trough serum ustekinumab concentrations (micrograms/mL); PK clinical responder analysis set (Study CNTO1275CRD3004)**

| | Ustekinumab | | | | | |
|---|---|---|---|---|---|---|
| | Pediatric | | | | | |
| | <40 kg | | ≥ 40 kg | | Adult | |
| | q12w | q8w | q12w | q8w | q12w | q8w |
| Analysis set | 10 | 11 | 34 | 30 | 129 | 127 |
| Average steady state trough concentration | | | | | | |
| N | 9 | 8 | 26 | 20 | 95 | 93 |
| Mean (SD) | 0.27 (0.261) | 3.09 (3.212) | 0.74 (0.585) | 2.29 (1.791) | 0.87 (0.908) | 2.50 (1.897) |
| Median | 0.29 | 1.70 | 0.69 | 1.64 | 0.62 | 2.14 |
| Range | (0.0; 0.7) | (0.6; 8.7) | (0.0; 1.9) | (0.3; 7.7) | (0.0; 5.9) | (0.0; 9.4) |
| IQ range | (0.00; 0.41) | (1.04; 5.00) | (0.25; 1.20) | (1.18; 2.66) | (0.26; 1.20) | (1.18; 3.22) |

Key: SD=standard deviation, IQ=interquartile
Note: Concentrations below the lowest quantifiable concentration are treated as zero in calculating the summary statistics.
Note: Trough serum ustekinumab at Weeks M-24 and M-36 in case of Q12W; Weeks M-24 and M-32 in case of Q8W for pediatric CRD3004 are averaged.
Note: Trough serum ustekinumab at Weeks M-24 and M-36 in case of Q12W; Weeks M-24, M-32 and M-40 in case of Q8W for adult study are averaged.

The average steady state serum ustekinumab concentrations in the overall paediatric CD population were comparable to those observed in the reference adult CD population who received q12w or q8w ustekinumab maintenance dosage (Table 6).

**Population PK Analysis**

The main objectives of this analysis were to characterise the PK of ustekinumab in paediatric patients with CD and to assess the similarity of ustekinumab PK between paediatric and adult patients with CD. This analysis was performed using the full paediatric dataset, which included 1,552 ustekinumab concentrations from 143 paediatric participants across the full body weight range of CRD3004 and CRD1001.

Previously, interim PopPK (and E-R analyses) were performed in paediatric participants with CD using data from 48 paediatric participants with body weight ≥40 kg for the interimDBL from CRD3004 as well as 44 paediatric participants across the full body weight range from CRD1001 (EMEA/H/C/000958/II/0108). These interim analyses were used to support an EMA submission for paediatric participants with body weight ≥40 kg. Compared to the interim analysis dataset, the full paediatric dataset included an additional 249 ustekinumab concentrations from 22 participants with body weight ≥40 kg and 303 ustekinumab concentrations from 29 participants with body weight <40 kg (new paediatric dataset).

The previously developed paediatric CD PopPK model from the interim analysis was applied to the full paediatric dataset without re-estimation of model parameters (MAXEVAL=0). To assess the predictive performance of the paediatric PopPK model from the interim analysis, GOF and VPC plots were made for the new paediatric dataset; these data were not used in the development of the paediatric PopPK model from the interim analysis and therefore represent the external evaluation. A series of sensitivity analyses were also performed to further evaluate the paediatric PopPK model from the interim analysis. A formal covariate analysis was not performed for the paediatric PopPK model because of the limited data from paediatric studies. Existing covariate relationships from the updated adult model were retained as fixed values in the paediatric PopPK model. Allometric scaling exponents on disposition parameters were fixed to the standard values (ie, 0.75 for CL and Q, and 1 for V2 and V3).

***Results***

Descriptive statistics of and baseline continuous and categorical covariates are presented in Table 5 and Table 6, respectively.

**Table 5: Demographic and baseline characteristics of pooled study data (continuous covariates)**

| Populations | All Participants from CNTO1275CRD3004 | New Participants from CNTO1275 CRD3004 | CNTO1275 CRD1001 | Full Paediatric Dataset (CNTO1275 CRD1001 and CNTO1275 CRD3004) | Adult Studies (CNTO1275 CRD3001 and CNTO1275 CRD3002) |
|---|---|---|---|---|---|
| **N** | 99 | 51 | 44 | 143 | 1,217 |
| **Weight (kg)** | | | | | |
| Mean (SD) | 48.5 (16.2) | 41.0 (15.5) | 43.1 (12.1) | 46.8 (15.2) | 71.1 (19.4) |
| Median | 47.2 | 39 | 42.9 | 45.9 | 68.4 |
| Range | (12.6-87.6) | (12.6-87.6) | (19.5-70.1) | (12.6-87.6) | (35.0-184) |
| **Age (Years)** | | | | | |
| Mean (SD) | 13.4 (2.76) | 12.3 (3.07) | 13.4 (2.74) | 13.4 (2.74) | 38.3 (12.7) |
| Median | 14 | 13 | 13 | 14 | 37 |
| Range | (2.00-17.0) | (2.00-17.0) | (6.00-17.0) | (2.00-17.0) | (18.0-75.0) |
| **Baseline Albumin (g/dL)** | | | | | |
| Mean (SD) | 4.11 (0.427) | 4.07 (0.488) | 3.95 (0.479) | 4.06 (0.448) | 3.52 (0.529) |
| Median | 4.1 | 4.1 | 4 | 4 | 3.6 |
| Range | (2.50-4.80) | (2.50-4.80) | (3.00-4.90) | (2.50-4.90) | (1.20-5.10) |
| **Baseline CRP (mg/L)** | | | | | |
| Mean (SD) | 19.2 (25.9) | 13.1 (18.8) | 23.1 (28.8) | 20.4 (26.8) | 17.6 (22.7) |
| Median | 8.3 | 6.5 | 12.9 | 10.2 | 9.15 |
| Range | (0.100-122) | (0.100-99.5) | (0.100-112) | (0.100-122) | (0.100-157) |

Abbreviations: CRD1001=CNTO1275CRD1001; CRD3001=CNTO1275CRD3001; CRD3002=CNTO1275CRD3002; CRD3004=CNTO1275CRD3004; CRP=C-reactive protein; N=number of participants; SD=standard deviation.

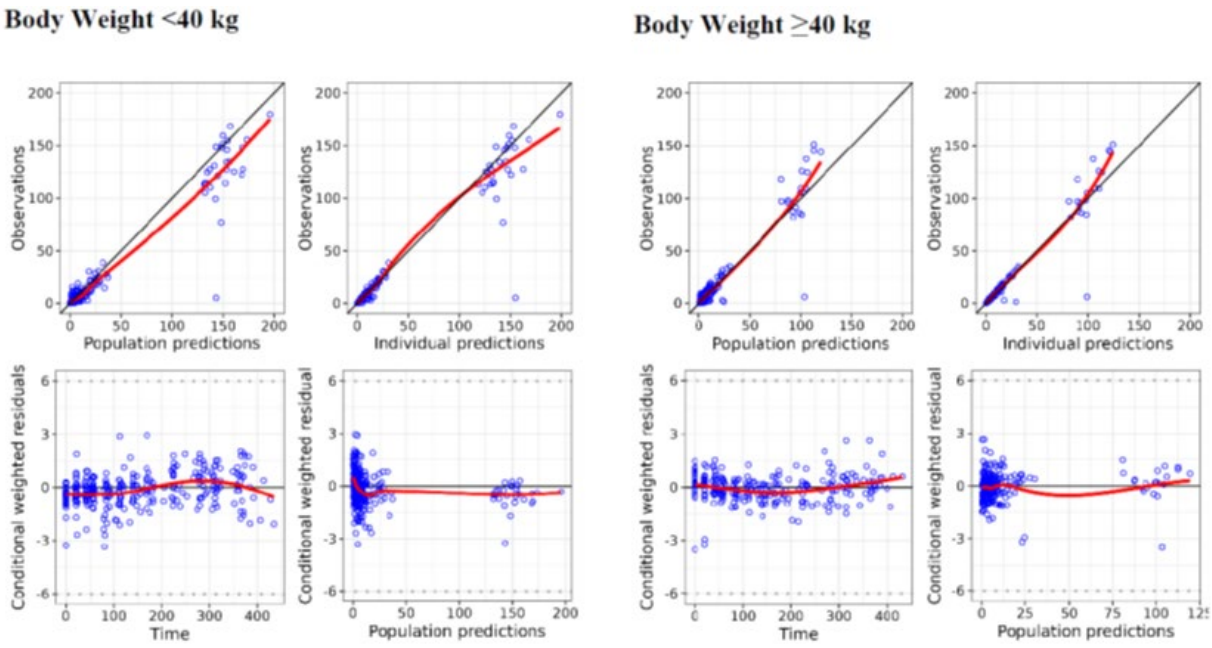
**Table 6: Demographic and baseline characteristics of pooled study data (categorical covariates)**

| Populations | All Participants from CNTO1275 CRD3004 | New Participants from CNTO1275 CRD3004 | CNTO1275 CRD1001 | Full Paediatric Dataset (CNTO1275 CRD1001 and CNTO1275 CRD3004) | Adult Studies (CNTO1275 CRD3001 and CNTO1275 CRD3002) |
|---|---|---|---|---|---|
| **N** | **99** | **51** | **44** | **143** | **1,217** |
| **Sex** | | | | | |
| Male | 59 (59.6%) | 32 (62.7%) | 18 (40.9%) | 77 (53.8%) | 537 (44.1%) |
| Female | 40 (40.4%) | 19 (37.3%) | 26 (59.1%) | 66 (46.2%) | 680 (55.9%) |
| **Race** | | | | | |
| **Caucasian** | **87 (87.9%)** | **43 (84.3%)** | **36 (81.8%)** | **123 (86.0%)** | **1,032 (84.8%)** |
| Black | 3 (3.0%) | 2 (3.9%) | 0 (0.0%) | 3 (2.1%) | 38 (3.1%) |
| Asian | 9 (9.1%) | 6 (11.8%) | 0 (0.0%) | 9 (6.3%) | 99 (8.1%) |
| Other | 0 (0.0%) | 0 (0.0%) | 2 (4.5%) | 2 (1.4%) | 27 (2.2%) |
| Missing | 0 (0.0%) | 0 (0.0%) | 6 (13.6%) | 6 (4.2%) | 21 (1.7%) |
| **TNF Failure Status** | | | | | |
| Failed TNF | 58 (58.6%) | 36 (70.6%) | 39 (88.6%) | 97 (67.8%) | 585 (48.1%) |
| Otherwise | 41 (41.4%) | 15 (29.4%) | 5 (11.4%) | 46 (32.2%) | 632 (51.9%) |
| **Immunogenicity** | | | | | |
| Positive | 3 (3.0%) | 2 (3.9%) | 1 (2.3%) | 4 (2.8%) | 27 (2.2%) |
| Otherwise | 96 (97.0%) | 49 (96.1%) | 43 (97.7%) | 139 (97.2%) | 1,190 (97.8%) |

Abbreviations: N=number of participants; TNF=tumor necrosis factor.

The GOF plots using the paediatric PopPK model from interim analysis for the new paediatric dataset showed that the PREDs and IPREDs aligned well along the identity line and the CWRES were generally centered along the zero line with homogenous variation relative to the PREDs and time (Figure 6). Minor numerical differences were noticed at the higher concentration range when comparing observations with PREDs and IPREDs in participants weighing <40 kg.

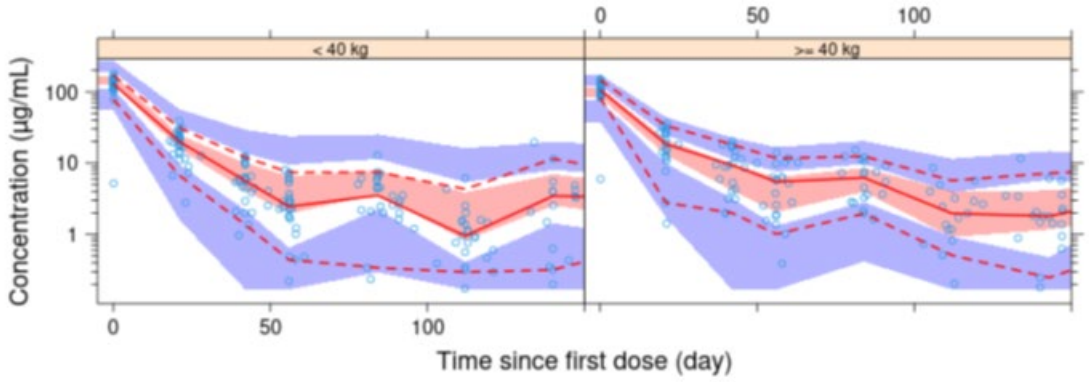
**Figure 6: Basic GOF plots using the final paediatric model for the new paediatric dataset in CNTO1275CRD3004**



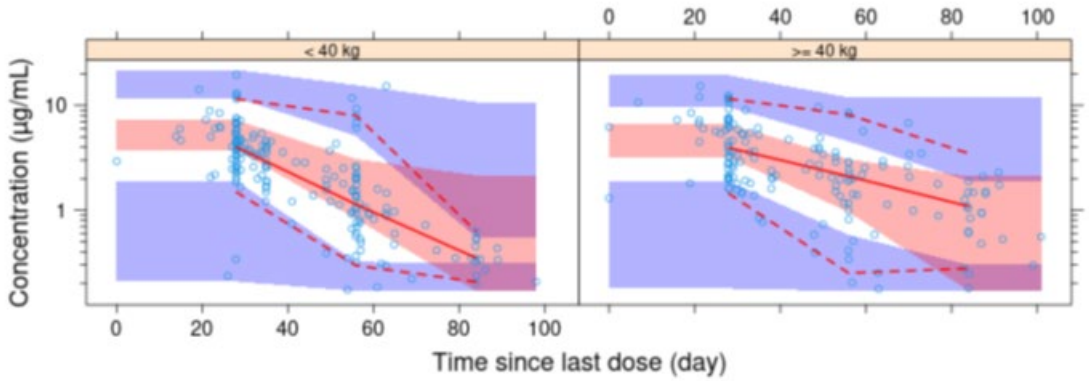

Units: Observations or predictions=µg/mL; Time=day.
Abbreviations: GOF=goodness-of-fit; PopPK=population pharmacokinetic(s).
Note: The black solid line is the line of identity or the zero line, and the red solid line is the trend line. The blue circles are the observations. The new paediatric dataset consists of 552 ustekinumab concentrations from 51 additional paediatric participants in CNTO1275CRD3004 that were not available during paediatric PopPK model development for the interim analysis. The left panels and the right panels represent the new paediatric participants with body weight <40 kg and ≥40 kg, respectively.

VPC plots using the paediatric PopPK model from interim analysis for the new paediatric dataset stratified by weight groups and treatment phase indicated that the model adequately captured the median concentration-time profile of ustekinumab, as well as the associated variabilities, across the weight groups and treatment phases in the new paediatric dataset (Figure 7). Of note: GOF and VPC plots created using the full paediatric dataset also showed adequate model performance (data not shown).

**Figure 7: VPCs using the final paediatric model for the new paediatric dataset in CNTO1275CRD3004 induction period, stratified by body weight <40 kg and ≥40 kg**




**Maintenance period, stratified by body weight <40 kg and ≥40 kg**




Abbreviations: CI=confidence interval; IV=intravenous; PopPK=population pharmacokinetic(s); SC=subcutaneous; VPC=visual predictive check(s).

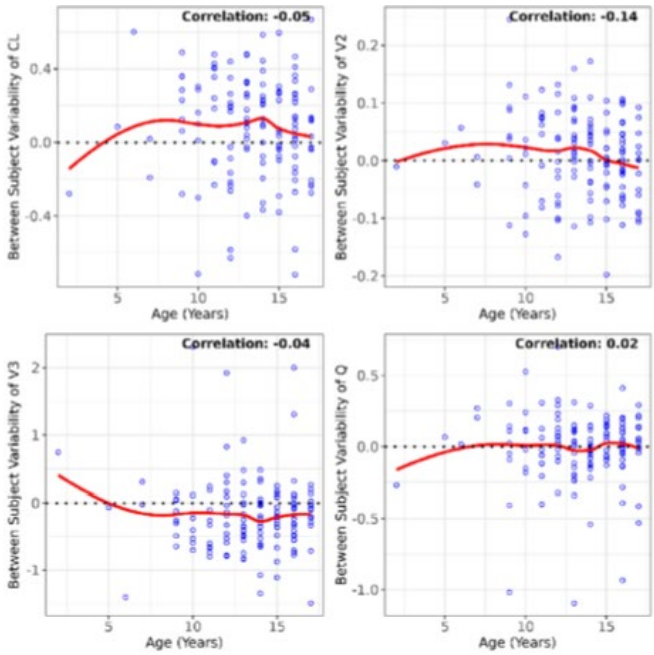
Note: The new paediatric dataset consists of 552 ustekinumab concentrations from 51 additional paediatric participants in CNTO1275CRD3004 that were not available during paediatric PopPK model development for the interim analysis. The upper panels show the time course following IV induction treatment, stratified by body weight <40 kg and ≥40 kg, whereas the lower panels show the time course following SC maintenance treatment, stratified by body weight <40 kg and ≥40 kg. Blue circles are observed data. Solid red lines are medians, dashed red lines are the 5th and 95th percentiles of the observations. The shaded red area represents the 95% CI of the median and the shaded blue areas represent the 95% CI of the 5th and 95th percentiles predicted by the model.

Sensitivity analysis was performed by re-estimating the structural PK parameters in the paediatric PopPK model from the interim analysis using the full paediatric dataset. The re-estimated structural PK parameters were similar to those of the original paediatric PopPK model from the interim analysis. Despite an increase in sample size, the covariate effects exhibited high imprecision in their estimates using the full paediatric dataset, and the direction of these covariate effects in the ETA plots from the paediatric base model aligned with existing findings in the adult model. A slight underprediction was observed in the VPC for paediatric participants weighing ≥40 kg following maintenance treatment.

These results confirmed that the paediatric PopPK model from the interim analysis was verified, and that no model update was needed. Therefore, the paediatric PopPK model from the interim analysis was considered to be the final paediatric model. The typical population values of CL, Q, V2, and V3 in participants with a median body weight of approximately 70 kg were 0.29 L/day, 0.17 L/day, 4.06 L, and 2.29 L, respectively. The typical values of ka and SC F1 were 0.18 $day^{-1}$ and 81%, respectively.

The correlations between age and ETAs on disposition parameters in the full paediatric dataset are presented in Figure 8.

**Figure 8: Scatter plot of age versus ETAs on disposition parameters for the final paediatric model in the full paediatric dataset**




Abbreviations: CL=clearance; ETA=individual random effect; Q=intercompartmental flow; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment; Week M-44=Maintenance Week 44.
Note: The full pediatric dataset is defined as 1,552 ustekinumab concentrations from 143 pediatric participants from CNTO1275CRD1001 and CNTO1275CRD3004 at the Week M-44 database lock.

No correlation was observed between age and ETA on CL, V2, V3, and Q, suggesting that disposition parameters of ustekinumab do not change across age within the paediatric participants, once the body weight effect was accounted for.

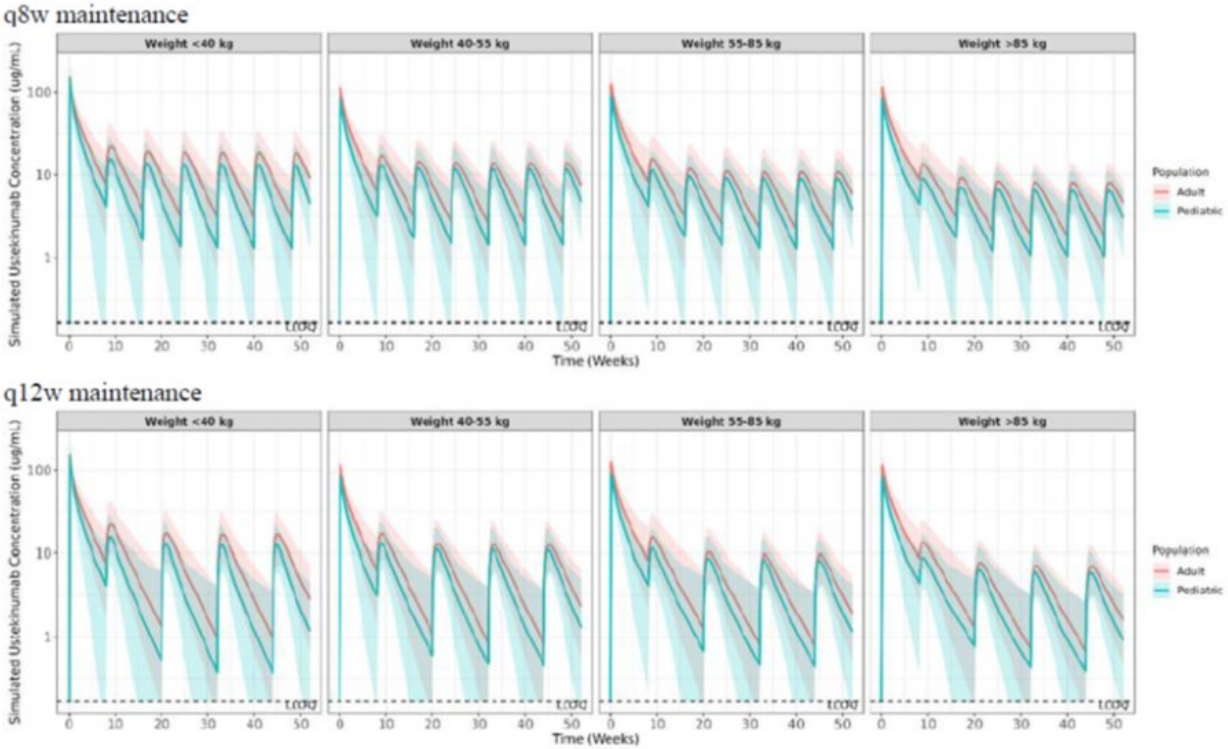
***PK simulations***

Simulations based on the paediatric PopPK model and the adult PopPK model were performed to compare the systemic exposures between paediatric participants with CD following the proposed dose regimens, and those in adult participants with CD who received ustekinumab at the approved standard dose regimen (i.e., weight-tier induction doses followed by 90 mg SC q8w or q12w).

*Comparison of simulated exposure between paediatric and adult participants by weight groups*

The overlay of simulated PK profiles in adult and paediatric participants is shown in Figure 9.

**Figure 9: Comparison of the simulated serum concentration-time profiles of ustekinumab by weight group in paediatric and adult participants**

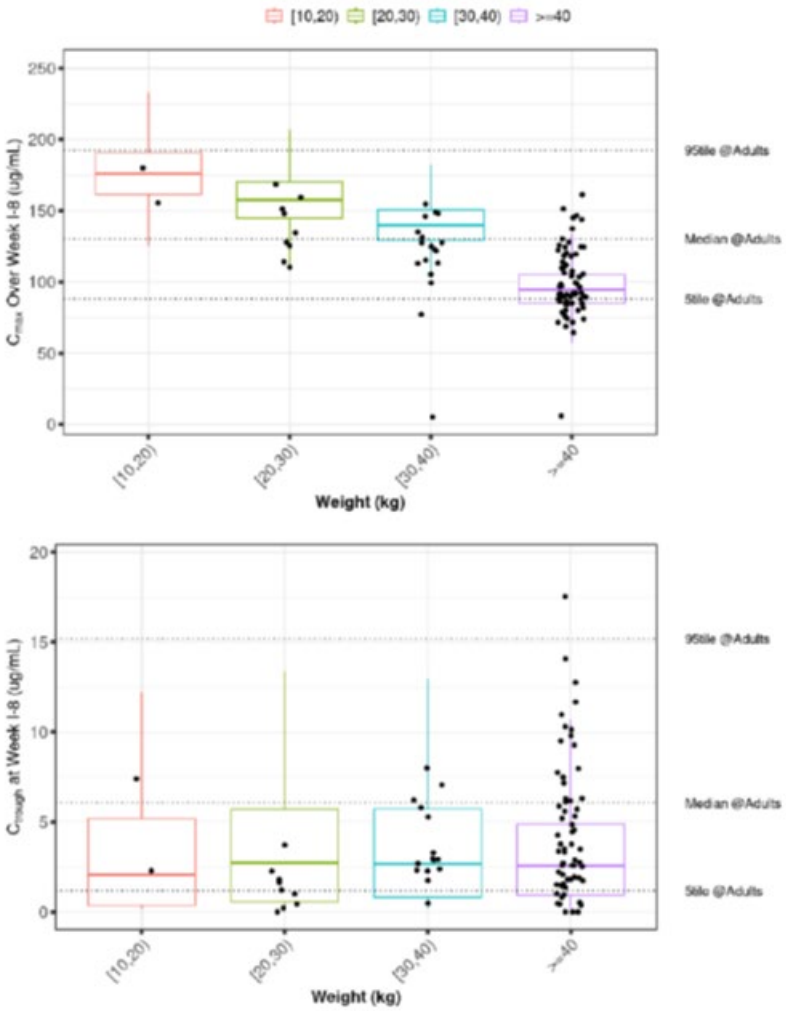



Abbreviations: IV=intravenous; LLOQ=lower limit of quantification; PK=pharmacokinetic(s); qXw=every X weeks.
Note: Lines represent medians of the simulated values. Shaded regions represent the 5th to 95th percentile ranges. The upper and lower panel show PK profiles of ustekinumab with single IV induction treatment followed by q8w or q12w maintenance treatment, respectively. For each weight group, simulation was performed based on 1,000 virtual paediatric or adult participants.

The concentration-time profiles of ustekinumab in paediatric participants largely overlapped with those in adult participants, where, on average, the predicted $C_{trough}$ in more than 71% of paediatric participants fell within the 90% prediction interval of adult exposures following either induction or maintenance treatment across weight groups

Additional simulations of PK profiles in paediatric participants stratified into body weight classes 10 to <20 kg, 20 to <30 kg, and 30 to <40 kg were performed, and these exposures were compared with model-predicted exposure in adults and paediatric participants ≥40 kg. Boxplots summaries of ustekinumab exposure metrics ($C_{max}$ and $C_{trough}$) following IV induction and SC maintenance ustekinumab treatment are presented in Figure 10 and Figure 11, respectively.

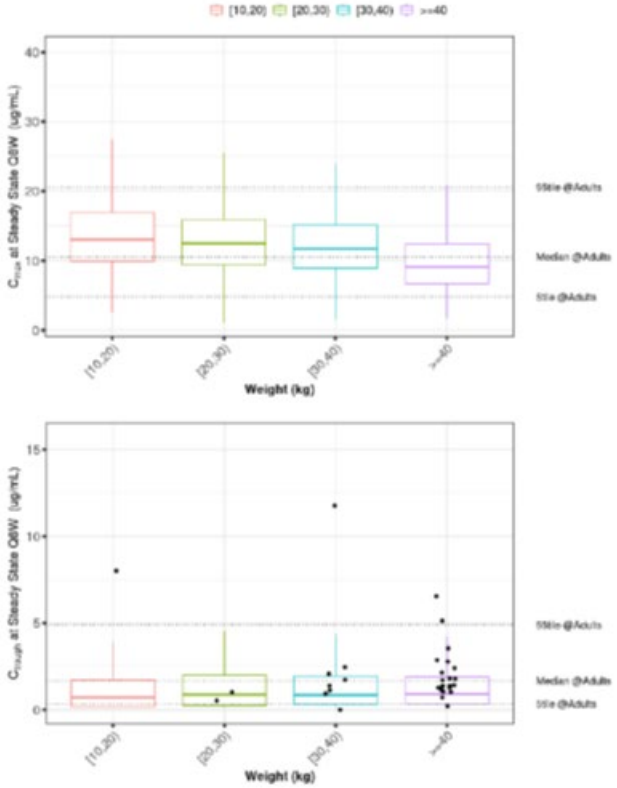
**Figure 10: Ustekinumab exposure metrics ($C_{max}$ and $C_{trough}$) by body weight subgroups, following tl proposed BSA-adjusted IV doses for paediatric participants with CD <40 kg, or approved body weight tiered fixed IV induction doses in paediatric participants with CD ≥40 kg**



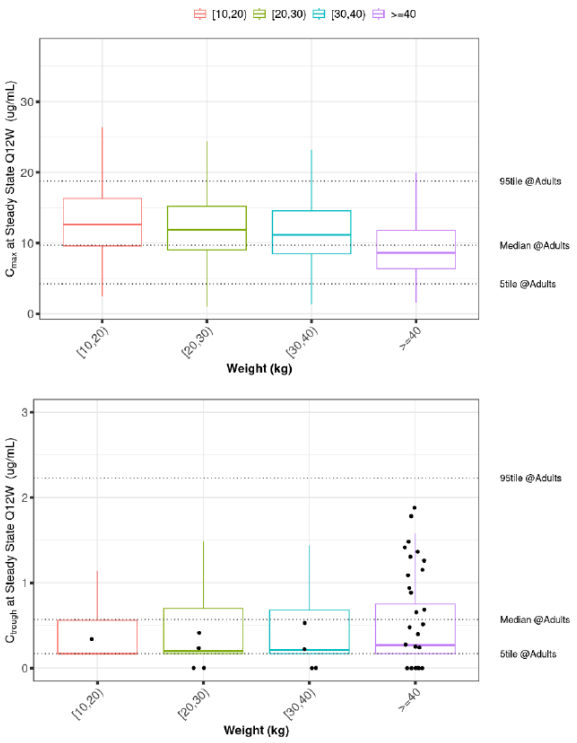

*Note: Horizontal dashed lines show the 90% prediction interval of adult exposures.*

**Figure 11: Ustekinumab exposure metrics (Steady-state $C_{max}$ and $C_{trough}$) by body weight subgroups, following the proposed BSA-adjusted SC doses for paediatric participants with CD <40 kg, or approved fixed SC maintenance doses in paediatric participants with CD ≥40 kg**

**A: q8w Dosing**




**B: q12w Dosing**




*Note: Horizontal dashed lines show the 90% prediction interval of adult exposures.*

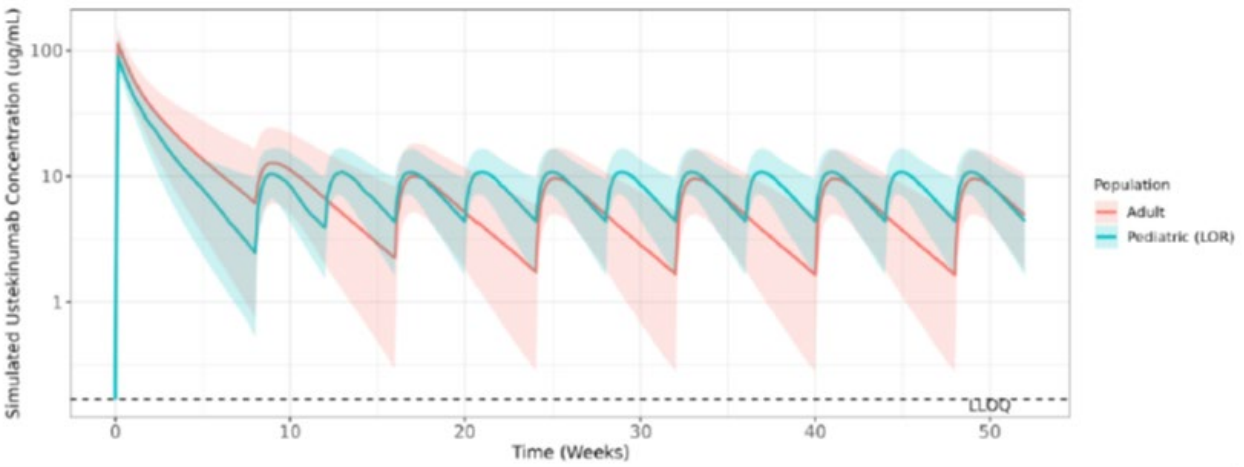
Overall, systemic ustekinumab exposures during induction and maintenance in the different body weight subgroups of participants <40 kg (10 to <20 kg, 20 to <30 kg, and 30 to <40 kg) following the proposed BSA-adjusted dosage were comparable to those who received approved ustekinumab doses in the ≥40 kg group. Furthermore, these ustekinumab exposures were generally within the range of those established to be safe and effective in the adult CD population.

*Exposure Optimising Substudy Comparison of simulated exposure between paediatric participants receiving q4w SC maintenance treatment and adults receiving q8w SC maintenance treatment*

In the Exposure Optimising Substudy of CRD3004, 26 paediatric participants experienced LOR and had low ustekinumab trough concentrations (<1.4 ug/mL). The median individual post hoc CL of ustekinumab in these participants was higher compared with those who did not experience LOR. Simulations were performed to compare exposure in LOR paediatric participants (with low ustekinumab exposure) who received q4w dosing with that in adults receiving q8w SC maintenance treatment.

As shown in Figure 12, the predicted concentration-time profiles of ustekinumab in paediatric participants who had low ustekinumab trough levels, experienced LOR, and received ustekinumab q4w largely overlapped with those in adult participants receiving q8w SC maintenance treatment. The maximum concentrations at steady state were predicted to be comparable between paediatric participants receiving q4w and adult participants receiving q8w, with $C_{max}$ 11.96% higher for q4w doses in paediatric participants. As expected, steady-state trough concentrations were predicted to be 167% higher in paediatric participants following q4w treatment compared with adults following q8w treatment in the maintenance period, resulting in a 53.4% increase in $AUC_{ss,q8w}$ in paediatric participants.

**Figure 12: Comparison of the simulated serum concentration-time profiles of ustekinumab in paediatric participants from CNTO1275CRD3004 who lost response and received q4w SC maintenance treatment with those in adult participants from CNTO1275CRD3001 and CNTO1275CRD3002 receiving the q8w SC maintenance treatment**




Abbreviations: EBE=empirical Bayesian estimates; LLOQ=lower limit of quantification; LOR=loss of response; qXw=every X weeks; SC=subcutaneous.

Note: Lines represent medians of the simulated values. Shaded regions represent the 5th to 95th percentile ranges. Comparison was made between 1,000 paediatric participants (sampling with replacement from the 26 paediatric LOR participants in CNTO1275CRD3004) and 1,196 adult participants from CNTO1275CRD3001 and CNTO1275CRD3002. The individual post-hoc EBE parameters from the final paediatric model and the updated adult model were used for paediatric and adult simulations, respectively.

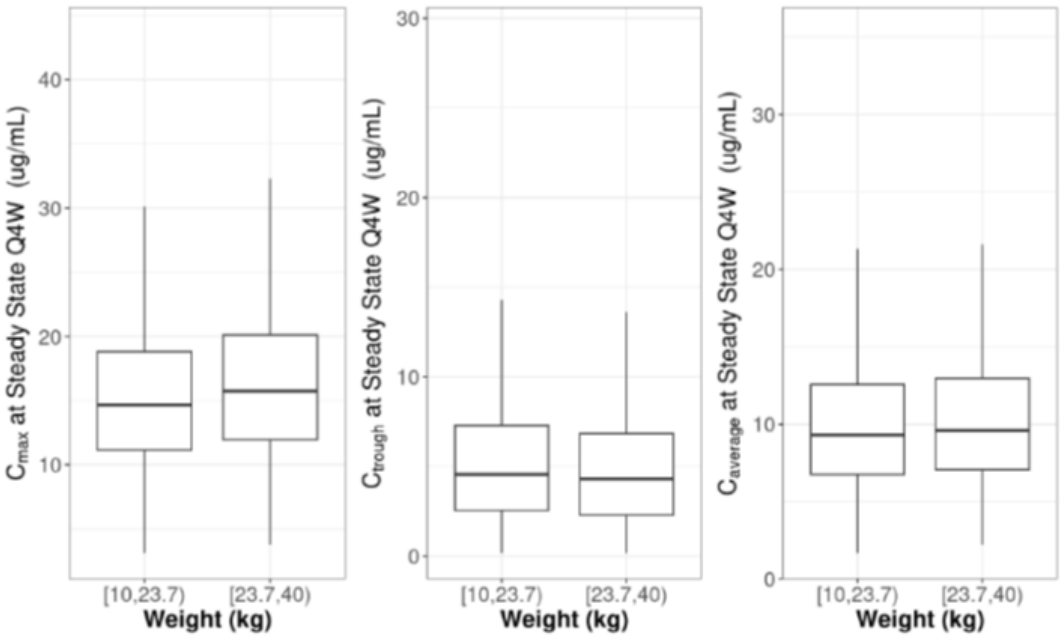
**Table 7: Median (90% prediction intervals) of simulated exposures of ustekinumab in paediatric participants from CNTO1275CRD3004 who were loss of response receiving qw4 SC maintenance treatment and adult participants from CNTO1275CRD3001 and CNTO1275CRD3002 receiving q8w SC maintenance treatment**

| | | N | Median (90% Prediction Intervals) |
|---|---|---|---|
| $AUC_{ss,q8w}$ (µg·day/mL) | Adult | 1,196 | 285.57 (129.9-575.14) |
| | Pediatric (LOR) | 1,000 | 438.19 (241.03-715.84) |
| | Difference | | 53.44 |
| $C_{max,ss,q8w}$ (µg/mL) | Adult | 1,196 | 9.7 (5.13-16.35) |
| | Pediatric (LOR) | 1,000 | 10.86 (7.21-16.67) |
| | Difference | | 11.96 |
| $C_{trough,ss,q8w}$ (µg/mL) | Adult | 1,196 | 1.65 (0.28-5.12) |
| | Pediatric (LOR) | 1,000 | 4.41 (1.64-9.48) |
| | Difference | | 167.27 |

Abbreviations: $AUC_{ss,q8w}$=area under the concentration-time curve over a SC maintenance dose interval of 8 weeks at steady state; $C_{max,ss,q8w}$=maximum concentration over a SC maintenance dose interval of 8 weeks at steady state; $C_{trough,ss,q8w}$=trough concentration over a SC maintenance dose interval of 8 weeks at steady state; LOR=loss of response; N=number of participants; qXw=every X weeks; SC=subcutaneous.
Note: The $AUC_{ss,q8w}$ for pediatrics was summarized over 2 dose intervals after q4w maintenance treatment.

As the lowest body weight of paediatric LOR participants was 23.7 kg, additional simulations were performed for q4w dosing for the overall paediatric population, and ustekinumab exposures at steady state ($C_{max}$, $C_{trough}$, and $C_{average}$) were compared between those with body weight ranging from 10 to <23.7 kg versus 23.7 to <40 kg (Figure 13).

**Figure 13: Comparison of ustekinumab exposure metrics (steady-state $C_{max}$, $C_{trough}$, and $C_{average}$) between paediatric CD participants 10 to <23.7 kg versus 23.7 to <40 kg following q4w dosing**




The comparison indicated similar exposure between groups.

## 2.4.3. Pharmacodynamics

No specific clinical PD studies were performed in paediatric patients with CD.

**Immunogenicity**

***Phase 3 CD Study CRD3004***

*Through Week I-8*

Among participants who received induction with approximately 6 mg/kg IV ustekinumab and had appropriate samples through Week I-8, 1 (1.0%) of 101 participants was positive for antibodies to ustekinumab through Week I-8. The participant positive for antibodies was positive for NAbs.

*From Week I-0 Through Week M-44*

Among participants who received ustekinumab during both induction and maintenance (i.e. participants who were in clinical response at Week I-8 or at Week M-8, had received at least 1 administration of ustekinumab during maintenance, and had appropriate samples for detection of antibodies to ustekinumab), 3 (3.3%) of 91 participants were positive for antibodies to ustekinumab through Week M-44. All 3 participants positive for antibodies were positive for NAbs.

***Comparison of immunogenicity between paediatric and adult participants with CD***

The incidence of antibodies to ustekinumab in paediatric participants (3.0%; 4 of 135 participants) was similar to the incidence in adult participants (3.1%; 9 of 287 participants) with CD (data not shown).

## 2.4.4. PK/PD modelling

**Exposure-response analyses for efficacy**

The E-R analysis for efficacy in paediatric participants with CD was performed for 3 clinical endpoints, including clinical remission and clinical response at Week I-8 in relation to $C_{trough,weekI8}$ and clinical remission at Week M-44 in relation to $C_{trough,weekM44}$. The main objectives were to characterise the relationships between ustekinumab exposure and clinical efficacy endpoints in paediatric participants with CD across the full body weight range and to assess the similarity of ustekinumab E-R between paediatric and adult patients with CD. The planned analysis methods for each endpoint are provided in Table 8.

**Table 8: Summary of E-R analysis for efficacy endpoints**

| Efficacy Endpoint | Study | Analysis Method |
|---|---|---|
| Clinical remission at Week I-8 (global primary endpoint) | CNTO1275CRD3004 (CNTO1275CRD1001 was included for modeling analysis) | Graphical exploratory analysis and modeling analysis |
| Clinical response at Week I-8 | CNTO1275CRD3004 | Graphical exploratory analysis |
| Clinical remission at Week M-44 (US-specific endpoint) | CNTO1275CRD3004 | Graphical exploratory analysis and modeling analysis |

Abbreviations: E-R=exposure-response; US=United States; Week I-8=Induction Week 8; Week M-44=Maintenance Week 44.

The current E-R analyses were performed using data across the full body weight range from the Week 44 DBL (WeekM44) of CRD3004 along with data across the full body weight range from the paediatric study CRD1001.

For the induction endpoints (clinical remission and clinical response at Week I-8), 99 paediatric participants from CRD3004 were included in the graphical exploratory E-R analysis (29 paediatric participants with body weight <40 kg and 70 paediatric participants with body weight ≥40 kg). An additional 41 paediatric participants from CRD1001 were included in the E-R modelling for clinical

remission at Week I-8 (18 paediatric participants with body weight <40 kg and 23 paediatric participants with body weight ≥40 kg).

For the maintenance endpoint (clinical remission at WeekM-44), 85 paediatric participants who were induction responders from CRD3004 were included in the graphical exploratory and modelling E-R analyses (21 paediatric participants with body weight <40 kg and 64 paediatric participants with body weight ≥40 kg).

To evaluate the similarity of the E-R relationship between paediatric and adult participants, available results from previous adult E-R analyses were used.

For the exploratory graphical ER analysis, the proportion of participants achieving the clinical efficacy endpoint at Week I-8 and Week M-44 was plotted by ustekinumab exposure tertile groups based on their model-predicted individual exposures. Results of the graphical exploratory analysis for paediatric participants were compared with those performed for adult participants.

For the ER modelling analyses, the previous adult linear logistic regression ER models for clinical remission at Week I-8 and at Week M-44, were refitted with the E-R data from paediatric Studies CRD3004 and CRD1001. As there were no placebo data in paediatric participants from CRD3004 and CRD1001, the placebo effect was fixed (by fixing the intercept of the linear logistic regression model) to that from the adult model and assumed to be the same. Then, covariates that were identified as significant in the adult models were explored by graphical analysis, including TNF failure status, baseline CDAI score, and baseline CRP. Covariate relationships that were not evident in the graphical analyses of the paediatric data were not included in the paediatric ER model analysis. Finally, the E-R data from paediatric participants were fitted with nonlinear logistic regression models with additive placebo and $E_{max}$ drug effects on the logit probability scale, which was based on the prior knowledge from the previous adult E-R model for clinical remission at Week I-8 and at Week M-44, as well as the previous paediatric E-R model for clinical remission at Week I-8 from the interim analysis. A GOF plot was used to compare the observed and model-predicted proportions of participants in clinical remission at Week I-8 and Week M-44 in the predicted exposure tertile bins.

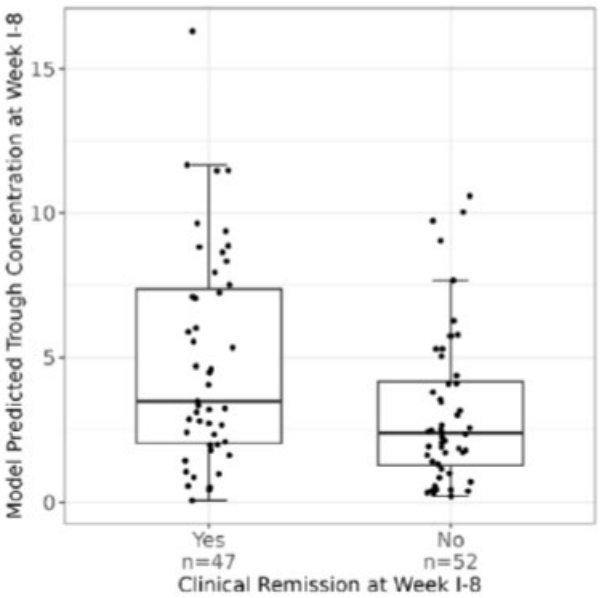
***Results***

Clinical Remission at Week I-8

*Exploratory graphical analysis*

Figure 14 shows the distribution of model-predicted $C_{trough,weekI8}$ in paediatric participants with and without clinical remission at Week I-8 from CRD3004. The model-predicted $C_{trough,weekI8}$ overlapped between paediatric participants with and without clinical remission, with numerically higher median $C_{trough,weekI8}$ observed in those with clinical remission.

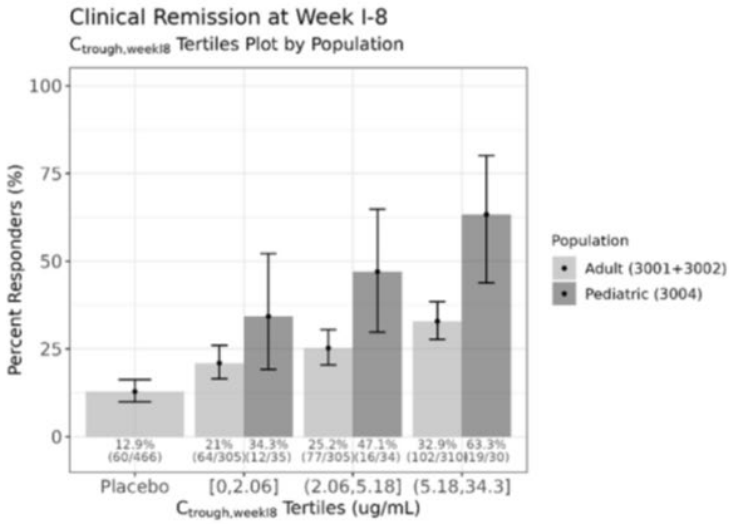
**Figure 14: E-R relationship for clinical remission at week 1-8 in paediatric CNTO1275CRD3004**




Abbreviations: CI=confidence interval; $C_{trough}$=trough concentration; E-R=exposure-response; N=number of participants; n=number of participants; Week I-X=Induction Week X.
Note: Error bars are the 95% CIs of response rates.
Note: Black dots are the model-predicted individual $C_{trough}$ at Week I-8. Clinical remission at Week I-8 in pediatric participants was summarized in participants who had measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m$^2$ (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275CRD3004 (N=99).

Figure 15 shows the E-R relationship of paediatric participants from CRD3004 compared to that of adult participants from CRD3001 and CRD3002. A similar positive E-R trend was observed for clinical remission at Week I-8 in relation to predicted $C_{trough,weekI8}$ in adult and paediatric participants, with a higher (but more variable) proportion of participants with clinical remission in paediatric participants in each predicted $C_{trough,weekI8}$ tertile group.

**Figure 15: E-R relationship for clinical remission at week 1-8 versus predicted $C_{trough,weekI8}$ in paediatric study CNTO1275CRD3004 and adult studies CNTO1275CRD3001 and CNTO1275CRD3002**




Abbreviations: 3001=CNTO1275CRD3001; 3002=CNTO1275CRD3002; 3004=CNTO1275CRD3004; CI=confidence interval; $C_{trough,weekI8}$=trough concentration for IV induction dose at Week I-8; E-R=exposure-response; IV=intravenous; N=number of participants; Week I-X=Induction Week X.

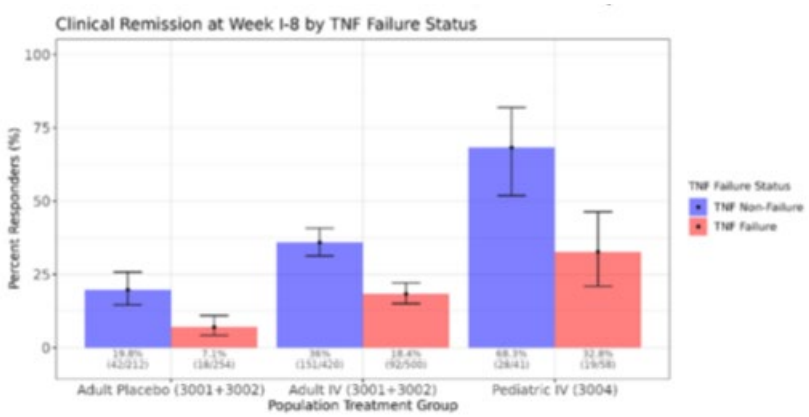
Note: Error bars are the 95% CIs of the proportions of participants with clinical response in the respective exposure tertile groups.

Note: E-R relationship in adults was summarized in participants who received ustekinumab 130 mg or ~6 mg/kg and placebo at Week I-0 from CNTO1275CRD3001 and CNTO1275CRD3002 (N=1,386). E-R relationship in paediatric participants was summarized in participants who have measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m$^2$ (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275CRD3004 (N=99). Exposure tertile cutoffs for $C_{trough,weekI8}$ were based on pooled data from paediatric Study CNTO1275CRD3004 and adult Studies CNTO1275CRD3001 and CNTO1275CRD3002.

Overall, the proportion of participants with clinical remission at Week I-8 was higher in paediatric participants (47 [46.5%] of 101 participants in CRD3004) compared with adult participants (136 [29.7%] of 458 participants in CRD3001 and CRD3002).

Similar to adults, at a given concentration, the proportion of participants with clinical remission at Week I-8 was higher in the TNF non-failure population compared with the TNF failure population in paediatric participants (Figure 16).

**Figure 16: Clinical remission at week I-8 in paediatric study CNTO1275CRD3004 and adult studies CNTO1275CRD3001 and CNTO1275CRD3002, stratified by TNF failure status**



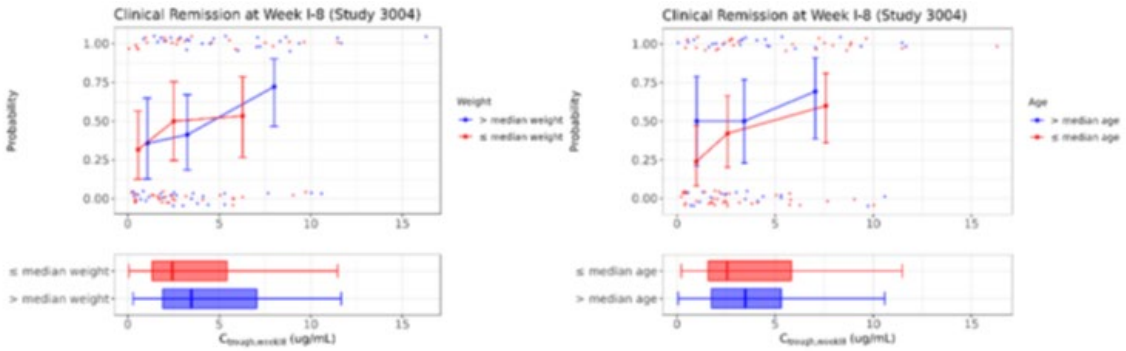

Abbreviations: 3001=CNTO1275CRD3001; 3002=CNTO1275CRD3002; 3004=CNTO1275CRD3004; CI=confidence interval; IV=intravenous; N=number of participants; TNF=tumor necrosis factor; Week I-X=Induction Week X.

Note: Error bars are the 95% CIs of the proportions of participants with clinical response in the respective exposure groups stratified by TNF failure status.

Note: Clinical remission at Week I-8 in adults was summarized in participants who received ustekinumab 130 mg or ~6 mg/kg and placebo at Week I-0 from CNTO1275CRD3001 and CNTO1275CRD3002 (N=1,386). Clinical remission at Week I-8 in paediatric participants was summarized in participants who have measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m$^2$ (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275CRD3004 (N=99).

The E-R relationship of clinical remission at Week I-8 and the predicted $C_{trough,weekI8}$ in paediatric Study CRD3004 stratified by age group or weight group is shown in Figure 17.

**Figure 17 E-R relationship of clinical remission at week I-8 versus the predicted $C_{trough,weekI8}$ in paediatric study CNTO1275CRD3004, stratified by age or weight group**




Abbreviations: 3004=CNTO1275CRD3004; $C_{trough,weekI8}$=trough concentration for IV induction dose at Week I-8; CI=confidence interval; E-R=exposure-response; IV=intravenous; N=number of participants; PopPK=population pharmacokinetic(s); Week I-X=Induction Week X.

Note: Connected dots with error bars are the observed median and 95% CIs of probability in the respective exposure tertile groups. Dots at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders, respectively, which were predicted based on the actual dose regimen and individual PopPK model parameter estimates in paediatric participants who have measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m$^2$ (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275CRD3004 (N=99). Box plots at the bottom represent the distribution of the individual model-predicted exposure metrics in subgroups.

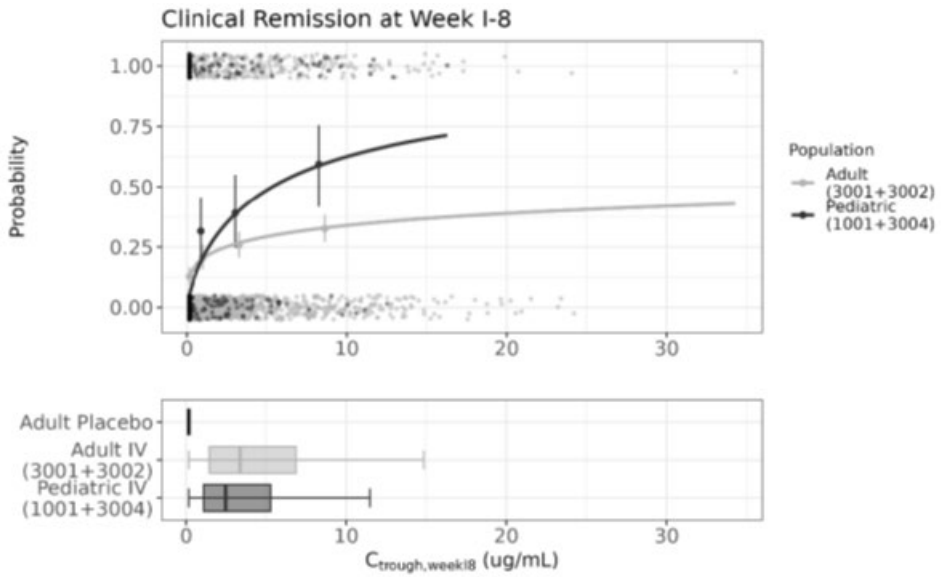
Note: Stratification for age was as follows: 2 to 14 years versus 14 to 17 years. Stratification for weight was as follows: 12.6 to 47.2 kg versus 47.2 to 87.6 kg.

Age and weight had no clear effect on the E-R relationship for clinical remission at Week I-8 in paediatric participants. The 95% CIs of the proportions of participants with clinical remission across the $C_{trough,weekI8}$ tertile groups were largely overlapping.

*Modelling analysis*

The linear logistic regression exploration demonstrated a similar positive E-R trend between clinical remission at Week I-8 and $C_{trough,weekI8}$ in adult and paediatric participants, while a higher probability of clinical remission was observed in paediatric participants (Figure 18).

**Figure 18: Linear logistic regression of clinical remission at week I-8 and $C_{trough,weekI8}$ in adult and paediatric participants**




Abbreviations: 1001=CNTO1275CRD1001; 3001=CNTO1275CRD3001; 3002=CNTO1275CRD3002; 3004=CNTO1275CRD3004; CI=confidence interval; $C_{trough,weekI8}$=trough concentration for IV induction dose at Week I-8; E-R=exposure-response; IV=intravenous; N=number of participants; PopPK=population pharmacokinetic(s); Week I-X=Induction Week X.

Note: Solid dots with error bars are the observed median and 95% CI of probability in the respective exposure tertile groups. The smoothed solid lines are logistic regression model-predicted E-R relationships of clinical remission at Week I-8 in adult or pediatric participants.

Note: Dots at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders for clinical remission at Week I-8, respectively, where the black dots represent the placebo group from adult studies and dark and light grey dots represent adult or pediatric participants receiving IV induction treatment, respectively. The individual exposure metrics were predicted based on actual doses and individual PopPK model parameter estimates in pediatric participants across the full body weight range who received ustekinumab at Week I-0 from CNTO1275CRD1001 and CNTO1275CRD3004 (N=140, left panel) or adults who received 130 mg or ~6 mg/kg ustekinumab or placebo at Week I-0 from CNTO1275CRD3001 and CNTO1275CRD3002 (N=1,386). Box plots at the bottom represent the distribution of the individual model-predicted exposure metrics in the placebo group from adults, and adults from CNTO1275CRD3001 and CNTO1275CRD3002 or pediatric participants from CNTO1275CRD1001 and CNTO1275CRD3004 receiving IV induction treatment.

The effect of TNF failure status was similar between adult and paediatric patients, where participants who had previously failed on TNF-antagonist therapy have a lower proportion of participants in clinical remission relative to the TNF non-failure subpopulation. The effect of TNF failure status on placebo effect and $EC_{50}$ was tested in the nonlinear logistic modeling of clinical remission at Week I-8 in paediatric participants. The effect of baseline PCDAI and baseline CRP on the E-R relationship for clinical remission at Week I-8 was not clear in paediatric participants compared with adult participants. Therefore, the effects of baseline PCDAI and baseline CRP were not included in the nonlinear logistic modeling of clinical remission at Week I-8.

The E-R relationship between $C_{trough,weekI8}$ and clinical remission at Week I-8 in paediatric participants with CD from CRD3004 and CRD1001 was characterised by an $E_{max}$ model with an additive placebo effect. As no placebo data are available in paediatric participants from CRD3004 and CRD1001, the placebo effect

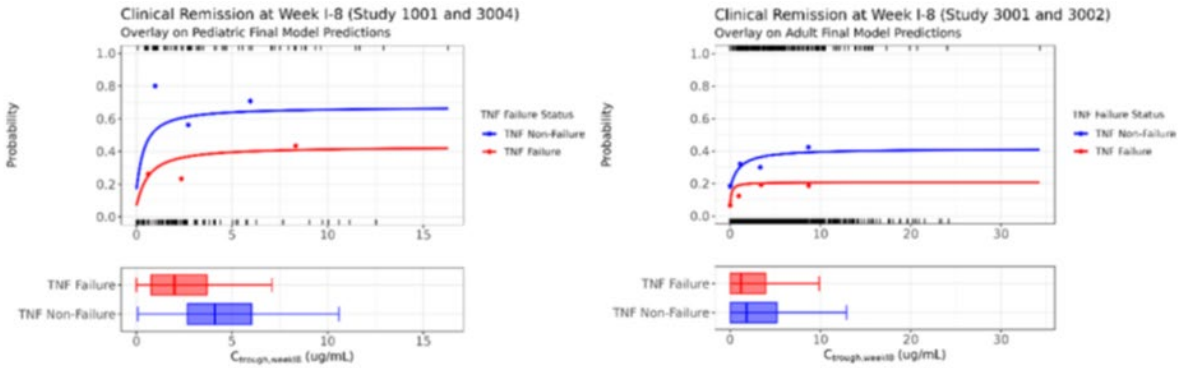
was fixed and assumed to be the same as that from the previously established adult model. The effect of anti-TNF failure status on the placebo effect was also retained from the previously established adult E-R model. Parameter estimates are presented in Table 9 and a GOF plot of the final model is shown in Figure 19. The larger RSE for $EC_{50}$ was likely the result of the limited data available at low concentrations due to the large induction dose (that limits the precision in the estimate at a relatively low $EC_{50}$ value).

**Table 9: Clinical remission at week I-8 – Final E-R model parameter estimates with fixed TNF failure status**

| Parameter | Estimate (RSE%) |
|---|---|
| **Placebo Effects (β)** | |
| $\beta_0$ | -1.60 Fixed |
| TNF Failure | -0.996 Fixed |
| **$E_{max}$** | |
| $E_{max,0}$ | 2.32 (18%) |
| **$EC_{50}$ (µg/mL)** | |
| $EC_{50,0}$ | 0.342 (134%) |

Abbreviations: $\beta_0$=logit probability for remission; $EC_{50}$=half maximal effective concentration; $E_{max}$=maximum drug effect; E-R=exposure-response; RSE=relative standard error; TNF=tumor necrosis factor; Week I-8=Induction Week 8.

**Figure 19: GOF plot of final paediatric model and final adult model for clinical remission at week I-8 in paediatric participants from CNTO1275CRD1001 and CNTO1275CRD3004 and adult participants from CNTO1275CRD3001 and CNTO1275CRD3002, stratified by TNF failure status**




Abbreviations: 1001=CNTO1275CRD1001; 3001=CNTO1275CRD3001; 3002=CNTO1275CRD3002; 3004=CNTO1275CRD3004; $C_{trough,weekI8}$=trough concentration for IV induction dose at Week I-8; $E_{max}$=maximum drug effect; E-R=exposure-response; GOF=goodness-of-fit; IV=intravenous; N=number of participants; PopPK=population pharmacokinetic(s); TNF=tumor necrosis factor; Week I-X=Induction Week X.

Note: Dots are the observed median of the probability in the respective exposure tertile groups. The solid smooth curves represent the model-predicted E-R relationships for subgroups stratified by TNF failure status while other covariates were fixed to be the same as the reference group in the final model. Short vertical lines at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders, respectively, which were predicted based on the actual dose regimen and individual PopPK model parameter estimates in paediatric participants across the full body weight range who received ustekinumab at Week I-0 from CNTO1275CRD1001 and CNTO1275CRD3004 (N=140, left panel) or adult participants who received 130 mg or ~6 mg/kg ustekinumab or placebo at Week I-0 in CNTO1275CRD3001 and CNTO1275CRD3002 (N=1,386, right panel). Box plots at the bottom of the figure represent the distribution of the individual model-predicted exposure metrics in subgroups.

The estimated $EC_{50}$ in the paediatric E-R model was 0.342 µg/mL, which is close to the value of 0.712 µg/mL from the previous adult E-R model, when compared to the broad range of $C_{trough}$ at Week I-8. This suggests that the E-R relationship between $C_{trough,weekI8}$ and clinical remission at Week I-8 in paediatric participants is likely similar to the E-R relationship in adults.

Sensitivity analyses were performed by estimating the $E_{max}$ and $EC_{50}$ of the paediatric E-R model for clinical remission at Week I-8 from the interim analysis, where the effect of TNF failure status on the placebo effect and on $EC_{50}$ were both retained and assumed the same as in the previous adult E-R model.

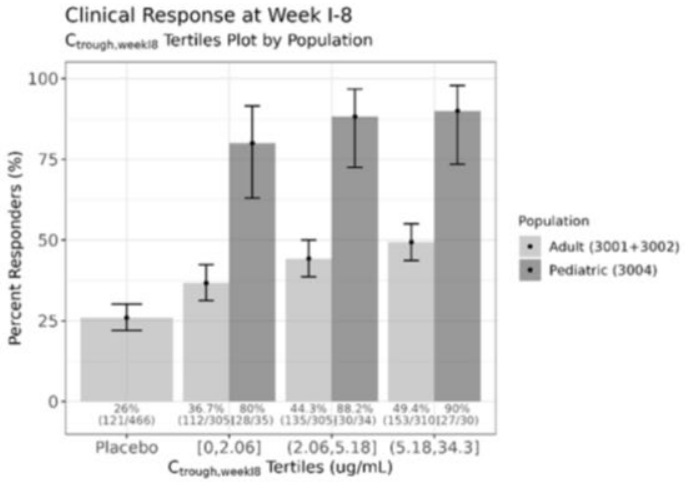
Underprediction of the observed median probability in the TNF non-failure subpopulation was observed in the GOF plot of this model (data not shown).

Clinical Response at Week I-8

*Exploratory graphical analysis*

Figure 20 shows the ER relationship for clinical response at Week I-8 in paediatric participants from CRD3004 in comparison with adult participants from CRD3001 and CRD3002. A similar positive E-R trend was observed for clinical response at Week I-8 in relation to predicted $C_{trough,weekI8}$ in adult and paediatric participants, with a higher (but more variable) proportion of participants with clinical response in paediatric participants in each predicted $C_{trough,weekI8}$ tertile group.

**Figure 20: E-R relationship of clinical response at week I-8 in paediatric study CNTO1275CRD3004 and adult studies CNTO1275CRD3001 and CNTO1275CRD3002**




Abbreviations: 3001=CNTO1275CRD3001; 3002=CNTO1275CRD3002; 3004=CNTO1275CRD3004; CI=confidence interval; $C_{trough,weekI8}$=trough concentration for IV induction dose at Week I-8; E-R=exposure-response; IV=intravenous; N=number of participants; Week I-X=Induction Week X.

Note: Error bars are the 95% CIs of the proportions of participants with clinical response in the respective exposure tertile groups.

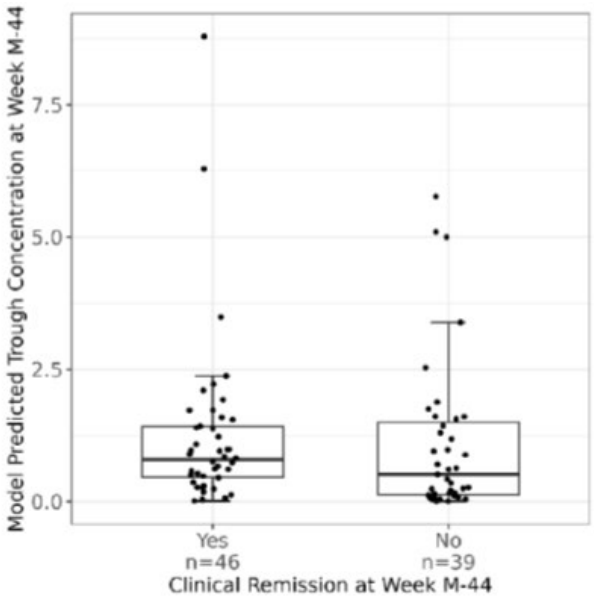
Note: The E-R relationship in adults was summarized in participants who received ustekinumab 130 mg or ~6 mg/kg and placebo at Week I-0 from CNTO1275CRD3001 and CNTO1275CRD3002 (N=1,386). The E-R relationship in paediatric participants was summarized in participants who have measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m$^2$ (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275CRD3004 (N=99). Exposure tertile cutoffs for $C_{trough,weekI8}$ were based on pooled data from paediatric Study CNTO1275CRD3004 and adult Studies CNTO1275CRD3001 and CNTO1275CRD3002.

Clinical Remission at Week M-44

*Exploratory graphical analysis*

Figure 21 shows the distribution of model-predicted $C_{trough,weekM44}$ in paediatric participants who were in clinical response at Week I-8 from CRD3004 with and without clinical remission at Week M-44. The model-predicted $C_{trough,weekM44}$ overlapped between paediatric participants with and without clinical remission, with numerically higher median $C_{trough,weekM44}$ observed in those with clinical remission.

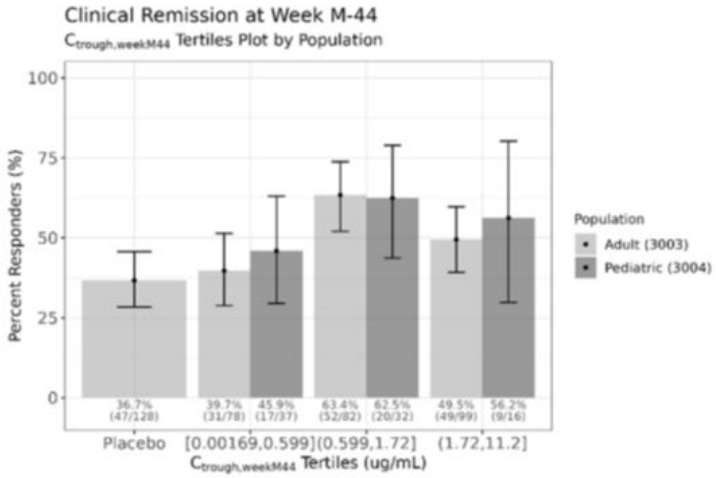
**Figure 21: E-R relationship for clinical remission at week M-44 in paediatric study CNTO1275CRD3004**




Abbreviations: CI=confidence interval; $C_{trough}$=trough concentration; E-R=exposure-response; n=number of participants; N=number of participants; qXw=every X weeks; SC=subcutaneous; Week M-X=Maintenance Week X.
Note: Error bars are the 95% CIs of response rates.
Note: Black dots are the model-predicted individual $C_{trough}$ at Week M-44. Clinical remission at Week M-44 in pediatric participants was summarized in participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m$^2$ (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275CRD3004 (N=85).

Figure 22 shows the E-R relationship of clinical remission at WeekM-44 in paediatric participants who were in clinical response at Week I-8 from CRD3004 in comparison with adult participants from CRD3003. A similar E-R trend was observed for clinical remission at Week M-44 in relation to predicted $C_{trough,weekM44}$ in adult and paediatric participants, with comparable proportions of participants with clinical remission in paediatric participants in each predicted $C_{trough,weekM44}$ tertile group.

**Figure 22: E-R relationship for clinical remission at week M-44 versus predicted $C_{trough,weekM44}$ in paediatric study CNTO1275CRD3004 and adult study CNTO1275CRD3003**



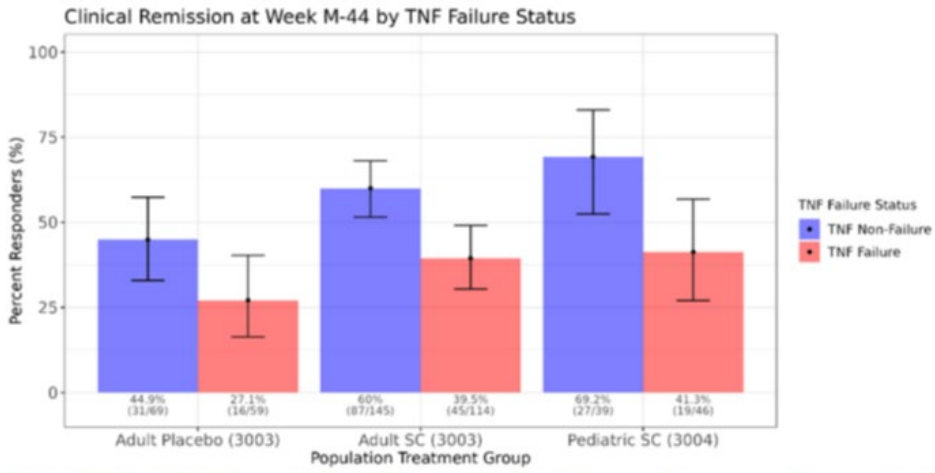

Abbreviations: 3003=CNTO1275CRD3003; 3004=CNTO1275CRD3004; $C_{trough,weekM44}$=trough concentration for SC maintenance dose at Week M-44; CI=confidence interval; E-R=exposure-response; N=number of participants; qXw=every X weeks; SC=subcutaneous; Week M-X=Maintenance Week X.

Note: Error bars are the 95% CIs of the proportions of participants with clinical response in the respective exposure tertile groups.

Note: The E-R relationship in adults was summarized in participants who were randomized to receive SC maintenance regimens of placebo, 90 mg q8w, or 90 mg q12w in CNTO1275CRD3003 (N=387). E-R relationship in paediatric participants was summarized in participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m$^2$ (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275CRD3004 (N=85). Exposure tertile cutoffs for $C_{trough,weekM44}$ were based on pooled data from paediatric Study CNTO1275CRD3004 and adult Study CNTO1275CRD3003.

Overall, the proportion of participants with clinical remission at Week M-44 in paediatric participants was comparable to that in adult participants (46 [54.1%] of 85 participants in CRD3004 and 131 [51%] of 257 participants in CRD3003). Similar to adults, the proportion of paediatric participants with clinical remission at Week M-44 was higher in the TNF non-failure population compared with the TNF failure population (Figure 23).

**Figure 23: Clinical remission at week M-44 in paediatric study CNTO1275CRD3004 and adult study CNTO1275CRD3003, stratified by TNF failure status**



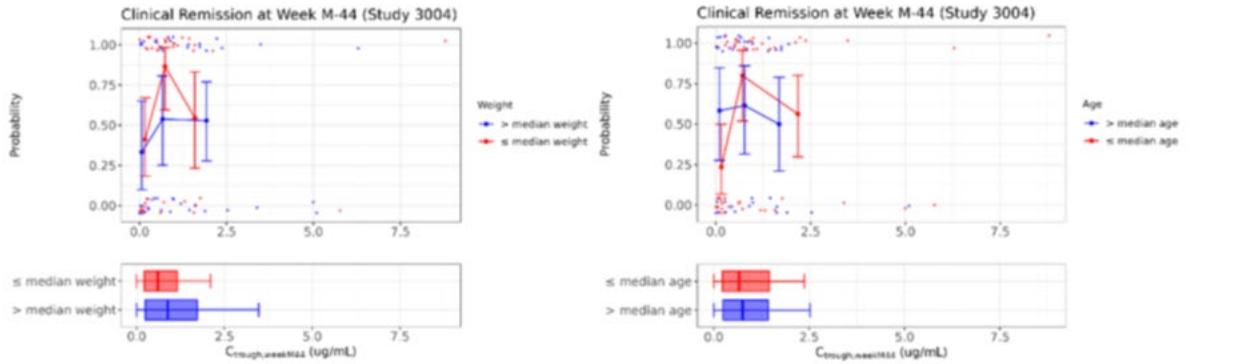

Abbreviations: 3003=CNTO1275CRD3003; 3004=CNTO1275CRD3004; CI=confidence interval; N=number of participants; qXw=every X weeks; SC=subcutaneous; TNF=tumor necrosis factor; Week M-X=Maintenance Week X.

Note: Error bars are the 95% CIs of response stratified by TNF failure status.

Note: Clinical remission at Week M-44 in adults was summarized in participants who were randomized to receive SC maintenance regimens of placebo, 90 mg q8w, or 90 mg q12w in CNTO1275CRD3003 (N=387). Clinical remission at Week M-44 in paediatric participants was summarized in participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m$^2$ (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275CRD3004 (N=85).

The E-R relationship of clinical remission at Week M-44 and the predicted $C_{trough,weekM44}$ in paediatric Study CRD3004 stratified by age group or weight group is shown in Figure 24.

**Figure 24: E-R relationship of clinical remission at week M-44 versus the predicted $C_{trough,weekM44}$ in paediatric study CNTO1275CRD3004, stratified by age or weight group**




Abbreviations: 3004=CNTO1275CRD3004; CI=confidence interval; E-R=exposure-response; $C_{trough,weekM44}$=trough concentration for SC maintenance dose at Week M-44; N=number of participants; PopPK=population pharmacokinetic(s); qXw=every X weeks; SC=subcutaneous; Week M-X=Maintenance Week X.

Note: Connected dots with error bars are the observed median and 95% CIs of probability in the respective exposure tertile groups. Dots at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders, respectively, which were predicted based on the actual dose regimen and individual PopPK model parameter estimates in paediatric participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m$^2$ (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275CRD3004 (N=85). Box plots at the bottom represent the distribution of the individual model-predicted exposure metrics in subgroups.

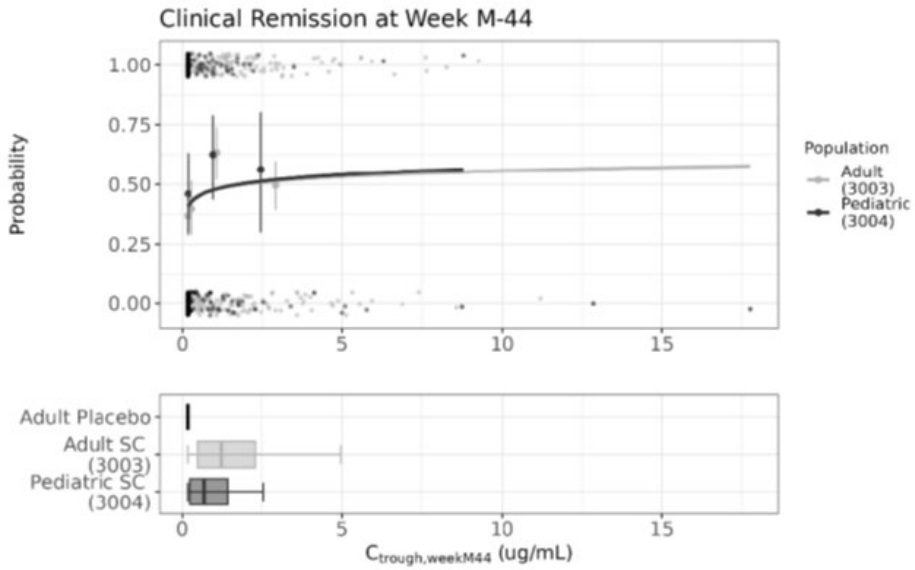
Note: Stratification for age was as follows: 2 to 14 years vs 14 to 17 years. Stratification for weight was as follows: 12.6-47.7 kg vs 47.7 -87.6 kg.

Age and weight had no clear effect on the E-R relationship for clinical remission at Week M-44 in paediatric participants who were in clinical response at Week I-8 from CRD3004. The 95% CIs of the proportions of participants with clinical remission across the $C_{trough,weekM44}$ tertile groups were largely overlapping for the age and weight subgroups.

*Modelling analysis*

The linear logistic regression exploration demonstrated a similar E-R trend between clinical remission at Week M-44 and $C_{trough,weekM44}$ in adult and paediatric participants (Figure 25).

**Figure 25: Linear logistic regression of clinical remission at week M-44 and $C_{trough,weekM44}$ in adult and paediatric participants**




Abbreviations: 3003=CNTO1275CRD3003; 3004=CNTO1275CRD3004; CI=confidence interval; $C_{trough,weekM44}$=trough concentration for SC maintenance dose at Week M-44; E-R=exposure-response; N=number of participants; PopPK=population pharmacokinetic(s); qXw=every X weeks; SC=subcutaneous; Week M-X=Maintenance Week X.

Note: Dots at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders for clinical remission at Week M-44, respectively, where the black dots represent the placebo group from adult studies, and dark and light grey dots represent adult or paediatric participants receiving SC maintenance treatment, respectively. The individual exposure metrics were predicted based on actual doses and individual PopPK model parameter estimates in paediatric participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m² (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275CRD3004 (N=85) or adults participants who were randomized to receive SC maintenance regimens of placebo, 90 mg q8w, or 90 mg q12w in CNTO1275CRD3003 (N=387). Box plots at the bottom represent the distribution of the individual model-predicted exposure metrics in the placebo group from adults, and adults from CNTO1275CRD3003 or paediatrics from CNTO1275CRD3004 receiving SC maintenance treatment.

The effect of TNF failure status was not clear in paediatric patients, likely due to the limited paediatric sample size. This effect could not be estimated well in the previous adult ER model. Therefore, the effect of TNF failure status was not explored in the nonlinear E-R model for clinical remission at Week M-44.

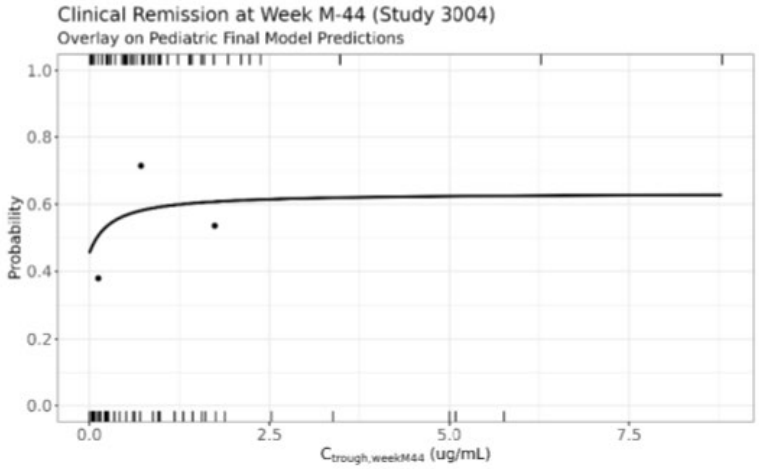
The E-R relationship between $C_{trough,weekM44}$ and clinical remission at Week M-44 in paediatric participants with CD who were induction responders from CRD3004 was adequately characterised by an $E_{max}$ model with an additive placebo effect. As no placebo data are available in paediatric participants from CRD3004, the placebo effect was fixed and assumed to be the same as that from the previously established adult model. Parameter estimates are presented in Table 10 and a GOF plot of the final model is shown in Figure 26. The large RSEs for $EC_{50}$ and $E_{max}$ were likely due to the limited paediatric sample size (N=85).

**Table 10: Clinical remission at week M-44 final $E_{max}$ E-R model parameter estimates with fixed TNF failure status**

| Parameter | Estimate (RSE%) |
|---|---|
| **Placebo Effects ($\beta_0$)** | -0.185 Fixed |
| **$E_{max}$** | 0.732 (50%) |
| **$EC_{50}$ (µg/mL)** | 0.31 (78%) |

Abbreviations: $\beta_0$=logit probability for remission; $EC_{50}$=half maximal effective concentration; $E_{max}$=maximum drug effect; E-R=exposure-response; RSE=relative standard error; TNF=tumor necrosis factor; Week M-44=Maintenance Week 44.

**Figure 26: GOF plot of final paediatric Emax model for clinical remission at week M-44 in paediatric participants from CNTO1275CRD3004**




Abbreviations: $C_{trough,weekM44}$=most recent trough concentration prior to Week M-44; $E_{max}$=maximum drug effect; E-R=exposure-response; GOF=goodness-of-fit; N=number of participants; PopPK=population pharmacokinetic(s); qXw=every X weeks; SC=subcutaneous; Week M-X=Maintenance Week X.

Note: Dots are the observed median of the probability in the respective exposure tertile groups. The solid smooth curve represents the model-predicted E-R relationship of the final model. Short vertical lines at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders, respectively, which were predicted based on the actual dose regimen and individual PopPK model parameter estimates in pediatric participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m$^2$ (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275CRD3004 (N=85).

**Exposure-response analyses for safety**

The relationship between ustekinumab exposure and safety was assessed by evaluating the association between serum ustekinumab concentrations (divided into quartiles) and the proportions of paediatric participants experiencing the selected safety events (i.e. infections, serious infections, and SAEs). The analyses were performed separately for induction and maintenance. The induction analyses were performed using ustekinumab concentration at Week I-8 (Week 8), while the maintenance analyses were performed using the ustekinumab average steady state trough concentration. All participants from CRD3004 and CRD1001 were included in the analysis of safety events regardless of the induction doses received.

**Table 11: Number of participants with 1 or more treatment-emergent infections, serious infections, and serious adverse events by serum ustekinumab concentration quartiles at week I-8 (week 8) and by average steady state trough serum ustekinumab concentration quartiles from week M-0 through week M-44/week 48; pharmacokinetic analysis set (CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Pooled CNTO1275CRD1001 and CNTO1275CRD3004 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Ustekinumab Concentrations at Week I-8[a,b] | | | | Ustekinumab Concentrations at Average Steady-State Trough[c,d,e] | | | |
| | ≤1st Quartile | >1st Quartile and ≤2nd Quartile | >2nd Quartile and ≤3rd Quartile | >3rd Quartile | ≤1st Quartile | >1st Quartile and ≤2nd Quartile | >2nd Quartile and ≤3rd Quartile | >3rd Quartile |
| Analysis set: PK Analysis Set | 33 | 32 | 33 | 32 | 25 | 25 | 25 | 24 |
| Average duration of follow-up (weeks) | 8.14 | 7.97 | 8.05 | 8.06 | 41.47 | 43.57 | 42.29 | 41.36 |
| Average exposure (number of administrations) | 1.00 | 1.00 | 1.00 | 1.00 | 8.64 | 8.96 | 7.64 | 6.63 |
| Participants with 1 or more treatment-emergent infections | 7 (21.2%) | 6 (18.8%) | 13 (39.4%) | 8 (25.0%) | 18 (72.0%) | 15 (60.0%) | 13 (52.0%) | 18 (75.0%) |
| Participants with 1 or more serious infection | 0 | 0 | 0 | 1 (3.1%) | 1 (4.0%) | 1 (4.0%) | 0 | 0 |
| Participants with 1 or more serious adverse events | 3 (9.1%) | 2 (6.3%) | 0 | 1 (3.1%) | 2 (8.0%) | 4 (16.0%) | 1 (4.0%) | 2 (8.3%) |

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PK=pharmacokinetic(s); qXw=every X weeks; Week I-X=Induction Week X; Week M-X=Maintenance Week X.

[a] 1st quartile=1.18 µg/mL, 2nd quartile=2.56 µg/mL, 3rd quartile=5.59 µg/mL.

[b] Quartiles are calculated based on ustekinumab concentration at Week I-8 (Week 8) for all participants from CNTO1275CRD3004 and CNTO1275CRD1001 regardless of the induction doses received.

[c] 1st quartile=0.37 µg/mL, 2nd quartile=1.21 µg/mL, 3rd quartile=2.15 µg/mL.

[d] Participants in CNTO1275CRD3004 who dose adjusted are counted in the treatment group they were randomized to at Week M-0, and their data from the time of dose-adjustment or substudy onward are not included.

[e] Quartiles are calculated based on ustekinumab concentration at steady.state visits for all participants from CNTO1275CRD3004 and CNTO1275CRD1001 regardless of the induction doses received. In case of q8w, trough serum ustekinumab concentrations at Week M-24 (Week 32) and Week M-32 (Week 40) are averaged. In case of q12w, trough serum ustekinumab concentrations at Week M-24 and Week M-36 are averaged.

Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 27.1.

There was no association between serum ustekinumab concentration and selected safety events including infections, serious infections and SAEs.

## 2.4.5. Discussion on clinical pharmacology

Methodologies and validations of the bioanalytical methods used to determine serum ustekinumab concentrations, and ADAs and NAbs to ustekinumab have previously been submitted and been considered acceptable. The additional data provided by the MAH in this submission is acceptable.

As the benefit/risk of ustekinumab has been established in adults and paediatric patients (≥40 kg) with CD, a key objective of this submission was to define a ustekinumab dose regimen in paediatric CD patients weighing <40 kg that would provide systemic ustekinumab exposure similar to that observed in adults and paediatric participants weighing ≥40 kg.

**Phase 1 study in paediatric participants (CRD1001)**

In study 1001, induction dosing in patients <40 kg was performed according to mg/kg at two dose levels (high and low). It is noted that in the high-induction dose group, except for the post-infusion samples at Week 0, serum ustekinumab concentrations over time in the <40 kg body weight subgroup were substantially lower than those of participants in the ≥40 kg body weight subgroup, who received a flat dose disregarding baseline bodyweight (see also discussion below).

**Phase 3 CD study in paediatric participants (CRD3004)**

In the pivotal paediatric study CRD3004, following the respective induction and maintenance dose regimens, ustekinumab concentrations in paediatric participants were within the range of concentrations observed in adults with CD receiving the approved ustekinumab dose regimen for this indication. This supports the suitability of the proposed paediatric dose regimens.

In some participants (n=26), loss of response during maintenance was associated with ustekinumab concentrations that were lower than the effective exposure range observed in adult Phase 3 studies (i.e. 8-week steady state level <1.4 ug/mL). An adjustment to q4w interval dosing resulted in an increase in systemic exposures to within the safe and effective adult exposure range. However, one participant reached exposures that exceeded those established for adults in the safety database (i.e. >7.2 ug/mL; the average 95$^{th}$ percentile of observed 8-week steady-state ustekinumab concentrations in adult trials). These findings highlight the importance of monitoring ustekinumab concentrations in patients who experience a loss of response - both before adjusting the dosing interval to q4w and after the adjustment - to ensure that ustekinumab exposure remains within an appropriate range. The proposed SmPC section 4.2 has been appropriately updated to include clear monitoring guidance for q4w dosing "Patients receiving treatment every 12 weeks who have a loss of response may increase their frequency to every 8 weeks (see sections 5.1 and 5.2). Patients receiving treatment every 12 or 8 weeks who lose response and have low ustekinumab trough levels (<1.4 µg/mL by a validated ECLIA or ELISA testing method or equivalent assay) may benefit from shortening the dosing interval to every 4 weeks if clinically indicated. A repeat trough level should be drawn at either 12 or 16 weeks after dose adjustment to every 4 weeks administration. If trough levels are >7.2 µg/mL and the patient has achieved response and is maintaining a response, the dosage interval may be changed to every 8 weeks."

**Population PK Analysis**

The 2-compartment interim paediatric PopPK model was externally evaluated using the new paediatric data subset of the full paediatric dataset. Parameter estimates were not re-estimated. Allometric scaling exponents were fixed to the standard values 0.75 for CL and Q, and 1 for V2 and V3. RSE were <20% for all parameter estimates except F1 with RSE of 21.80%. Eta-shrinkage of IIV of CL, V2 and V3 were 4%, 30% and 7%, respectively. Predictive performance of the paediatric model was shown to be adequate for performing dosing simulations and for predicting exposure metrics for the ER analyses. Correlation plots of age and between-participant variabilities on disposition parameters suggested that the disposition parameters of ustekinumab in paediatric participants do not change across ages after accounting for the body weight effect.

Simulations showed that the proposed posology of ustekinumab for paediatric CD patients with body weight <40 kg is adequate across the expected body weight range. Overall, ustekinumab exposures during induction and maintenance in the different body weight subgroups of participants <40 kg (10 to <20 kg, 20 to <30 kg, and 30 to <40 kg) following the proposed BSA-adjusted dosage were comparable to those who received approved ustekinumab doses in the ≥40 kg group. Furthermore, ustekinumab exposures in the different body weight subgroups of participants <40 kg were generally within the range of those established to be safe and effective in the adult CD population.

PK simulations of paediatric participants with LOR receiving q4w SC maintenance treatment compared with adult participants receiving q8w SC maintenance treatment showed large overlap in ustekinumab exposure between the groups. A comparison of simulated exposures in paediatric LOR participants with weight 10 - <23.7 kg versus 23.7 – 40 kg indicated similar exposure between groups. Overall, the simulations support the change in dosing frequency to q4w in paediatric LOR patients across the expected body weight range.

**Immunogenicity**

The incidence of antibodies to ustekinumab was low in paediatric participants (3.0%) and consistent with the immunogenicity profile of ustekinumab in adult participants (3.1%) with CD. Given the low incidence of antibodies to ustekinumab in the paediatric studies, the impact of immunogenicity on PK, efficacy, or safety could not be determined.

**Exposure-response analyses for efficacy**

A similar positive E-R trend was observed between $C_{trough,weekI8}$ and clinical remission at Week I-8 in adult and paediatric participants, with a higher probability of clinical remission observed in paediatric participants. This was demonstrated both graphically and in the modelling analysis. However, the modelling analysis has certain limitations. e.g. the precision of $EC_{50}$ estimate of the nonlinear regression model due to limited data at low concentrations. In addition, the placebo effect and the influence of TNF failure status on the placebo response were fixed to values derived from the adult ER models. Therefore, findings from the modelling analysis should be viewed cautiously.

A similar positive E-R trend was observed for clinical response at Week I-8 in relation to $C_{trough,weekI8}$ in adult and paediatric participants, but with a higher probability of clinical response in paediatric participants in each trough tertile group.

Following maintenance ustekinumab treatment, no clear trend was observed between steady state $C_{trough}$ and clinical remission at Week M-44 paediatric participants with CD, but responses were high at all exposures. A similar trend was observed in adult participants with CD. In the graphical analysis, the proportion of participants with clinical remission at Week M-44 in paediatric participants was comparable to that in adult participants. Similar to the induction model, the placebo effect in the model for clinical remission at Week M-44 was fixed to the value from the adult model and $EC_{50}$ was estimated with similar limitations to precision, but the precision was improved relative to the induction model. This is likely due to relatively more samples being available in the lower range of concentrations.

The E-R relationship for clinical remission at Week I-8 and Week M-44 was not affected by the age or body weight of paediatric participants with CD. Similar to the finding in adults, at a given ustekinumab concentration, the proportion of paediatric participants in clinical remission at Week I-8 and Week M-44 was higher in the anti-TNF non-failure population compared with the anti-TNF failure population.

**Exposure-response analyses for safety**

There was no association between serum ustekinumab concentration and selected safety events including infections, serious infections and SAEs.

### 2.4.6. Conclusions on clinical pharmacology

The totality of observed and simulated data support the view that the proposed ustekinumab doses for paediatric CD patients (≥2 years) will result in ustekinumab exposures that are comparable to those established to be safe and effective in the adult CD population.

## *2.5. Clinical efficacy*

### 2.5.1. Main study

**Study CRD3004, phase 3**

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

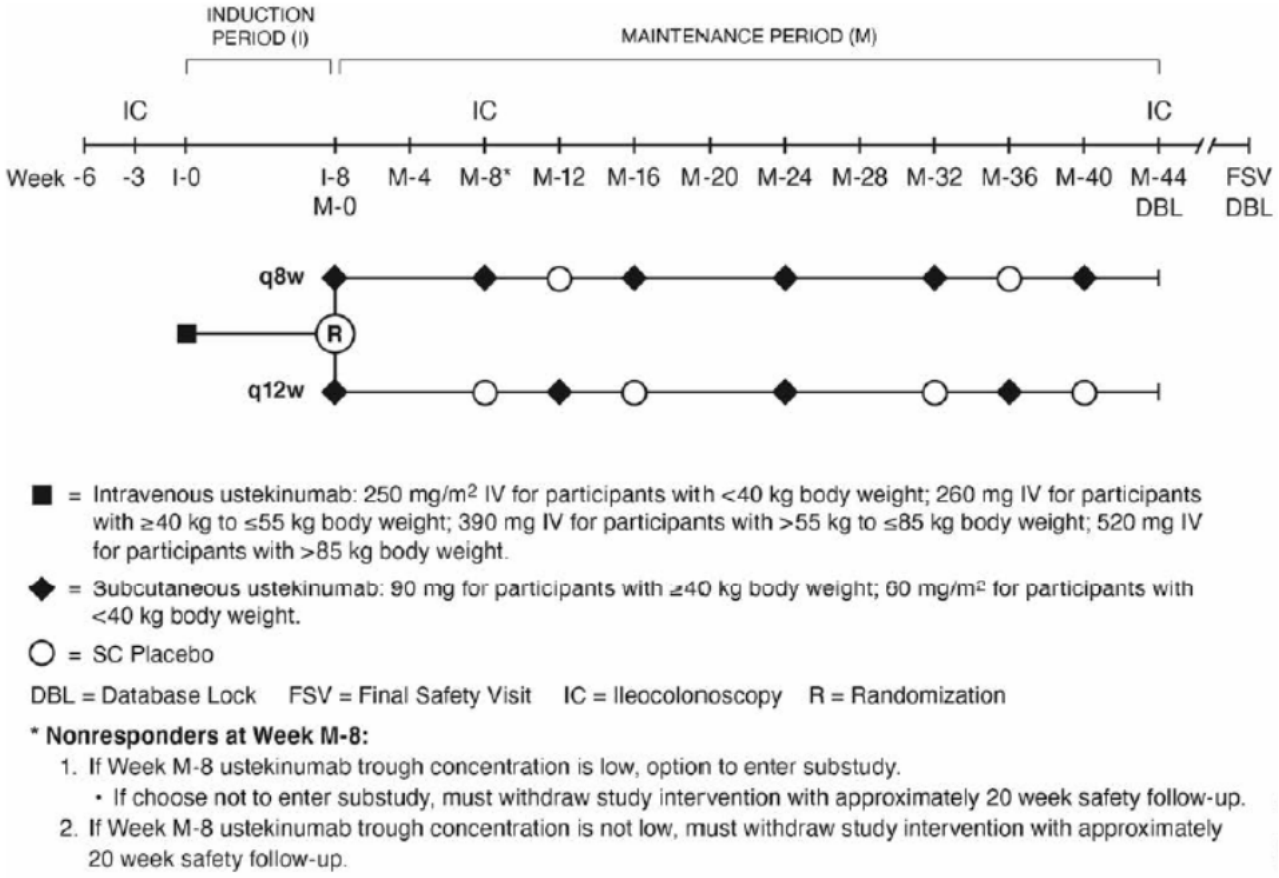
**Study Number:** CNTO1275CRD3004

An interim report for this study was previously assessed in procedure EMEA/H/C/000958/II/0108 to support an extension of indication for paediatric patients ≥40kg. This patient group now includes 73 children and thus an additional 25 children have been included in this population since the former application. The study details are being reported here for completeness.

#### *Methods*

This was a Phase 3, multicentre interventional study consisting of an open-label induction period with a single IV ustekinumab induction dose followed by a maintenance period with a randomised, double blind, parallel-group 2-arm study design, exploring 2 different SC Ustekinumab maintenance dose regimens in paediatric participants 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 (i.e., TNF$\alpha$ antagonist or vedolizumab) and/or conventional therapies (i.e., IV or oral corticosteroids or the immunomodulators AZA, 6-MP, and MTX) or be dependent upon corticosteroids.

**Figure 27: Schematic overview of the CNTO1275CRD3004 study**




All participants randomised into the maintenance period who experienced a loss of response (LOR) and had steady-state ustekinumab trough concentration ≥1.4 μg/mL were eligible for a dose adjustment as part of the main study to the q8w dosing regimen. Participants who had a LOR during the maintenance period of the main study and had a trough serum ustekinumab concentration of <1.4 μg/mL during the maintenance period (Week M-8 or Week M-32) were eligible to enrol in the optional Exposure Optimisation Substudy (EOS) and were administered open-label SC ustekinumab q4w dosing regimen.

## Study participants

The main inclusion and exclusion criteria are summarised below:

Inclusion criteria:

- 2 to <18 years of age, inclusive with a body weight ≥10 kg.
- Medically stable on the basis of physical examination, medical history, and vital signs performed at screening.
- 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.
- Must have moderately to severely active Crohn's disease (as defined by a baseline PCDAI score >30).
- 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, or an abnormal CRP (>0.3

mg/dL or 3.0 mg/L at screening) OR Faecal calprotectin of ≥250 mg/kg or ≥250 μg/g at screening.

- Prior or current medication for Crohn's disease must include at least 1 of the following: Have received biologic therapy for the treatment of paediatric Crohn's disease and have a documented history of failure to respond to or not tolerate the biologic therapy or be naive to biologic therapy.
- Must meet concomitant medication dose stability criteria prior to the first administration of study intervention.
- Must meet contraceptive requirements.
- Participants must be up to date with varicella and measles, mumps, and rubella in agreement with current local immunisation guidelines for immunosuppressed participants before Week I-0.
- Have negative stool results for enteric pathogens.
- Have screening laboratory test results as follows:
    - Haemoglobin ≥8.0 g/dL.
    - White blood cells (WBC)≥2.5 x 103 cells/μL (SI: ≥2.5 x109 cells/L).
    - Neutrophils ≥1.5 x 103 cells/ μL (SI: ≥1.5 x109 cells/L).
    - Platelets ≥100 x 103 cells/ μL (SI: ≥100 x109 cells/L).
    - Serum alanine transaminase (ALT) and aspartate transaminase (AST) levels not exceeding 2 times the upper limit of normal for the central laboratory.
- Must be willing and able to adhere to the lifestyle restrictions specified in this protocol.

Exclusion Criteria

- 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.
- Currently has or is suspected to have an abscess.
- Has had any kind of bowel resection within 6 months or any other intra-abdominal surgery within 3 months prior to Week I-0.
- Presence of a stoma.
- Has received any of the specified prescribed medications or therapies within the specified period (including any biologic agent targeting IL-12/23 or IL-23, including, but not limited to, briakinumab, brazikumab, guselkumab, mirikizumab (formerly LY3074828), and risankizumab).
- Have a history of, or ongoing, chronic or recurrent infectious disease.
- Presence or history of any malignancy.
- 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.
- Has any condition that, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

## Treatments

Induction Period

For participants with body weight ≥40 kg: Multiple vials of ustekinumab 5 mg/mL liquid in vial (LIV) were diluted to an appropriate concentration using an appropriate diluent for IV administration.

Maintenance Period

For randomised participants with body weight <40 kg: Ustekinumab 90 mg/mL LIV was supplied as a single-use, sterile solution in 2 mL vials. Each 1 mL of ustekinumab solution contained 90 mg ustekinumab. Ustekinumab 90 mg/mL could be used for SC administration at a dose strength of 45 mg in 0.5 mL nominal volume. As doses were determined based upon the BSA of participants, the contents of the vial(s) were withdrawn using a standard graduated syringe to the required dose volume.

For randomised participants with body weight ≥40 kg: Ustekinumab was also to 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 contained 90 mg ustekinumab.

Placebo administrations had the same appearance as the respective ustekinumab administrations.

## Objectives

***Primary Objectives***

The global primary objectives of this study were, in paediatric 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 (PK).

***Secondary Objectives***

The global secondary objectives of this study were, in paediatric participants with moderately to severely active Crohn's disease:

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

## Outcomes/endpoints

**Primary endpoint**

- Clinical remission at Week I-8.

**Secondary endpoints**

- 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.

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

**Other**

- Histologic assessments based on the Global Histology Activity Score (GHAS), Geboes score, and Robarts Histopathology Index (RHI).

Change from baseline in:

- CRP concentrations.
- Faecal calprotectin and faecal 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.
- IMPACT-III scores at Week M-44 for participants ≥10 years of age at Week I-0.

## Sample size

With a sample size of 90 participants enrolled and assuming 90% of the participants in this study are biologic failures, the precision (i.e., half width of the 95% CI) in estimating the true proportion of paediatric participants in clinical remission at Week I-8 is 8.7% (assuming the proportion of participants in clinical remission is 22.8% at Week I-8 [based on a weighted average from the biologic-failure population from the ustekinumab adult study CNTO1275CRD3001 {20.9%; approximately 6 mg/kg treatment group} and from the non-biologic-failure population from the ustekinumab adult study CNTO1275CRD3002{40.2%; approximately 6 mg/kg treatment group}]). Given that success was evaluated by the totality of the data, a sample size of 90 participants enrolled was considered sufficient to determine efficacy under the extrapolation concept for both the global objectives and the US-specific objectives.

The original planned total sample size was approximately 90 participants with at least 24 participants <40 kg including at least 5 participants <30 kg. However, subsequent PIP modification justified reduction in the data needed amongst participants weighing at least 40 kg, while maintaining sample size requirements for those <40 kg.

## Randomisation

Central randomisation was implemented in this study. At Week M-0, participants (induction responders and induction non-responders) were randomly assigned to 1 of 2 intervention groups based on a

computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor. The randomisation was balanced by using permuted block randomisations and was stratified by response status at Week I-8 (induction responder/induction non-responder) and weight (<40 kg, ≥40 kg). Clinical response status at Week I-8 was determined by the PCDAI.

## Blinding (masking)

To maintain the study blind during the maintenance period, placebo injections were used, and they were of identical in appearance to ustekinumab. The investigator was not provided with randomisation codes. The codes were maintained within the IWRS, which had the functionality to allow the investigator to break the blind for an individual participant. Sponsor personnel remained 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 who reviewed the PK interim analysis and a sponsor unblinded group for preparing the EMA submission for the participants ≥40 kg included in the interim analysis.

## Statistical methods

Data were summarised using descriptive statistics. Continuous variables were summarised using the number of observations, mean, SD, median, IQ range, minimum and maximum, as appropriate. Categorical values were summarised using the number of observations and percentages as appropriate. Unless otherwise specified, the Wilson score method was used to construct the 95% CI for binary endpoints where a proportion and the respective 95% CI were reported. Graphical data displays (e.g., line plots) were also used to summarise the data.

**Table 12: Study populations for analysis**

| | Ustekinumab IV | Ustekinumab SC | | | |
|---|---|---|---|---|---|
| | Not randomized | q12w | q8w | Combined | Total |
| All Enrolled[a] | 4 | 49 | 48 | 97 | 101 |
| Full Analysis Set | 4 | 49 | 48 | 97 | 101 |
| Full Randomized Analysis Set | 0 | 49 (100.0%) | 48 (100.0%) | 97 (100.0%) | 97 (96.0%) |
| Full Clinical Responder Analysis Set | 0 | 44 (89.8%) | 41 (85.4%) | 85 (87.6%) | 85 (84.2%) |
| All Responder Analysis Set | 0 | 45 (91.8%) | 46 (95.8%) | 91 (93.8%) | 91 (90.1%) |
| Safety Analysis Set | 4 (100.0%) | 49 (100.0%) | 48 (100.0%) | 97 (100.0%) | 101 (100.0%) |
| Safety Randomized Analysis Set | 0 | 49 (100.0%) | 48 (100.0%) | 97 (100.0%) | 97 (96.0%) |
| Safety Clinical Responder Analysis Set | 0 | 44 (89.8%) | 41 (85.4%) | 85 (87.6%) | 85 (84.2%) |
| PK Analysis Set | 2 (50.0%) | 49 (100.0%) | 48 (100.0%) | 97 (100.0%) | 99 (98.0%) |
| PK Randomized Analysis Set | 0 | 48 (98.0%) | 47 (97.9%) | 95 (97.9%) | 95 (94.1%) |
| PK Clinical Responder Analysis Set | 0 | 44 (89.8%) | 41 (85.4%) | 85 (87.6%) | 85 (84.2%) |
| PK All Responder Analysis Set | 0 | 45 (91.8%) | 46 (95.8%) | 91 (93.8%) | 91 (90.1%) |
| Immunogenicity Analysis Set | 4 (100.0%) | 49 (100.0%) | 48 (100.0%) | 97 (100.0%) | 101 (100.0%) |
| Immunogenicity Clinical Responder Analysis Set | 0 | 43 (87.8%) | 41 (85.4%) | 84 (86.6%) | 84 (83.2%) |
| Immunogenicity All Responder Analysis Set | 0 | 44 (89.8%) | 46 (95.8%) | 90 (92.8%) | 90 (89.1%) |
| Substudy Analysis Set | 0 | 11 (22.4%) | 15 (31.3%) | 26 (26.8%) | 26 (25.7%) |

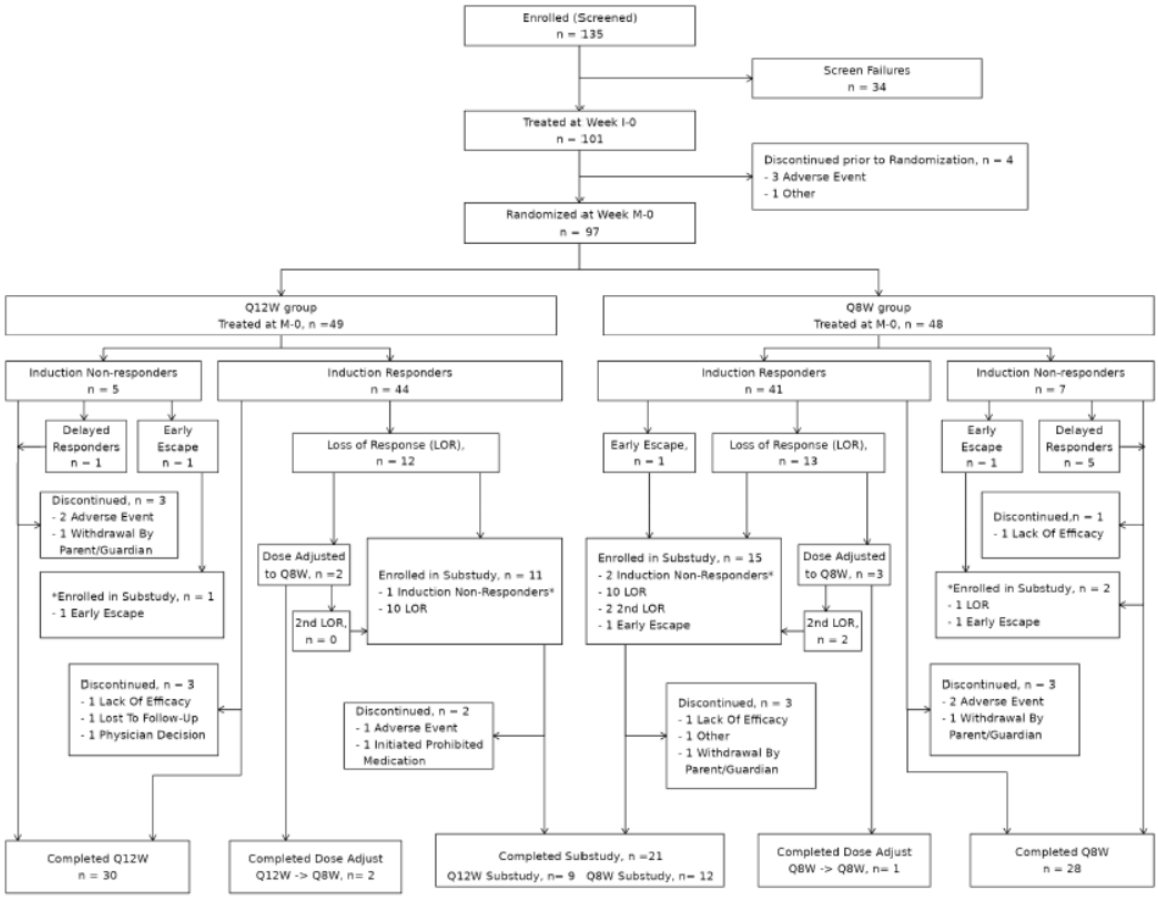
[a] Excludes 34 subjects who were screen failures.

## *Results*

## Participant flow

Of the 135 participants screened for the study, 34 (25.2%) participants were screen failures, and 101 participants were enrolled into the study.

**Figure 28: Disposition of randomised participants**




All 101 participants from the FAS (participants who received an administration of study intervention in induction at Week I-0) were enrolled in 29 study sites across 8 countries (52 [51.5%] participants in Poland, 21 [20.8%] participants in Belgium, 7 [6.9%] participants in Hungary, 6 [5.9%] participants each in the United Kingdom, USA, and Japan, 2 [2.0%] participants in Germany, and 1 [1.0%] participant in Israel). The number of participants by region, country, and site at baseline in the FASRES (participants who were randomised 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) was similar to the FAS.

85 participants (44 participants in the q12w treatment group and 41 participants in the q8w treatment group) were randomised 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 analysis set).

No participant discontinued study intervention due to COVID-19 related reasons. From Week M-0 through Week M-44, 10 (11.8%) of 85 participants in the FASCR discontinued study intervention (5 [11.4%] participants in the q12w treatment group and 5 [12.2%] participants in the q8w treatment group). Reasons for discontinuation of study intervention were similar to the Safety Analysis Set.

All 101 participants in the Safety Analysis Set (Table 13) were treated at Week I-0. A total of 97 participants were randomised at Week M-0 and received either the q12w (49 participants) or q8w (48 participants) ustekinumab SC dose regimen. Of the 97 participants who were randomised at Week M-0, 85 participants were induction responders. A total of 5 (5.2%) participants who experienced LOR during maintenance dose adjusted from q12w to q8w (n=2) or received a sham adjustment (remained on q8w; n=3). A total of 26 (26.8%) of 97 participants enrolled in the EOS. Among these, 3 (3.1%) were

induction nonresponders who met the early escape criteria (participants who did not achieve clinical response based on the PCDAI by Week M-8) and 23 (23.7%) participants experienced LOR and had low ustekinumab levels during the maintenance period 6.

Only 1 (1.0%) of 101 participants from the Safety Analysis Set prematurely terminated study participation during the induction period due to withdrawal by parent or guardian. A total of 10 (9.9%) participants prematurely terminated study participation from Week M-0 through Week M-44; 7 of the 10 participants were in the q12w treatment group. Common reasons for premature termination of study participation included withdrawal by parent or guardian, withdrawal by participant, or lost to follow-up. Other reasons occurred in 1 participant each.

**Table 13: Treatment disposition from week M-0 through week M-44; safety analysis set (Study CNTO1275CRD3004)**

| | Ustekinumab IV | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | q12w | | | q8w | | | |
| | Not Randomized | q12w | q12w->q8w | Combined | q8w | q8w->q8w | Combined | Total |
| Analysis set: Safety | 4 | 47 | 2 | 49 | 45 | 3 | 48 | 101 |
| Subjects randomized at Week M-0 | 0 | 47 (100.0%) | 2 (100.0%) | 49 (100.0%) | 45 (100.0%) | 3 (100.0%) | 48 (100.0%) | 97 (96.0%) |
| Subjects treated at Week M-0 | 0 | 47 (100.0%) | 2 (100.0%) | 49 (100.0%) | 45 (100.0%) | 3 (100.0%) | 48 (100.0%) | 97 (96.0%) |
| Subjects entered into substudy | 0 | 11 (23.4%) | 0 | 11 (22.4%) | 13 (28.9%) | 2 (66.7%) | 15 (31.3%) | 26 (25.7%) |
| Discontinued study treatment through Week M-44 | 1 (25.0%) | 8 (17.0%) | 0 | 8 (16.3%) | 6 (13.3%) | 0 | 6 (12.5%) | 15 (14.9%) |
| Reason for termination | | | | | | | | |
| Adverse event of worsening of Crohn's disease | 0 | 3 (6.4%) | 0 | 3 (6.1%) | 2 (4.4%) | 0 | 2 (4.2%) | 5 (5.0%) |
| Adverse event other than worsening of Crohn's disease | 0 | 0 | 0 | 0 | 1 (2.2%) | 0 | 1 (2.1%) | 1 (1.0%) |
| Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lack of efficacy | 0 | 1 (2.1%) | 0 | 1 (2.0%) | 1 (2.2%) | 0 | 1 (2.1%) | 2 (2.0%) |
| Lost to follow-up | 0 | 1 (2.1%) | 0 | 1 (2.0%) | 0 | 0 | 0 | 1 (1.0%) |
| Non-compliance with study drug | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Physician decision | 0 | 1 (2.1%) | 0 | 1 (2.0%) | 0 | 0 | 0 | 1 (1.0%) |
| Pregnancy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Initiated prohibited medication | 0 | 1 (2.1%) | 0 | 1 (2.0%) | 0 | 0 | 0 | 1 (1.0%) |
| Product quality complaint | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Protocol deviation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Site terminated by sponsor | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Study terminated by sponsor | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Weight is less than 10 kg for 2 consecutive visits | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Withdrawal by parent or guardian | 0 | 1 (2.1%) | 0 | 1 (2.0%) | 2 (4.4%) | 0 | 2 (4.2%) | 3 (3.0%) |
| Withdrawal by subject | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 1 (25.0%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.0%) |
| Covid-19 related | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DIAGNOSIS OF LRBA/CTLA4 GENETIC DISORDER AFTER ENROLLMENT | 1 (25.0%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.0%) |

Note: Data from the time of substudy onward are not included.

## Conduct of the study

No participants were unblinded during the maintenance period.

### *Major Protocol Deviations*

Major protocol deviations (MPD) for this study were categorised as follows: developed withdrawal criteria but not withdrawn, entered but did not satisfy criteria, of which none occurred, along with received a disallowed concomitant treatment, received incorrect dose during maintenance, and other. A participant could have had multiple deviations and could have been included under more than 1 deviation category.

During the induction period through Week I-8, 8 (7.9%) of 101 participants in the FAS had an MPD. The MPDs were either classified as "other" (6 [5.9%] participants), with the most common "other" deviation criterion being missed assessments (e.g., incompletion of PCDAI and CDAI diaries prior to scheduled visit) or as participants who received the incorrect IV dose during induction (2 [2.0%] participants).

**Table 14: Summary of participants with MPDs from week M-0 through week M-44**

| | Ustekinumab SC | | |
|---|---|---|---|
| | Randomized at Week M-0 | | |
| | q12w | q8w | Combined |
| Analysis set: Full Randomized | 49 | 48 | 97 |
| Subjects with major protocol deviations | 14 (28.6%) | 7 (14.6%) | 21 (21.6%) |
| Developed withdrawal criteria but not withdrawn | 0 | 0 | 0 |
| Entered but did not satisfy criteria | 0 | 0 | 0 |
| Received a disallowed concomitant treatment | 2 (4.1%) | 0 | 2 (2.1%) |
| Received incorrect dose during maintenance | 1 (2.0%) | 0 | 1 (1.0%) |
| Other | 11 (22.4%) | 7 (14.6%) | 18 (18.6%) |
| Missed visit/assessment due to COVID-19 | 0 | 0 | 0 |

Note: Subjects may appear in more than one category.

Similar to the induction period, the most common category of MPDs was "other" in both the q12w and q8w treatment groups in the FASR (participants who were randomised in the maintenance period of the study and received at least 1 administration of study intervention during maintenance) during the maintenance period from Week M-0 through Week M-44. The most common deviations categorised as "other" were missed study visits and missed assessments (eg, PCDAI and CDAI diary information). Additionally, in the q12w treatment group, 2 participants received a disallowed concomitant treatment (both participants started rescue therapy without meeting the LOR criteria) and 1 participant received an incorrect dose during maintenance.

No participants had an MPD related to COVID-19 from Week I-0 through Week M-44.

***Ustekinumab Administration Deviations***

A total of 3 (3.0%) of 101 participants in the FAS had a study intervention administration deviation:

- 2 participants (1 participant in the q12w treatment group and 1 participant in the q8w treatment group) received an incorrect dose of ustekinumab treatment during the induction period on Day 1. Both participants received doses that were slightly greater than the correct dose (the participant in the q8w treatment group received an excess of 0.8 mL, while the participant in the q12w treatment group received an excess of 1.6 mL). These amounts were not considered clinically relevant by the sponsor and therefore did not affect the validity or integrity of the data, or participant safety.
- 1 participant in the q12w treatment group was dispensed and administered the wrong medication kit during the maintenance period on Day 239; however, the kit included the proper study treatment (and dose).

***Other Protocol Deviations***

At enrollment, there were no participants who did not meet the inclusion or exclusion criteria in this study. The number of participants with minor protocol deviations related to COVID-19 was low and these deviations were not considered to impact the integrity of the study or the interpretation of the findings.

## Baseline data

Baseline demographic characteristics were similar across treatment groups in the FAS (Table 15).

**Table 15: Summary of demographics at baseline; full analysis set (Study CNTO1275CRD3004)**

| | Ustekinumab IV | | | | |
|---|---|---|---|---|---|
| | | Ustekinumab SC | | | |
| | Not randomized | q12w | q8w | Combined | Total |
| Analysis set: Full | 4 | 49 | 48 | 97 | 101 |
| Age, years | | | | | |
| N | 4 | 49 | 48 | 97 | 101 |
| Mean (SD) | 13.3 (1.50) | 13.5 (2.92) | 13.4 (2.65) | 13.5 (2.77) | 13.5 (2.73) |
| Median | 14.0 | 14.0 | 14.0 | 14.0 | 14.0 |
| Range | (11; 14) | (5; 17) | (2; 17) | (2; 17) | (2; 17) |
| IQ range | (12.5; 14.0) | (12.0; 16.0) | (12.0; 15.0) | (12.0; 16.0) | (12.0; 15.0) |
| 2-11 years | 1 (25.0%) | 12 (24.5%) | 7 (14.6%) | 19 (19.6%) | 20 (19.8%) |
| 2-5 years | 0 | 1 (2.0%) | 1 (2.1%) | 2 (2.1%) | 2 (2.0%) |
| 6-11 years | 1 (25.0%) | 11 (22.4%) | 6 (12.5%) | 17 (17.5%) | 18 (17.8%) |
| 12-17 years | 3 (75.0%) | 37 (75.5%) | 41 (85.4%) | 78 (80.4%) | 81 (80.2%) |
| Sex | | | | | |
| N | 4 | 49 | 48 | 97 | 101 |
| Female | 2 (50.0%) | 21 (42.9%) | 18 (37.5%) | 39 (40.2%) | 41 (40.6%) |
| Male | 2 (50.0%) | 28 (57.1%) | 30 (62.5%) | 58 (59.8%) | 60 (59.4%) |
| Race | | | | | |
| N | 4 | 49 | 48 | 97 | 101 |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 | 0 |
| Asian | 0 | 5 (10.2%) | 4 (8.3%) | 9 (9.3%) | 9 (8.9%) |
| Black or African American | 0 | 2 (4.1%) | 1 (2.1%) | 3 (3.1%) | 3 (3.0%) |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 |
| White | 3 (75.0%) | 42 (85.7%) | 43 (89.6%) | 85 (87.6%) | 88 (87.1%) |
| Multiple | 0 | 0 | 0 | 0 | 0 |
| Not reported | 1 (25.0%) | 0 | 0 | 0 | 1 (1.0%) |
| Unknown | 0 | 0 | 0 | 0 | 0 |
| Weight, (kg) | | | | | |
| N | 4 | 49 | 48 | 97 | 101 |
| Mean (SD) | 44.0 (7.37) | 48.8 (17.77) | 48.6 (14.80) | 48.7 (16.28) | 48.5 (16.03) |
| Median | 41.8 | 47.2 | 47.6 | 47.5 | 47.2 |
| Range | (38; 54) | (16; 88) | (13; 85) | (13; 88) | (13; 88) |
| IQ range | (38.6; 49.4) | (38.3; 61.7) | (39.5; 58.3) | (39.3; 59.0) | (39.0; 58.3) |
| <40 kg | 2 (50.0%) | 13 (26.5%) | 14 (29.2%) | 27 (27.8%) | 29 (28.7%) |
| <30 kg | 0 | 8 (16.3%) | 3 (6.3%) | 11 (11.3%) | 11 (10.9%) |
| ≥30 - <40 kg | 2 (50.0%) | 5 (10.2%) | 11 (22.9%) | 16 (16.5%) | 18 (17.8%) |
| ≥40 kg | 2 (50.0%) | 36 (73.5%) | 34 (70.8%) | 70 (72.2%) | 72 (71.3%) |
| ≥40 - ≤55 kg | 2 (50.0%) | 21 (42.9%) | 17 (35.4%) | 38 (39.2%) | 40 (39.6%) |
| >55 - ≤85 kg | 0 | 14 (28.6%) | 17 (35.4%) | 31 (32.0%) | 31 (30.7%) |
| >85 kg | 0 | 1 (2.0%) | 0 | 1 (1.0%) | 1 (1.0%) |
| Body mass index, kg/m² | | | | | |
| N | 4 | 49 | 48 | 97 | 101 |
| Mean (SD) | 17.4 (2.09) | 18.4 (3.79) | 18.7 (3.50) | 18.5 (3.63) | 18.5 (3.58) |
| Median | 17.4 | 17.4 | 18.0 | 17.5 | 17.5 |
| Range | (15; 20) | (13; 29) | (14; 30) | (13; 30) | (13; 30) |
| IQ range | (15.7; 19.1) | (15.5; 21.7) | (16.0; 21.1) | (15.8; 21.2) | (15.8; 21.1) |
| Underweight <18.5 | 2 (50.0%) | 30 (61.2%) | 25 (52.1%) | 55 (56.7%) | 57 (56.4%) |
| Normal 18.5-<25 | 2 (50.0%) | 17 (34.7%) | 21 (43.8%) | 38 (39.2%) | 40 (39.6%) |
| Overweight 25-<30 | 0 | 2 (4.1%) | 1 (2.1%) | 3 (3.1%) | 3 (3.0%) |
| Obese ≥30 | 0 | 0 | 1 (2.1%) | 1 (1.0%) | 1 (1.0%) |
| Body mass index Z score[a] | | | | | |
| N | 4 | 49 | 48 | 97 | 101 |
| Mean (SD) | -0.42 (0.737) | -0.24 (0.867) | -0.08 (1.074) | -0.16 (0.973) | -0.17 (0.963) |
| Median | -0.39 | -0.48 | -0.37 | -0.46 | -0.46 |
| Range | (-1.2; 0.3) | (-1.7; 2.6) | (-1.3; 4.1) | (-1.7; 4.1) | (-1.7; 4.1) |
| IQ range | (-1.04; 0.20) | (-0.82; 0.35) | (-0.87; 0.43) | (-0.83; 0.42) | (-0.84; 0.35) |

[a] Age and sex-specific

The majority of participants were white. More than half of the participants were male and classified as underweight (BMI of <18.5 kg/m2).

Additionally, negative BMI z-scores were observed for both females (mean [SD] and median BMI z-scores of -0.07 [0.771] and -0.31, respectively; range: -1.2; 2.6) and males (mean [SD] and median BMI z-scores of -0.24 [1.076] and -0.52, respectively; range: -1.7; 4.1), with 17 (16.8%) of 101 participants who were classified as having mild malnutrition (defined as a BMI z-score of >-2 to ≤-1).

***Subgroup Analyses***

Results of the demographic subgroup analyses by weight and age in the FAS were generally consistent with the overall study population and across FAS, FASCR, and FASRES sets. There were several differences between the participants by age (e.g., lower weight and BMI z-scores in the younger population [2 to 11 years of age] versus the older population [12 to 17 years of age]) and weight (e.g., a greater proportion of participants <40 kg were categorised as underweight and had lower BMI z-scores than participants ≥40 kg).

**Baseline Crohn's Disease Characteristics and Relevant Medical History**

The clinical disease characteristics at baseline for the FAS were well balanced across treatment groups and were representative of a population with moderately to severely active CD. In the total population at baseline:

- The mean (SD) duration of CD was 2.6 (2.24) years.
- Ileocolonic disease was present in 58 (58.6%) of 99 participants.
- The median PCDAI score was 40.00 (mean [SD]: 41.16 [7.62]), with 44 (43.6%) of 101 participants with a PCDAI score of >40, indicating severe disease activity.
- The median CDAI score was 348.05 (mean [SD]: 365.20 [120.588]).
- The median SES-CD score was 12.0 (mean [SD]: 12.6 [7.14]).
- The median fecal calprotectin level was 1,859.0 mg/kg (mean [SD]: 2,765.7 [3,121.24] mg/kg).
- The median CRP concentration was 8.30 mg/L (mean [SD]: 19.20 [25.787] mg/L).
- Abnormal fecal calprotectin (>250 mg/kg) occurred in 92 (92.9%) of 99 participants and abnormal CRP (>3 mg/L) occurred in 72 (71.3%) of 101 participants.

A history of ileitis, aphthous stomatitis, and arthritis was reported for >20% of participants. A total of 16 (15.8%) of 101 participants had a history of COVID-19; the outcome was considered recovered or resolved in all 16 participants. No participant reported alcohol, tobacco/nicotine, or opioid use.

***Subgroup Analyses***

Several notable differences in baseline characteristics are as follows:

- A numerically greater proportion of younger participants 2 to 11 years of age had ileocolonic disease than in older participants aged 12 to 17 years (14 [70.0%] of 20 participants versus 44 [54.3%] of 81 participants, respectively).
- A numerically greater proportion of participants <40 kg had ileocolonic disease compared with participants weighing ≥40 kg (22 [75.9%] of 29 participants versus 36 [50.0%] of 72 participants, respectively).
- In the prior biologic status subgroups, participants who had previously failed biologic therapy had a longer CD disease duration (mean [SD]: 3.2 [2.29] years versus 1.9 [1.95] years, respectively), greater ileocolonic GI involvement (39 [68.4%] of 57 participants versus 19 [43.2%] of 44 participants, respectively), and higher mean (SD) and median CRP scores (21.83 [28.246] mg/L; median: 10.50 mg/L versus 15.79 [22.052] mg/L; median: 7.05 mg/L, respectively) than the non-biologic failure subgroup.
- Additionally, participants who had previously failed biologic therapy had higher SES-CD mean (SD) and median scores indicating higher endoscopic disease activity (13.9 [7.79]; median: 14.0 versus 10.8 [5.82]; median: 9.0, respectively), and a greater proportion of participants were

categorised with severe disease severity as assessed by the SES-CD (22 [38.6%] of 57 participants versus 9 [20.9%] of 43 participants, respectively) than the non-biologic failure subgroup.

Baseline disease characteristics based on the age and weight subgroups were generally similar in the FASCR to the FAS. Of note, the sample size in the FAS and FASCR in the younger age groups (notably in participants 2 to 5 years of age) and the <30 kg and ≥30 to <40 kg weight subgroups were very small limiting conclusions on baseline disease characteristics.

While the clinical responders at Week M-0 had generally similar baseline demographic results to those in the FAS, there were very few participants who were delayed responders at Week M-8 (n=6) limiting conclusions.

**Prior Crohn's Disease Medications and Therapies**

**Table 16: Summary of Corticosteroids and immunomodulator prior failure status; FAS (Study CNTO1275CRD3004)**

| | Ustekinumab IV | | | | |
|---|---|---|---|---|---|
| | | Ustekinumab SC | | | |
| | Not randomized | q12w | q8w | Combined | Total |
| Analysis set: Full | 4 | 49 | 48 | 97 | 101 |
| Subjects with inadequate response, intolerance, or dependence to corticosteroids and/or 6-MP/AZA/MTX | 4 (100.0%) | 39 (79.6%) | 40 (83.3%) | 79 (81.4%) | 83 (82.2%) |
| Corticosteroids | | | | | |
| Subjects with inadequate response, intolerance or dependence to corticosteroids | 3 (75.0%) | 23 (46.9%) | 26 (54.2%) | 49 (50.5%) | 52 (51.5%) |
| Subjects with inadequate response | 3 (75.0%) | 20 (40.8%) | 18 (37.5%) | 38 (39.2%) | 41 (40.6%) |
| Subjects intolerant | 0 | 0 | 3 (6.3%) | 3 (3.1%) | 3 (3.0%) |
| Subjects dependent | 1 (25.0%) | 9 (18.4%) | 14 (29.2%) | 23 (23.7%) | 24 (23.8%) |
| Immunomodulators (AZA, 6-MP or MTX) | | | | | |
| Subjects with inadequate response or intolerance to immunomodulators (6-MP/AZA/MTX) | 2 (50.0%) | 28 (57.1%) | 24 (50.0%) | 52 (53.6%) | 54 (53.5%) |
| Subjects with inadequate response | 2 (50.0%) | 25 (51.0%) | 16 (33.3%) | 41 (42.3%) | 43 (42.6%) |
| Subjects intolerant | 0 | 6 (12.2%) | 10 (20.8%) | 16 (16.5%) | 16 (15.8%) |

All participants had either failed or had been intolerant to either conventional therapy or biologic therapy. A majority of participants had a history of inadequate response, intolerance, or dependence to corticosteroids and immunomodulators. The proportions of these participants were similar across the q12w and q8w treatment groups.

**Table 17: Summary of CD-related biological medication history; FAS (Study CNTO1275CRD3004)**

| | Ustekinumab IV | | | | |
|---|---|---|---|---|---|
| | | Ustekinumab SC | | | |
| | Not randomized | q12w | q8w | Combined | Total |
| Analysis set: Full | 4 | 49 | 48 | 97 | 101 |
| Subjects without a history of biological failure | 2 (50.0%) | 24 (49.0%) | 18 (37.5%) | 42 (43.3%) | 44 (43.6%) |
| Biologic-naive | 2 (50.0%) | 23 (46.9%) | 18 (37.5%) | 41 (42.3%) | 43 (42.6%) |
| Biologic-experienced, but not documented failure | 0 | 1 (2.0%) | 0 | 1 (1.0%) | 1 (1.0%) |
| Subjects with a history of biological failure | 2 (50.0%) | 25 (51.0%) | 30 (62.5%) | 55 (56.7%) | 57 (56.4%) |
| Primary nonresponse, secondary nonresponse, or intolerance to | | | | | |
| Only anti-TNF (NOT to vedolizumab) | 2 (50.0%) | 25 (51.0%) | 29 (60.4%) | 54 (55.7%) | 56 (55.4%) |
| Primary nonresponse | 1 (25.0%) | 11 (22.4%) | 7 (14.6%) | 18 (18.6%) | 19 (18.8%) |
| Secondary nonresponse | 1 (25.0%) | 14 (28.6%) | 18 (37.5%) | 32 (33.0%) | 33 (32.7%) |
| Intolerance | 0 | 6 (12.2%) | 8 (16.7%) | 14 (14.4%) | 14 (13.9%) |
| At least one anti-TNF (regardless of vedolizumab) | 2 (50.0%) | 25 (51.0%) | 30 (62.5%) | 55 (56.7%) | 57 (56.4%) |
| Primary nonresponse | 1 (25.0%) | 11 (22.4%) | 8 (16.7%) | 19 (19.6%) | 20 (19.8%) |
| Secondary nonresponse | 1 (25.0%) | 14 (28.6%) | 18 (37.5%) | 32 (33.0%) | 33 (32.7%) |
| Intolerance | 0 | 6 (12.2%) | 8 (16.7%) | 14 (14.4%) | 14 (13.9%) |
| Any anti-TNF and vedolizumab | 0 | 0 | 1 (2.1%) | 1 (1.0%) | 1 (1.0%) |
| Primary nonresponse | 0 | 0 | 1 (2.1%) | 1 (1.0%) | 1 (1.0%) |
| Secondary nonresponse | 0 | 0 | 0 | 0 | 0 |
| Intolerance | 0 | 0 | 0 | 0 | 0 |
| Vedolizumab (regardless of anti-TNF) | 0 | 0 | 1 (2.1%) | 1 (1.0%) | 1 (1.0%) |
| Primary nonresponse | 0 | 0 | 1 (2.1%) | 1 (1.0%) | 1 (1.0%) |
| Secondary nonresponse | 0 | 0 | 0 | 0 | 0 |
| Intolerance | 0 | 0 | 0 | 0 | 0 |

All participants used CD medication prior to Week I-0. More than half of the participants had a history of biologic failure. Participants with a history of biologic/TNF exposure were numerically higher in the q8w treatment group than the q12w treatment group. Of the participants without a history of biologic failure, 1 participant was biologic-experienced without documented failure while the remaining participants were biologic-naïve.

A total of 70 of 101 participants previously received nutritional treatments for CD. Exclusive enteral nutrition was the most common therapy, given to 42 of 101 participants as primary CD therapy. Additionally, 40 of 101 participant utilised another form of dietary therapy other than exclusive enteral nutrition to try to improve CD. The most frequently followed diet therapies were a CD exclusion diet (20 [50.0%] participants), followed by a partial or total liquid diet (14 [35.0%] participants

***Subgroup Analyses***

Data for the clinical responders at Week M-0 in the FASRES were consistent with data from the FAS. There were very few participants who were delayed responders at Week M-8 (n=6) limiting conclusions.

**Concomitant Therapies**

Baseline CD-related medications were similar across treatment interventions. Among the FAS participants, at baseline, a majority of participants were receiving 1 or more concomitant medications for CD (e.g., corticosteroids [including budesonide and beclomethasone dipropionate], immunomodulators, and/or 5-ASA) (Table 18).

**Table 18: Summary of CD-related concomitant medication at baseline; FAS (Study CNTO1275CRD3004)**

| | Ustekinumab IV | | | | |
|---|---|---|---|---|---|
| | | Ustekinumab SC | | | |
| | Not randomized | q12w | q8w | Combined | Total |
| Analysis set: Full | 4 | 49 | 48 | 97 | 101 |
| Any CD-related Concomitant Medication | 3 (75.0%) | 37 (75.5%) | 32 (66.7%) | 69 (71.1%) | 72 (71.3%) |
| Antibiotic | 0 | 3 (6.1%) | 3 (6.3%) | 6 (6.2%) | 6 (5.9%) |
| Amoxicillin | 0 | 1 (2.0%) | 0 | 1 (1.0%) | 1 (1.0%) |
| Clarithromycin | 0 | 0 | 0 | 0 | 0 |
| Ciprofloxacin | 0 | 0 | 0 | 0 | 0 |
| Doxycycline | 0 | 0 | 0 | 0 | 0 |
| Levofloxacin | 0 | 0 | 0 | 0 | 0 |
| Metronidazole | 0 | 2 (4.1%) | 3 (6.3%) | 5 (5.2%) | 5 (5.0%) |
| Rifaximin | 0 | 0 | 0 | 0 | 0 |
| Vancomycin | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 0 |
| Corticosteroids | 2 (50.0%) | 10 (20.4%) | 13 (27.1%) | 23 (23.7%) | 25 (24.8%) |
| Budesonide | 1 (25.0%) | 6 (12.2%) | 8 (16.7%) | 14 (14.4%) | 15 (14.9%) |
| Beclomethasone dipropionate | 0 | 1 (2.0%) | 0 | 1 (1.0%) | 1 (1.0%) |
| Hydrocortisone | 0 | 0 | 0 | 0 | 0 |
| Methylprednisolone | 1 (25.0%) | 0 | 4 (8.3%) | 4 (4.1%) | 5 (5.0%) |
| Prednisolone | 0 | 2 (4.1%) | 2 (4.2%) | 4 (4.1%) | 4 (4.0%) |
| Prednisone | 0 | 1 (2.0%) | 0 | 1 (1.0%) | 1 (1.0%) |
| Other | 0 | 0 | 0 | 0 | 0 |
| Immunomodulatory drugs | 2 (50.0%) | 23 (46.9%) | 18 (37.5%) | 41 (42.3%) | 43 (42.6%) |
| 6-Mercaptopurine | 0 | 1 (2.0%) | 0 | 1 (1.0%) | 1 (1.0%) |
| Azathioprine | 2 (50.0%) | 18 (36.7%) | 16 (33.3%) | 34 (35.1%) | 36 (35.6%) |
| Methotrexate | 0 | 4 (8.2%) | 2 (4.2%) | 6 (6.2%) | 6 (5.9%) |
| 5-Aminosalicylate (5-ASA) | 0 | 16 (32.7%) | 16 (33.3%) | 32 (33.0%) | 32 (31.7%) |
| Balsalazide | 0 | 0 | 0 | 0 | 0 |
| Sulfasalazine | 0 | 0 | 1 (2.1%) | 1 (1.0%) | 1 (1.0%) |
| Mesalamine | 0 | 16 (32.7%) | 15 (31.3%) | 31 (32.0%) | 31 (30.7%) |
| Olsalazine | 0 | 0 | 0 | 0 | 0 |
| Other aminosalicylates | 0 | 0 | 0 | 0 | 0 |

Note: Subjects may appear in more than one category.
Note: Baseline is defined as the observation at Week I-0.

***Subgroup Analyses***

The proportions of participants receiving concomitant CD medications in the FAS were generally similar across the treatment groups in the age and weight subgroups, with the exception of the following:

- A numerically higher proportion of participants <40 kg received immunomodulatory drugs than participants ≥40 kg (16 [55.2%] of 29 participants versus 27 [37.5%] of 72 participants, respectively).

Participants receiving concomitant CD medications in the FASCR based on the age and weight subgroups were generally similar to the overall population. Concomitant therapy data for the clinical responders at Week M-0 in the FASRES were also generally similar to the overall population. There were very few participants in the younger age/lighter weight groups and those who were delayed responders at Week M-8 (n=6) limiting conclusions.

**Exposure**

The median total number of IV infusions and SC injections received was 5.0 (5.0 in the q12w treatment group [n=49] and 7.0 in the q8w treatment group [n=48]), with a median total duration of IV and SC treatment exposure of 44.3 weeks (44.1 and 48.1 weeks in the q12w and q8w treatment groups, respectively). The median total dose of IV and SC ustekinumab administrations was 660.0 mg (620.0 mg in the q12w treatment group and 800.0 mg in the q8w treatment group).

**Compliance With Intervention**

Ustekinumab was administered as an IV infusion (Week I-0) and an SC injection (all time points specified for study intervention administration in Figure 1 except Week I-0). No participants missed a study intervention administration during the study. All 101 participants in the Safety Analysis Set received the full IV induction dose at Week I-0, with the exception of 2 participants. One participant had an infusion related hypersensitivity SAE, which necessitated stopping their infusion, and 1 participant had reported nonserious AEs that were temporally associated with infusion of study intervention that led to discontinuation of study intervention.

Additionally, all 97 participants in the SASR who were randomised into the maintenance period of the study received at least 1 SC dose of study intervention during the maintenance period. No participant missed a dose due to COVID-19 related reasons during the maintenance period.

**Exposure Optimisation Substudy Study Participants**

Participants who did not achieve clinical response based on the PCDAI by Week M-8 (induction nonresponders) and participants in the maintenance period who had a confirmed LOR (protocol defined increase of PCDAI at 2 consecutive visits at least 7 days apart) and had low steady-state trough ustekinumab concentrations (low exposure) were eligible to participate in the optional EOS and receive the q4w dose regimen.

**EOS Study Disposition**

Of the 97 participants who were randomised in the maintenance period of the main study, 26 (26.8%) participants enrolled in the EOS (Table 19).

**Table 19: Number of subjects with confirmed loss of response / dose adjustment who entered the exposure optimisation substudy; FAS (CNT01275CRD3004)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | Randomized at Week M-0 | | |
| | q12w[a] | q8w[a] | Combined |
| Analysis set: Full Randomized | 49 | 48 | 97 |
| Total number of subjects who experienced a confirmed loss of response[b] | 12 (24.5%) | 14 (29.2%) | 26 (26.8%) |
| Total number of subjects who had low exposure | 11 (22.4%) | 13 (27.1%) | 24 (24.7%) |
| Total number of subjects who entered substudy | 10 (20.4%) | 13 (27.1%) | 23 (23.7%) |
| Total number of subjects who met early escape criteria | 1 (2.0%) | 2 (4.2%) | 3 (3.1%) |
| Total number of subjects who entered substudy | 1 (2.0%) | 2 (4.2%) | 3 (3.1%) |

[a] Subjects are counted in the treatment group they were randomized to at Week M-0.
[b] Loss of Response is defined as protocol-defined increase of PCDAI at 2 consecutive visits at least 7 days apart. If the second visit occurs at an unscheduled visit, it will be mapped to the subsequent scheduled visit.

Of the 26 participants who entered the EOS, 21 (80.8%) completed a minimum of 16 weeks of substudy treatment. The reasons for the 5 (19.2%) participants who discontinued the EOS treatment included an AE of worsening of Crohn's disease, participant initiated prohibited medication, lack of efficacy, other (high ustekinumab trough concentration of >7.2 µg/mL, so the participant was not able to proceed on the q4w dose regimen), and withdrawal by parent or guardian (this participant also discontinued participation in the study prior to Week M44). One participant who had a missing Substudy Week 16 sPCDAI assessment was excluded from the EOS efficacy analysis.

Seven participants in the EOS had an MPD. Two participants received the wrong treatment or incorrect dose and the remaining MPDs were listed as "other," with the most common deviation criterion being missed assessments.

**Demographic and Other Baseline Characteristics**

Overall, the demographic and clinical characteristics were similar to those of the main study participants. However, there was a numerically larger proportion of EOS participants exhibiting severe CD disease activity (PCDAI >40) (14 [53.8%] of 26 participants) than in the main study (44 [43.6%] of 101 participants). Additionally, a larger proportion of participants in the EOS had a history of biologic failure, with 21 (80.8%) participants compared with 57 (56.4%) participants in the main study.

## Outcomes and estimation

Unless otherwise noted, efficacy analyses were based on the FAS (N=101) for induction endpoints through Week I-8 and the FASCR for maintenance endpoints from Week M-0 through Week M-44, which included 85 participants who were randomised 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. For the FASCR, participants were analysed according to the intervention group to which they were randomised regardless of the intervention they actually received.

**Primary endpoint**

The primary endpoint (Global Primary Estimand 1) was clinical remission at Week I-8, defined as a PCDAI score of ≤10 points. Overall, the proportion of participants in clinical remission increased through the induction period up to Week I-8, with 46.5% of participants who achieved clinical remission at Week I-8.

**Table 20: Primary endpoint analysis (Global primary estimand 1) - subjects clinical remission at week I-8; FAS (Study CNTO1275CRD3004)**

| | Ustekinumab IV |
|---|---|
| Analysis set: Full | 101 |
| Week I-8 | |
| N | 101 |
| Subjects in clinical remission[a,b,c,d] | 47 (46.5%) |
| 95% CI for proportion of subjects in clinical remission[e] | (37.1%, 56.2%) |

[a] Clinical remission is defined as PCDAI score ≤10 points.
[b] ICEs include: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4.
[c] ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 are considered not to be in clinical remission at Week I-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing clinical remission data from the time of the event onward (ie, hypothetical strategy).
[d] After accounting for the ICEs, subjects who have missing clinical remission are considered not to be in clinical remission at Week I-8.
[e] The confidence intervals are based on the Wilson statistic.

Through Week I-8, 3 (3.0%) of 101 participants had at least 1 ICE, although none of the ICEs occurred in participants with a PCDAI ≤10 (criteria for clinical remission). One participant had an ICE categorised as "discontinuation due to lack of efficacy or AE of worsening Crohn's disease" and 2 participants had an ICE categorised as "discontinued study intervention due to reasons other than lack of efficacy or an AE of worsening Crohn's disease or COVID-19 related reasons."

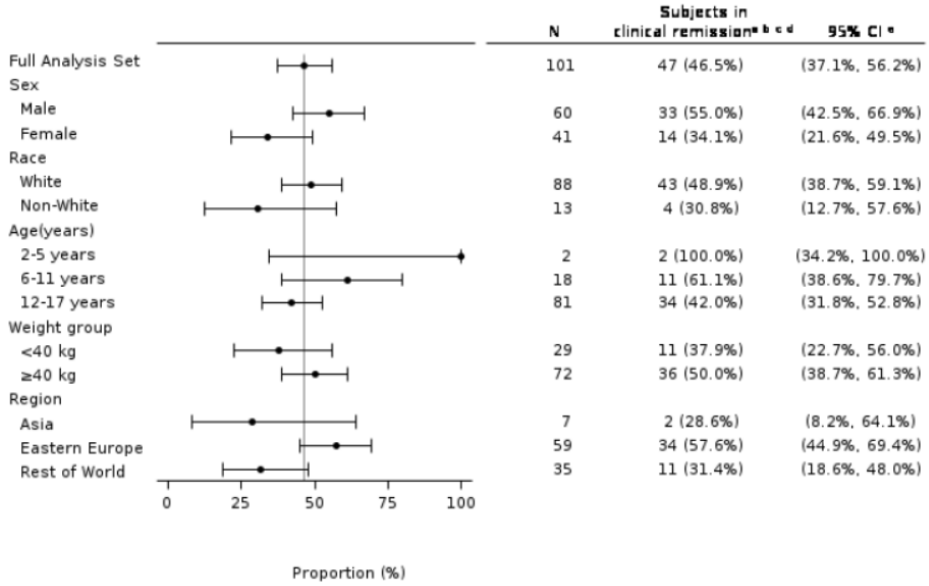
All PCDAI subscores were missing for 4 (4.0%) of the 101 participants. These participants discontinued treatment prior to Week I-8 and were classified as nonresponders (of note, 1 of the 4 participants was a nonrandomised participant who only received an IV induction dose of ustekinumab, but discontinued study intervention during the predicted maintenance period of the study [Day 84] due to a genetic disorder diagnosis). In addition, 13 (12.9%) participants had 1 PCDAI subscore missing at Week I-8. These 13 participants had a missing laboratory score at the Week I-8 visit.

***Subgroup Analyses***

The consistency of efficacy for clinical remission at Week I-8 was examined in subgroup analyses based on predefined demographics and baseline clinical disease characteristics.

The results from these subgroup analyses were consistent with those observed in the overall study population, except the proportion of participants who achieved clinical remission was higher among the subgroup of non-biologic failure participants (29 [65.9%] of 44 participants; 95% CI: 51.1%, 78.1%) than the biologic failure participants (18 [31.6%] of 57 participants; 95% CI: 21.0%, 44.5%).

**Table 21: Primary endpoint analysis (Global primary estimand 1) - subjects clinical remission at week I-8 by Demographics and Baseline Disease Characteristics; FAS (Study CNTO1275CRD3004)**




**Secondary endpoints**

**Table 22: Summary of the results of secondary endpoint analysis (global and US secondary estimand 1 to 5) through week M-8; full analysis set (Study CNTO1275CRD3004)**

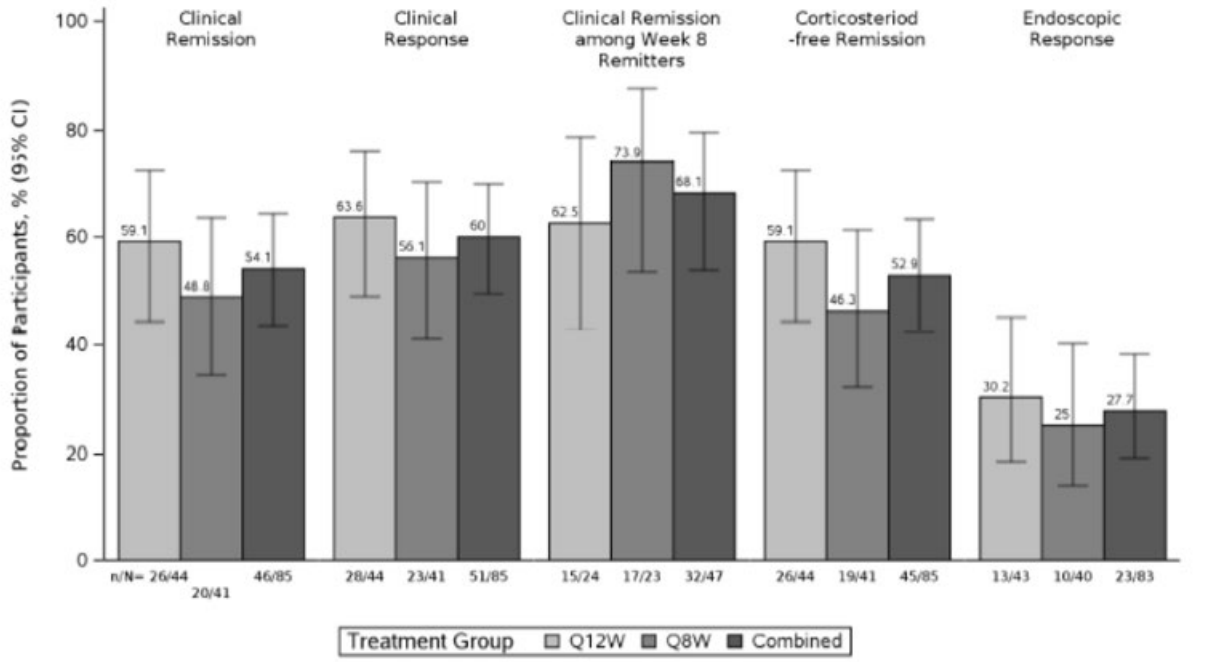
| | Ustekinumab IV |
|---|---|
| Analysis set: Full | 101 |
| Week I-8 | |
| N | 101 |
| Subjects in clinical remission[a,b,c,d] | 47 (46.5%) |
| 95% CI for proportion of subjects in clinical remission[e] | (37.1%, 56.2%) |
| Week I-6 | |
| N | 101 |
| Subjects in clinical remission[a0,b,c,d] | 46 (45.5%) |
| 95% CI for proportion of subjects in clinical remission[e] | (36.2%, 55.2%) |
| Week I-8 | |
| N | 101 |
| Subjects in clinical response[a1,b,c1,d1] | 85 (84.2%) |
| 95% CI for proportion of subjects in clinical response[e] | (75.8%, 90.0%) |
| Week I-6 | |
| N | 101 |
| Subjects in clinical response[a2,b,c,d] | 90 (89.1%) |
| 95% CI for proportion of subjects in clinical response[e] | (81.5%, 93.8%) |
| Subjects randomized with baseline SES-CD score ≥3 | 94 |
| Week M-8 | |
| N | 94 |
| Subjects in endoscopic response[a3,b,c2,d2,f] | 34 (36.2%) |
| 95% CI for proportion of subjects in endoscopic response[e] | (27.2%, 46.2%) |
| Week M-8 | |
| N | 97 |
| Subjects randomized in clinical response[a1,b,c2,d2,f] | 83 (85.6%) |
| 95% CI for proportion of subjects in clinical response[e] | (77.2%, 91.2%) |

[a] Clinical remission is defined as PCDAI score ≤10 points.
[a0] Clinical remission is defined as sPCDAI score ≤10 points.
[a1] 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.
[a2] Clinical response is defined as a reduction from baseline in the sPCDAI score of ≥10.
[a3] Endoscopic response is defined as a reduction in the SES-CD score of ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3.
[b] ICEs include: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4.
[c] ICEs strategies: Subjects that have ICEs 1-3, and 5 prior to Week I-6 are not considered to be in endpoint at Week I-6 (ie. composite strategy). Subjects with ICE 4 prior to Week I-6 are considered to have missing endpoint data from the time of the event onward (ie. hypothetical strategy).
[c1] ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 are considered not to be in endpoint at Week I-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy).
[c2] ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 are considered not to be in endpoint at Week M-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy).
[d] After accounting for the ICEs, subjects who have missing endpoint data are considered not to be in endpoint at Week I-6.
[d1] After accounting for the ICEs, subjects who have missing endpoint are considered not to be in Endpoint at Week I-8.
[d2] After accounting for the ICEs, subjects who have missing endpoint are considered not to be in Endpoint at Week M-8.
[e] The confidence intervals are based on the Wilson statistic.
[f] The endpoints are evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate response due to induction.

**Maintenance Period**

The results of the analyses of the global and US-specific secondary endpoints from Week M-0 through Week M-44 are provided in Table 22. Overall, these data suggest that both the q12w regimen and the q8w regimen are efficacious.

**Figure 29: Histogram with confidence interval of secondary endpoints through week M-44; full clinical responder analysis set (Study CNTO1275CRD3004)**




Note: Clinical remission is defined as PCDAI score ≤10 points.
Note: 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.
Note: Corticosteroid-free remission is defined as PCDAI score of ≤10 points and not receiving corticosteroids for at least 90 days prior to Week M-44.
Note: Endoscopic response is defined as a reduction in the SES-CD score of ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3.
Note: refer to individual table tefsec07ag, tefsec09agu, tefsec11agu, tefsec10agu and tefsec08agu respectively.

**Table 23: Summary of the results of secondary endpoint analysis (global and US secondary estimand 6 to 10) at week M-44; full clinical responder analysis set (Study CNTO1275CRD3004)**

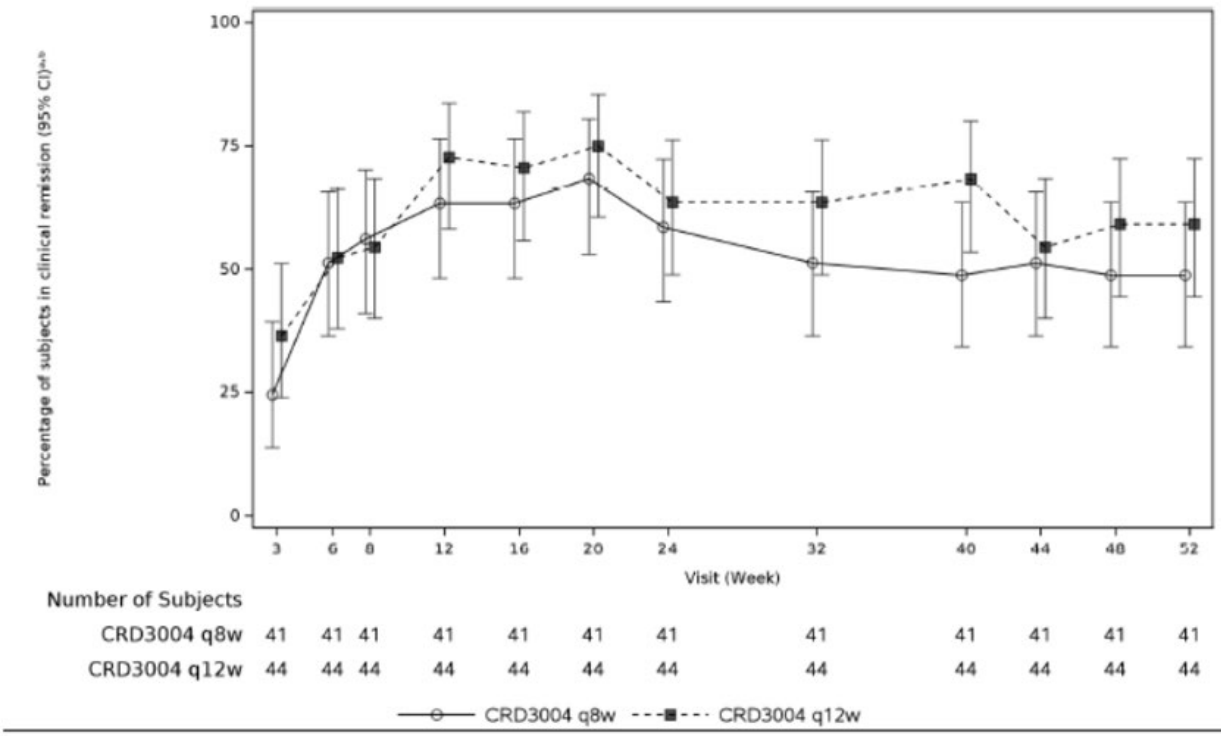
| | Ustekinumab SC | | |
|---|---|---|---|
| | Randomized at Week M-0 | | |
| | q12w | q8w | Combined |
| Analysis set: Full Clinical Responder | 44 | 41 | 85 |
| Week M-44 | | | |
| N | 44 | 41 | 85 |
| Subjects in clinical remission[a,b,c,d] | 26 (59.1%) | 20 (48.8%) | 46 (54.1%) |
| 95% CI for proportion of subjects in clinical remission[e] | (44.4%, 72.3%) | (34.3%, 63.5%) | (43.6%, 64.3%) |
| Difference in proportion (95% CI)[f] | | -10.7% (-31.6%, 10.2%) | |
| Subjects with baseline SES-CD score ≥3 | 43 (97.7%) | 40 (97.6%) | 83 (97.6%) |
| Week M-44 | | | |
| N | 43 | 40 | 83 |
| Subjects in endoscopic response[a1,b,c,d] | 13 (30.2%) | 10 (25.0%) | 23 (27.7%) |
| 95% CI for proportion of subjects in endoscopic response[e] | (18.6%, 45.1%) | (14.2%, 40.2%) | (19.2%, 38.2%) |
| Difference in proportion (95% CI)[f] | | -4.8% (-23.7%, 14.1%) | |
| Week M-44 | | | |
| N | 44 | 41 | 85 |
| Subjects in clinical response[a2,b,c,d] | 28 (63.6%) | 23 (56.1%) | 51 (60.0%) |
| 95% CI for proportion of subjects in clinical response[e] | (48.9%, 76.2%) | (41.0%, 70.1%) | (49.4%, 69.8%) |
| Difference in proportion (95% CI)[f] | | -7.5% (-28.3%, 13.3%) | |
| Week M-44 | | | |
| N | 44 | 41 | 85 |
| Subjects in corticosteroid-free clinical remission[a3,b,c,d] | 26 (59.1%) | 19 (46.3%) | 45 (52.9%) |
| 95% CI for proportion of subjects in corticosteroid-free clinical remission[e] | (44.4%, 72.3%) | (32.1%, 61.3%) | (42.4%, 63.2%) |
| Difference in proportion (95% CI)[f] | | -13.1% (-34.0%, 7.7%) | |
| Subjects who are in clinical remission at Week I-8 | 24 (54.5%) | 23 (56.1%) | 47 (55.3%) |
| Week M-44 | | | |
| N | 24 | 23 | 47 |
| Subjects in clinical remission[a1,b,c,d] | 15 (62.5%) | 17 (73.9%) | 32 (68.1%) |
| 95% CI for proportion of subjects in clinical remission[e] | (42.7%, 78.8%) | (53.5%, 87.5%) | (53.8%, 79.6%) |
| Difference in proportion (95% CI)[f] | | 11.2% (-14.9%, 37.4%) | |

[a] Clinical remission is defined as PCDAI score ≤10 points.
[a1] Endoscopic response is defined as a reduction in the SES-CD score of ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3.
[a2] 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.
[a3] Corticosteroid-free remission is defined as PCDAI score of ≤10 points and not receiving corticosteroids for at least 90 days prior to Week M-44.
[b] ICEs include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6.
[c] ICEs strategies: Subjects that have ICEs 1-5, and 7 prior to Week M-44 are not considered to be in endpoint at Week M-44 (ie. composite strategy). Subjects with ICE 6 prior to Week M-44 are considered to have missing endpoint data from the time of the event onward (ie. hypothetical strategy).
[d] After accounting for the ICEs, subjects who have missing endpoint data are considered not to be in endpoint at Week M-44.
[e] The confidence intervals are based on the Wilson statistic.
[f] The confidence intervals are based on the Wald statistic with Mantel-Haenszel weight.

**Clinical Remission and Clinical Response Over Time**

A line plot of the percentage of participants achieving clinical remission by visit through Week M-44 is presented in Figure 30. Overall, the proportion of participants who achieved clinical remission increased through Week I-8. During the maintenance period from Week M-0 through Week M-44, the proportions of participants in clinical remission were maintained in both the q12w and q8w treatment groups.

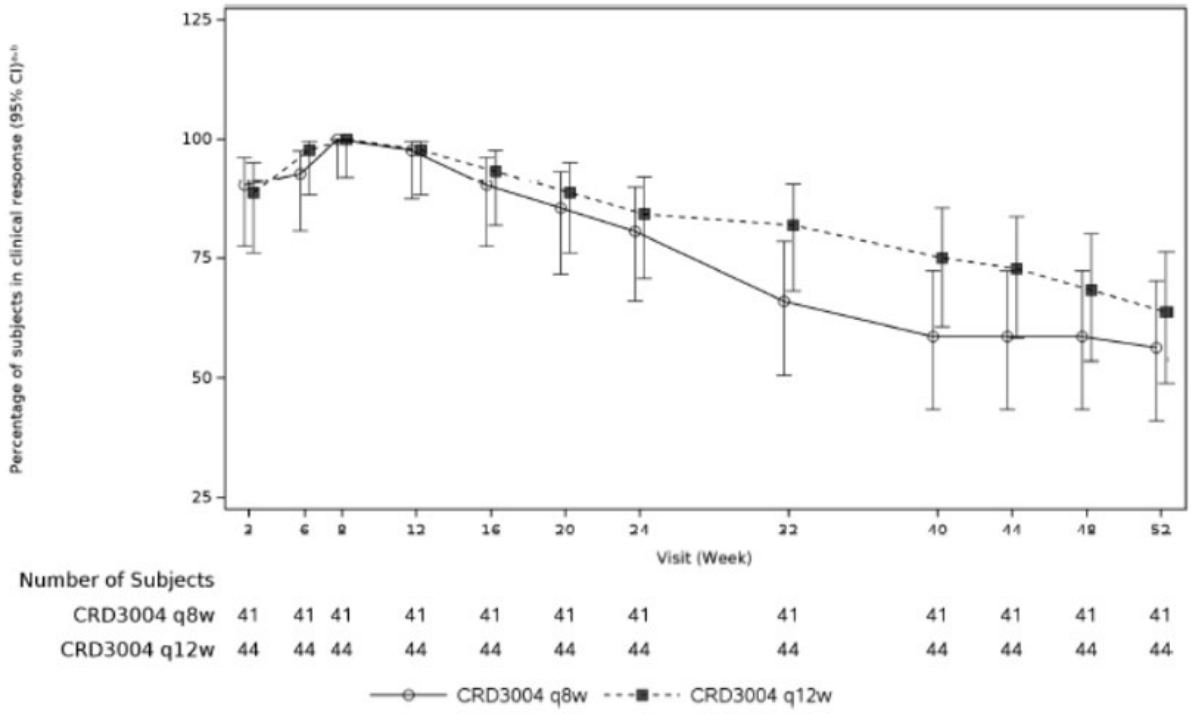
**Figure 30: Line plot of percentage of subjects achieving clinical remission by visit through week M-44; full clinical responder analysis set (Study CNTO1275CRD3004)**




Note: Clinical remission is defined as PCDAI score ≤10 points. The timepoints are at Week I-8, M-8, M-16, M-32 and M-44.
Note: Clinical remission is defined as sPCDAI score ≤10 points. The timepoints are at Week I-3, I-6, M-4, M-12, M-24, M-36 and M-40.

Additionally, the proportion of participants who achieved clinical response through Week M-44 is presented in Figure 31. Overall, the proportion of participants who achieved clinical response increased during the induction period through Week I-8. A modest downward trend was observed until Week M-32, at which point, the decrease in the proportion of participants who achieved clinical response began to stabilise.

**Figure 31: Line plot of percentage of subjects achieving clinical response by visit through week M-44; full clinical responder analysis set (Study CNTO1275CRD3004)**




Note: 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. The visits for PCDAI score are Week I-8, M-8, M-16, M-32 and M-44.
Note: Clinical response is defined as a reduction from baseline in the sPCDAI score of ≥10. The visits for sPCDAI are Week I-3, I-6, M-4, M-12, M-24, M-36 and M-40.

**Tertiary endpoints**

The tertiary and exploratory endpoints, serum and fecal biomarkers, nutritional parameters, additional endoscopic endpoints, fistula related endpoints, hospitalization and surgeries, and MINI (Mucosal Inflammation Noninvasive Index) assessments, all showed consistent improvement and/or sustained maintenance over time during induction and for both the q12w and q8w treatment groups during the maintenance phase of the study. There was no marked differentiation between the q12w and q8w treatment groups (data not shown).

The tertiary analyses to explore differences between PCDAI and PCDAI diary (scored using prospective diary data) scores for remission/response related assessments showed that clinical response and remission had generally consistent results when either PCDAI score was used.

**Growth**

Based on observed scores, at baseline, mean (SD) BMI z-scores were near or below zero in females (-0.066 [0.7709]; median score of -0.311) and males (-0.244 [1.0757]; median score of -0.524). The change from baseline in BMI z-scores at Week I-8 demonstrated a numerical increase (improvement) from baseline in BMI z-scores for both females (mean [SD]: 0.179 [0.3269]; median: 0.094) and males

(mean [SD]: 0.137 [0.2894]; median: 0.134). However, the BMI z-score in males (mean [SD]: -0.111 [1.0290]; median: -0.375) remained below zero, and low negative z-score values were observed within the score range for each group (range: -1.38 to 3.00 for females and -1.70 to 4.18 for males).

At Week M-44, change from baseline BMI z-scores showed an increase in both the q12w and q8w treatment groups. In the combined treatment groups females had a slightly larger increase in BMI change from baseline z-scores (mean [SD]: 0.284 [0.5293]; median: 0.269) than males (mean [SD]: 0.125 [0.5642]; median: 0.086). Negative BMI z-score values less than -1 were observed in the lower range of the male q12w (-1.45) and q8w (-1.45) treatment groups. Low negative BMI z-scores are an indication of mild malnutrition (defined as BMI z-score -1 to -1.9), and were notable in males and females at baseline, but only persisted in the males at Week M-44.

Additionally, at Week M-44, the median height z-score was 0.173. However, at Week M-44, change from baseline in height z-scores did not provide strong evidence of treatment level catch-up growth (mean [SD] change from baseline scores of 0.004 [0.2628] and 0.023 [0.2801] in the combined treatment groups for females and males, respectively; median scores of 0.012 and 0.010, respectively). Nevertheless, 6 participants had a >0.5 point change in height z-scores.

**Nutritional parameters**

Overall, no notable shifts from baseline were observed in the nutritional parameters 25-hydroxyvitamin D or MMA, but serum iron values showed an improvement from baseline.

**IMPACT-III Scores**

Health-related QoL was measured using the IMPACT-III assessment for participants aged ≥10 years at Week I-0. The IMPACT-III total score ranges from 35 to 175 (Otley 2002; Otley 2006). The questionnaire's 35 items cover multiple subdomains/concepts of HRQoL, including bowel symptoms, systemic symptoms, emotional functioning, social functioning, and body image. A higher score indicates that patients have a better overall HRQoL. Alternatively, a lower score indicates that the disease has negatively affected patient HRQoL. Table 24 and Table 25 present IMPACT-III raw and transformed total baseline scores and change to Week M-44 total scores, respectively for CNTO1275CRD3004 (q12w, q8w, and combined treatment groups). Raw and transformed mean change scores overall and for the q12w and q8w treatment groups indicated that HRQoL numerically improved with ustekinumab treatment over 44 weeks, with clinically meaningful increases (using distribution-based methodology) in mean IMPACT-III total scores in both treatment groups observed at Week M-44.

**Table 24: Tertiary endpoint analysis: Summary of change from baseline in IMPACT-III scores at week M-44 for subjects at least 10 years of age at week I-0; full clinical responder analysis set (Study CNTO1275CRD3004)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | Randomized at Week M-0 | | |
| | q12w | q8w | Combined |
| Analysis set: Full Clinical Responder | 44 | 41 | 85 |
| Subjects ≥10 years of age at Week I-0 | 38 (86.4%) | 38 (92.7%) | 76 (89.4%) |
| IMPACT-III scores | | | |
| Baseline[a] | | | |
| N | 32 | 31 | 63 |
| Mean (SD) | 103.3 (25.46) | 100.0 (24.41) | 101.7 (24.80) |
| Median | 102.5 | 99.0 | 101.0 |
| Range | (40; 143) | (53; 142) | (40; 143) |
| Week M-44[b,c] | | | |
| N | 30 | 29 | 59 |
| Mean (SD) | 124.5 (26.93) | 119.7 (23.67) | 122.1 (25.28) |
| Median | 133.0 | 123.0 | 127.0 |
| Range | (40; 159) | (67; 161) | (40; 161) |
| Week M-44 Change from baseline[b,c] | | | |
| N | 28 | 26 | 54 |
| Mean (SD) | 18.0 (25.24) | 20.4 (31.13) | 19.1 (27.99) |
| Median | 2.0 | 0.0 | 0.0 |
| Range | (-10; 87) | (0; 96) | (-10; 96) |

Key: SD = standard deviation
Note: The IMPACT-III presents five Likert response options per question, scored 0 to 4.
[a] Baseline is defined as the last observation prior to or at the time of the first study intervention.
[b] ICEs include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6.
[c] ICEs strategies: Subjects that have ICEs 1-5, and 7 prior to a visit are considered to have no change from baseline for that endpoint at that visit and subsequent visit. Subjects with ICE 6 have their data assumed missing after the ICE 6 occurred..

**Table 25: Tertiary endpoint analysis: Summary of change from baseline in IMPACT-III transformed scores at week M-44 for subjects at least 10 years of age at week I-0; full clinical responder analysis set (Study CNTO1275CRD3004)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | Randomized at Week M-0 | | |
| | q12w | q8w | Combined |
| Analysis set: Full Clinical Responder | 44 | 41 | 85 |
| Subjects ≥10 years of age at Week I-0 | 38 (86.4%) | 38 (92.7%) | 76 (89.4%) |
| IMPACT-III Transformed Scores | | | |
| Baseline[a] | | | |
| N | 32 | 31 | 63 |
| Mean (SD) | 48.8 (18.18) | 46.5 (17.44) | 47.6 (17.72) |
| Median | 48.2 | 45.7 | 47.1 |
| Range | (4; 77) | (13; 76) | (4; 77) |
| Week M-44[b,c] | | | |
| N | 30 | 29 | 59 |
| Mean (SD) | 64.0 (19.24) | 60.5 (16.91) | 62.2 (18.06) |
| Median | 70.0 | 62.9 | 65.7 |
| Range | (4; 89) | (23; 90) | (4; 90) |
| Week M-44 Change from baseline[b,c] | | | |
| N | 28 | 26 | 54 |
| Mean (SD) | 12.8 (18.03) | 14.6 (22.24) | 13.7 (19.99) |
| Median | 1.4 | 0.0 | 0.0 |
| Range | (-7; 62) | (0; 69) | (-7; 69) |

Key: SD = standard deviation
Note: The IMPACT-III presents five Likert response options per question, scored 0 to 4. Transformed scores reflects a linear transformation on a range of 0-100, as follows: 0=100; 1=75; 2=50; 3=25; 4=0.
[a] Baseline is defined as the last observation prior to or at the time of the first study intervention.
[b] ICEs include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention
due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6.
[c] ICEs strategies: Subjects that have ICEs 1-5, and 7 prior to a visit are considered to have no change from baseline for that endpoint at that visit and subsequent visit. Subjects with ICE 6 have their data assumed missing after the ICE 6 occurred..

Table 26 presents selected subdomains of the IMPACT-III, including patient-reported "signs/symptoms," "emotional," and "well-being." To aid in the interpretability of efficacy findings in HRQoL, key stakeholders have identified a 0.5 SD as a reasonable minimum threshold for establishing clinically meaningful improvement in HRQoL concepts (Homco 2019; Norman 2003). Mean change scores for the combined treatment group indicated that all 3 subdomains numerically improved (exceeding the 0.5 SD threshold for clinically meaningful improvement) in HRQoL with ustekinumab treatment over 44 weeks. Finally, mean subdomain improvements were comparable (range: 12.3 to 22.6) to the mean change observed for IMPACT-III transformed total score (13.7).

**Table 26: Tertiary endpoint analysis: Summary of change from baseline in selected domains of IMPACT-III transformed scores at week M-44 for subjects at least 10 years of age at week I-0; full clinical responder analysis set (Study CNTO1275CRD3004)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | Randomized at Week M-0 | | |
| | q12w | q8w | Combined |
| Analysis set: Full Clinical Responder | 44 | 41 | 85 |
| Subjects ≥10 years of age at Week I-0 | 38 (86.4%) | 38 (92.7%) | 76 (89.4%) |
| Well-being scores | | | |
| Baseline[a] | | | |
| N | 32 | 31 | 63 |
| Mean (SD) | 41.1 (19.94) | 37.7 (20.65) | 39.4 (20.20) |
| Median | 40.6 | 35.4 | 39.6 |
| Range | (4; 94) | (6; 79) | (4; 94) |
| Week M-44[b,c] | | | |
| N | 30 | 29 | 59 |
| Mean (SD) | 64.2 (23.75) | 57.6 (23.55) | 60.9 (23.68) |
| Median | 70.8 | 60.4 | 64.6 |
| Range | (4; 96) | (10; 98) | (4; 98) |
| Week M-44 Change from baseline[b,c] | | | |
| N | 28 | 26 | 54 |
| Mean (SD) | 20.7 (24.41) | 20.0 (28.74) | 20.4 (26.33) |
| Median | 8.3 | 0.0 | 3.1 |
| Range | (-6; 77) | (0; 85) | (-6; 85) |
| Signs/symptoms | | | |
| Baseline[a] | | | |
| N | 32 | 31 | 63 |
| Mean (SD) | 37.8 (21.33) | 34.7 (20.62) | 36.3 (20.88) |
| Median | 39.3 | 32.1 | 35.7 |
| Range | (0; 93) | (4; 79) | (0; 93) |
| Week M-44[b,c] | | | |
| N | 30 | 29 | 59 |
| Mean (SD) | 62.9 (24.40) | 56.5 (24.95) | 59.7 (24.66) |
| Median | 67.9 | 53.6 | 67.9 |
| Range | (4; 93) | (11; 96) | (4; 96) |
| | | | |
| Mean (SD) | 11.6 (21.68) | 13.0 (20.48) | 12.3 (20.92) |
| Median | 0.0 | 0.0 | 0.0 |
| Range | (-29; 54) | (-4; 61) | (-29; 61) |

Key: SD = standard deviation
Note: The IMPACT-III presents five Likert response options per question, scored 0 to 4. Transformed scores reflects a linear transformation on a range of 0-100, as follows: 0=100; 1=75; 2=50; 3=25; 4=0.
[a] Baseline is defined as the last observation prior to or at the time of the first study intervention.
[b] ICEs include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention
due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6.
[c] ICEs strategies: Subjects that have ICEs 1-5, and 7 prior to a visit are considered to have no change from baseline for that endpoint at that visit and subsequent visit. Subjects with ICE 6 have their data assumed missing after the ICE 6 occurred..

**Alternative Scoring Systems (PCDAI, Alternative PCDAI, sPCDAI, CDAI)**

**Clinical Remission**

Numerous CD activity scoring systems (PCDAI, alternative PCDAI, sPCDAI, PCDAI history scores using a prospective diary, and the adult scoring system CDAI) were examined across the CD clinical development program.

Overall, sPCDAI score data were generally similar to the primary definition of clinical remission (PCDAI ≤ 10) and the alternative definition of clinical remission (PCDAI <10). However, the proportions of participants achieving clinical remission at Week I-8 and Week M-44 based on PCDAI diary scores using a prospective diary were numerically lower (with overlapping CIs) than the primary definition of clinical remission (PCDAI ≤10). The differences between the PCDAI and PCDAI diary scores were due to missing diaries. Consequently the history score subcomponent was calculated with imputed item scores for abdominal pain, stools, and general well-being.

**Table 27: Tertiary endpoint analysis: Number of subject in clinical remission as assessed by PCDAI/sPCDAI/CDAI scores; full analysis set or full clinical responder analysis set (Study CNTO1275CRD3004)**

| | | PCDAI | | PCDAI per Diary Data | | CDAI | |
|---|---|---|---|---|---|---|---|
| | sPCDAI | ≤10 | <10 | ≤10 | <10 | | Sensitivity analysis - among subjects with non-missing CDAI score |
| Clinical Remission at Week I-6 | | | | | | | |
| N | 101 | NA | NA | NA | NA | NA | NA |
| Subjects in clinical remission | 46 (45.5%) | | | | | | |
| 95% CI | (36.2%, 55.2%) | | | | | | |
| Clinical Remission at Week I-8 | | | | | | | |
| N | NA | 101 | 101 | 101 | 101 | 101 | 68 |
| Subjects in clinical remission | | 47 (46.5%) | 40 (39.6%) | 37 (36.6%) | 36 (35.6%) | 30 (29.7%) | 26 (38.2%) |
| 95% CI | | (37.1%, 56.2%) | (30.6%, 49.4%) | (27.9%, 46.4%) | (27.0%, 45.4%) | (21.7%, 39.2%) | (27.6%, 50.1%) |
| Clinical Remission at Week M-40 | | | | | | | |
| N | 85 | NA | NA | NA | NA | NA | NA |
| Subjects in clinical remission | 46 (54.1%) | | | | | | |
| 95% CI | (43.6%, 64.3%) | | | | | | |
| Clinical Remission at Week M-44 | | | | | | | |
| N | NA | 85 | 85 | 85 | 85 | 85 | 56 |
| Subjects in clinical remission | | 46 (54.1%) | 43 (50.6%) | 40 (47.1%) | 35 (41.2%) | 33 (38.8%) | 25 (44.6%) |
| 95% CI | | (43.6%, 64.3%) | (40.2%, 61.0%) | (36.8%, 57.6%) | (31.3%, 51.8%) | (29.2%, 49.5%) | (32.4%, 57.6%) |

Note: Adapted from tables tefcrem01_g, tefcrem01_u, tefter08a, tefter08b, tefter08b01, tefter08d, tefter08e, tefter08e01, tefter09a, tefter09b, tefter09c, tefter09d, tefter09e, tefter09f.

**Clinical Response**

Clinical response was also assessed using sPCDAI, PCDAI diary, and CDAI scores. As noted above, these scores were summarised for completeness. Without a complementary placebo comparison for each of the scoring systems in the paediatric population, it is not possible to gauge the actual performance of these scoring systems. A similar trend in the proportions of participants achieving clinical response were observed based on the PCDAI, alternative PCDAI, and sPCDAI, but PCDAI diary scores using a prospective diary tended to be slightly lower, but mirrored the pattern seen in PCDAI clinical remission. These differences were also due to missing history score data.

**Table 28: Tertiary endpoint analysis: Number of subject in clinical response as assessed by PCDAI/sPCDAI/CDAI scores; full analysis set or full clinical responder analysis set (Study CNTO1275CRD3004)**

| | | | | CDAI | |
|---|---|---|---|---|---|
| | sPCDAI | PCDAI | PCDAI per Diary Data | | Sensitivity analysis - among subjects with non-missing CDAI score |
| Clinical Response at Week I-6 | | | | | |
| N | 101 | NA | NA | NA | NA |
| Subjects in clinical response | 90 (89.1%) | | | | |
| 95% CI | (81.5%, 93.8%) | | | | |
| Clinical Response at Week I-8 | | | | | |
| N | NA | 101 | 101 | 101 | 68 |
| Subjects in clinical response | | 85 (84.2%) | 69 (68.3%) | 42 (41.6%) | 38 (55.9%) |
| 95% CI | | (75.8%, 90.0%) | (58.7%, 76.6%) | (32.5%, 51.3%) | (44.1%, 67.1%) |
| Clinical Response at Week M-8 | | | | | |
| N | NA | 85 | 85 | 85 | 56 |
| Subjects in clinical response | | 78 (91.8%) | 68 (80.0%) | 43 (50.6%) | 38 (67.9%) |
| 95% CI | | (84.0%, 96.0%) | (70.3%, 87.1%) | (40.2%, 61.0%) | (54.8%, 78.6%) |
| Clinical Response at Week M-40 | | | | | |
| N | 85 | NA | NA | NA | NA |
| Subjects in clinical response | 54 (63.5%) | | | | |
| 95% CI | (52.9%, 73.0%) | | | | |
| Clinical Response at Week M-44 | | | | | |
| N | NA | 85 | 85 | 85 | 56 |
| Subjects in clinical response | | 51 (60.0%) | 46 (54.1%) | 40 (47.1%) | 32 (57.1%) |
| 95% CI | | (49.4%, 69.8%) | (43.6%, 64.3%) | (36.8%, 57.6%) | (44.1%, 69.2%) |

Note: Adapted from tables tefter10b, tefter10c, tefter10c01, tefter10d, tefter10e, tefter10f, tefter10f01, tefsec03agu, tefsup29a, tefsup29b.

**Clinical-biomarker Response**

At Week I-8, there were 54 (53.5%; 95% CI: 43.8%, 62.9%) of 101 participants in clinical-biomarker response (defined as a reduction from baseline in the PCDAI score of ≥12.5 points, total PCDAI score not more than 30 points, and a ≥50% reduction from baseline in CRP, fecal calprotectin, or fecal lactoferrin). At Week M-44, there were 35 (41.2%) of 85 participants in the combined treatment group in clinical-biomarker response. The proportion of participants who achieved clinical-biomarker response was lower in the q12w treatment group than the q8w treatment group; however, the CIs overlapped.

**Corticosteroid-free Clinical Remission**

At Week I-8, there were 43 (42.6%; 95% CI: 33.4%, 52.3%) of 101 participants in corticosteroid-free clinical remission as assessed by an alternative definition (a PCDAI score ≤10 points and not receiving corticosteroids for at least 30 days prior to the visit).

At Week M-44, there were 45 (52.9%; 95% CI: 42.4%, 63.2%) of 85 participants in the combined group in corticosteroid-free clinical remission. The proportions of participants in corticosteroid-free remission over time were either numerically higher in the q12w treatment group than the q8w-treatment group (with overlapping CIs) or similar between treatment groups.

**Clinical Remission at Week M-44 for Participants who Were in Clinical Remission at Week I-8**

Among the 47 (55.3%) of 85 participants who were in clinical remission at Week I-8, there were 32 (68.1%; 95% CI: 53.8%, 79.6%) participants in the combined treatment group in clinical remission at Week M-44 as assessed by the PCDAI. The proportions of participants in clinical remission over time were generally similar between treatment groups.

**Change From Baseline in PCDAI, sPCDAI, and CDAI Scores Over Time**

At Week I-8, an improvement in the change from baseline in the PCDAI score was observed, with a mean (SD) and median score change of -27.08 (13.442) and -27.50, respectively.

From Week M-0 to Week M-44, improvements were maintained through Week M-44, with similar change from baseline scores reported between the q12w and the q8w treatment groups.

**Change From Baseline in Components of the PCDAI, sPCDAI, and CDAI Scores Over Time**

At Week I-8, improvements in mean (SD) change from baseline PCDAI component scores were observed for all of the PCDAI components (symptoms history, laboratory, growth, physical examination, and extraintestinal manifestations), with the greatest improvement reported in the symptom history component (range 0 to 30), (mean [SD] and median change from baseline scores: -15.2 [9.37] and -15.0, respectively), followed by extraintestinal manifestations (range 0 to 10) (-2.5 [3.29] and 0.0, respectively), and physical examination scores (0 to 20) (-4.9 [4.71] and -5.00, respectively).

From Week M-0 through Week M-44, a similar pattern of improvement in mean change from baseline scores were observed for all PCDAI components. The most notable change was in the symptom history component of the PCDAI, with the combined treatment group showing a mean (SD) change from baseline score of -12.8 (11.60; median score of -15.0). Overall, similar change scores were reported between the q12w and the q8w treatment groups for each component.

Similar improvements were also observed through Week I-8 and from Week M-0 to Week M-44 for each component of the sPCDAI and CDAI based on change from baseline scores.

**Corticosteroid-free Clinical Remission Among Participants Who Received Corticosteroids at Week I-0**

At Week M-44, 6 (75.0%) of 8 participants in the q12w treatment group and 6 (54.5%) of 11 participants in the q8w treatment group (12 [63.2%] of 19 participants in the combined treatment group) who received corticosteroids at Week I-0 achieved clinical remission (PCDAI score of ≤10 and not receiving corticosteroids for at least 90 days prior to Week M-44).

**SES-CD and SEMA-CD Related Endoscopic Endpoints Over Time**

***Endoscopic remission***

While this study did not have eligibility criteria stipulating a minimum SES-CD score, endoscopic remission was assessed in participants with a baseline SES-CD score of ≥3. An SES-CD score was missing for 1 participant, and 2 participants had an SES-CD score of <3. At Week M-8, 18.1% of participants achieved endoscopic remission as assessed by the SES-CD (defined as an SES-CD score of ≤2 in participants with a baseline SES-CD score of ≥3). At Week M-44, 15.7% of participants were in endoscopic remission; these results were consistent between the q12w and q8w treatment groups.

The numbers and proportions of participants who achieved endoscopic remission at Week M-8 (18 [18.6%] of 97 participants) and Week M-44 (13 [15.3%] of 85 participants), defined by an SES-CD score of ≤2 (alternative SES-CD definition), were similar to the primary definition. Additionally, the proportion of participants who achieved endoscopic remission based on the SEMA-CD (defined as a SEMA-CD score of ≤ 1 in participants with a baseline SEMA-CD score of ≥2) was slightly higher at Week M-44 (20.0%) compared with the SES-CD (15.7%).

***Endoscopic response***

At baseline, 94 (96.9%) out of 97 participants had a baseline SES-CD score of ≥3. At Week M-8, 36.2% of participants achieved endoscopic response as assessed by the SES-CD (defined as a reduction in the SES-CD score of ≥50% or SES-CD score ≤2 in participants with a baseline SES-CD score of ≥3). At Week M-44, 27.7% of the participants achieved endoscopic response as assessed by the SES-CD; these results were generally similar between the q12w and q8w treatment groups.

The numbers and proportions of participants who achieved endoscopic response at Week M-8 (34 [35.1%] of 97 participants) and Week M-44 (23 [27.1%] of 85 participants) based on an alternative SES-CD definition (reduction in the SES-CD score of ≥50%) was similar to the primary definition.

Additionally, the proportion of participants who achieved endoscopic response as assessed by the SEMA-CD (defined as a reduction in the SEMA-CD from baseline of ≥50% or SEMA-CD score ≤1 in participants with a baseline SEMA-CD score of ≥2) was generally consistent with the SES-CD.

***Clinical meaningful endoscopic improvement***

At Week M-8, 58.5% of participants achieved clinically meaningful endoscopic improvement as assessed by the SES-CD (defined as a reduction in SES-CD of ≥3 points from baseline in participants with a baseline SES-CD score of ≥3). At Week M-44, 37.3% of participants achieved clinically meaningful endoscopic improvement; these results were consistent between treatment groups.

The proportion of participants who were in clinically meaningful endoscopic improvement as assessed by the SEMA-CD (defined as a reduction in SEMA-CD of ≥2 points from baseline in participants with a baseline SEMA-CD score of ≥2) was generally consistent with the SES-CD.

**Table 29: Number of subjects in SEMA-CD and SES-CD related endpoints at week M-8 and at week M-44; full randomised analysis set or full clinical responder analysis set (Study CNTO1275CRD3004)**

| | SEMA-CD | SES-CD |
|---|---|---|
| Endoscopic Remission at Week M-44 | | |
| N | 75 | 83 |
| Subjects in endoscopic remission | 15 (20.0%) | 13 (15.7%) |
| 95% CI | (12.5%, 30.4%) | (9.4%, 25.0%) |
| Endoscopic Response at Week M-8 | | |
| N | 86 | 94 |
| Subjects in endoscopic response | 33 (38.4%) | 34 (36.2%) |
| 95% CI | (28.8%, 48.9%) | (27.2%, 46.2%) |
| Endoscopic Response at Week M-44 | | |
| N | 75 | 83 |
| Subjects in endoscopic response | 21 (28.0%) | 23 (27.7%) |
| 95% CI | (19.1%, 39.0%) | (19.2%, 38.2%) |
| Clinical meaningful Endoscopic improvement at Week M-8 | | |
| N | 86 | 94 |
| Subjects in clinical meaningful endoscopic improvement | 43 (50.0%) | 55 (58.5%) |
| 95% CI | (39.7%, 60.3%) | (48.4%, 67.9%) |
| Clinical meaningful Endoscopic improvement at Week M-44 | | |
| N | 75 | 83 |
| Subjects in clinical meaningful endoscopic improvement | 27 (36.0%) | 31 (37.3%) |
| 95% CI | (26.1%, 47.3%) | (27.7%, 48.1%) |

Note: SEMA-CD related endpoints are based on subjects with baseline SEMA-CD score ≥2 and SES-CD related endpoints are based on subjects with baseline SES-CD score ≥3.
Note: ICEs include for Week M-8: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4.
Note: ICEs strategies for Week M-8: Subjects with ICEs 1-3, and 5 prior to Week I-8 are considered not to be in endpoint at Week M-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy).
Note: ICEs include for Week M-44: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6.
Note: ICEs strategies for Week M-44: Subjects that have ICEs 1-5, and 7 prior to Week M-44 are not considered to be in endpoint at Week M-44 (ie. composite strategy). Subjects with ICE 6 prior to Week M-44 are considered to have missing endpoint data from the time of the event onward (ie. hypothetical strategy).
Note: After accounting for the ICEs, subjects who have missing endpoint are considered not to have achieved the endpoint at that visit.
Note: The confidence intervals are based on the Wilson statistic.
Note: Adapted from tables tefter17a, tefter17b.

***Endoscopic Improvement***

At Week M-8, 19 (20.4%) of 93 participants achieved endoscopic improvement (defined as the complete absence of any mucosal ulcerations among participants who presented with an ulceration in at least 1 ileocolonic segment at induction baseline).

At Week M-44, 14 (17.1%) of 82 participants in the combined treatment group achieved endoscopic improvement. A numerically higher proportion of participants were in the q8w treatment group (9 [22.5%] of 40 participants; 95% CI: 12.3%, 37.5%) than the q12w treatment group (5 [11.9%] of 42 participants; 95% CI: 5.2%, 25.0%); however, the CIs overlapped.

***Change From Baseline in SES-CD Scores and SEMA-CD Scores***

An improvement in the SES-CD score was observed at Week M-8, with a mean (SD) and median change from baseline score of -3.80 (6.884) and -3.00, respectively. Generally similar findings were observed at Week M-44, with mean (SD) and median change from baseline scores of -2.65 (5.908) and -1.00,

respectively in the q12w treatment group and -2.56 (5.532) and 0.00, respectively in the q8w treatment group. Results based on the SEMA-CD scores were consistent with the SES-CD scores.

**Fistula Related Endpoints Over Time**

At Week I-8, 4 (57.1%) of 7 participants who had 1 or more fistulas at baseline achieved complete fistula response, defined as complete fistula closure of all draining fistulas among participants with 1 or more fistulas at baseline.

At Week M-44, 2 (50.0%) of 4 participants (both in the q8w treatment group) achieved complete fistula response.

**Hospitalisations and Surgeries Over Time**

At Week I-8, no participants had CD-related hospitalisations or surgeries. At Week M-44, 6 (7.1%) of 85 participants (3 participants in each treatment group) had CD-related hospitalisations (no participants had CD-related surgeries).

**Mucosal Inflammation Noninvasive Index**

Mucosal healing has become a goal of therapy for CD, as this may be associated with improved, long-term outcomes. The MINI is a novel, newly-validated, non-invasive index designed to assess mucosal inflammation in children with CD (Cozijnsen 2020).

Of the 85 participants at Week M-44, 6 (7.1%) participants, 9 (10.6%) participants, and 12 (14.1%) participants had a MINI score of <6, <7, or <8, respectively at Week M-8. At Week M-44, 9 (10.6%) participants, 10 (11.8%) participants, and 11 (12.9%) participants had a MINI score of <6, <7, or <8, respectively. These results were similar between the q12w and q8w treatment groups.

Improvements in change from baseline MINI scores were also observed at each visit, with mean (SD) and median change from baseline scores of -5.9 (5.22) and -5.0, respectively in the combined treatment group at Week M-8, and -4.6 (6.18) and -2.0, respectively in the combined treatment group at Week M-44. Improvements in change from baseline MINI scores were observed for both the q12w and q8w treatment groups at Week M-8 and Week M-44.

**Supplementary Analysis by Responder Status**

Only 6 participants were delayed responders at Week M-8 limiting therefore conclusions regarding clinical remission, endoscopic response, corticosteroid-free clinical remission, clinical response, or PCDAI scores.

**Supplementary Analysis Based on PCDAI Diary Data**

Clinical remission and response in paediatric participants with CD were also evaluated using PCDAI diary data. Instead of a recall period of 1 week, participants used a take-home electronic diary to prospectively record stool frequency, abdominal pain, and general well-being symptoms during the 7 days prior to the scheduled visits.

**Clinical Remission using PCDAI diary data**

At Week I-8, 37 (36.6%) of 101 participants achieved clinical remission using PCDAI diary data (PCDAI score of ≤10 points). At Week M-44, the overall proportion of participants who achieved clinical remission using diary data was 40 (47.1%), with generally similar proportions observed between the treatment groups (22 [50.0%] of 44 participants in the q12w treatment group and 18 [43.9%] of 41 participants in the q8w treatment group).

A total of 4 (4.0%) of the 101 participants discontinued treatment prior to completing the Week I-8 visit, had all PCDAI subscores missing at Week I-8, and were classified as nonresponders. A total of 23 (22.8%) participants had 1 PCDAI subscore missing at Week I-8. Of these, 13 (12.9%) participants had a

missing laboratory score and 11 (10.9%) participants had a missing history score. The laboratory and history scores were imputed using LOCF and the Week I-8 PCDAI scores were calculated.

Similarly, 10 (11.8%) of 85 participants had all PCDAI subscores missing at Week M-44 and were classified as nonresponders. A total of 28 (32.9%) participants had 1 PCDAI subscore missing at week M-44. Of these, 10 (11.8%) participants had a missing laboratory score and 24 (28.2%) participants had a missing history score. The laboratory and history scores were imputed using LOCF and the Week M-44 PCDAI scores were calculated.

Clinical remission was also assessed using an alternative definition of PCDAI (PCDAI diary score of <10 points). The proportion of participants achieving clinical remission using this alternative definition was similar to the proportion of participants who achieved clinical remission based on a PCDAI diary score of ≤ 10 points.

**Clinical Response PCDAI using diary data**

At Week I-8, 69 (68.3%) of 101 participants achieved clinical response (defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30) using PCDAI diary data. At Week M-44, the overall proportion of participants who achieved clinical response using diary data was 46 (54.1%) of 85 participants and was similar between treatment groups (25 [56.8%] of 44 participants in the q12w treatment group and 21 [51.2%] of 41 participants in the q8w treatment group).

**Change From Baseline in PCDAI Diary Scores**

Improvements in PCDAI scores were observed from baseline, with mean (SD) and median change from baseline scores of -22.40 (13.614) and -22.10, respectively at Week I-8. Improvements in PCDAI scores were also observed at Week M-44, with mean (SD) and median change from baseline scores of -18.64 (17.518) and -17.50, respectively in the combined treatment group. These results were generally similar between the q12w and q8w treatment groups.

**Efficacy Assessments Among Participants Who Had a Dose Adjustment**

Induction responders in the CNTO1275CRD3004 study who experienced LOR were eligible for dose adjustment (q12w→q8w or q8w→q8w [a sham adjustment]) from Week M-8 (Week M-16 for delayed responders), unless they had documented low ustekinumab exposure at Week M-8, in which case they were eligible for the EOS.

A total of 5 (5.2%) of 97 randomised participants dose adjusted from ustekinumab through Week M-44 (2 participants who dose adjusted to ustekinumab q8w and 3 participants who received a sham adjustment).

All 5 participants were clinical responders at Week M-0. However, due to the small sample size, no conclusions can be drawn on the impact of dose adjustment on clinical remission, endoscopic response, or clinical response at Week M-44, or clinical remission and clinical response 16 weeks after dose adjustment.

**Supplementary Analysis Excluding COVID-19 Participants**

No participant discontinued study participation due to COVID-19. Therefore, clinical response, clinical remission, and endoscopic response at Week I-8 and Week M-44 were the same as the main estimands.

***Subgroup Analyses***

Efficacy results for the key efficacy endpoints by age and weight subgroups are briefly summarised below. Notable differences are indicated, with the exception of categories with a very small number of participants (n <10), limiting conclusions (eg, in participants 2 to 5 years of age and the <30 kg and ≥30 to <40 kg weight subgroups).

**Age**

Results of the key efficacy endpoints by age in the induction period were generally consistent between the younger (2 to 11 years of age) and older (12 to 17 years of age) study populations, with the exception of the following:

- A numerically higher proportion of participants in the younger age subgroup (14 [70.0%] of 20 participants; 95% CI: 48.1%, 85.5%) versus the older age subgroup (32 [39.5%] of 81 participants; 95% CI: 29.6%, 50.4%) achieved clinical remission at Week I-6; however, the CIs overlapped.
- Similarly, a numerically higher proportion of participants in the younger age subgroup (13 [65.0%] participants; 95% CI: 43.3%, 81.9%) versus the older age subgroup (34 [42.0%] participants; 95% CI: 31.8%, 52.8%) achieved clinical remission at Week I-8; however, the CIs overlapped.

During the maintenance period, generally similar trends were observed between the 2 to 11 years and 12 to 17 years of age subgroups. While the clinical responders at Week M-0 in the FASRES had generally similar key efficacy endpoint results to those in the FASCR, there were very few participants who were delayed responders at Week M-8 (n=6) limiting conclusions.

**Weight**

Results of the key efficacy endpoints by weight in the induction period were generally consistent between the <40 kg and ≥40 kg populations, with the exception of the following:

- At Week I-8, a numerically higher proportion of participants in the ≥40 kg subgroup (64 [88.9%] of 72 participants; 95% CI: 79.60%, 94.30%) achieved clinical response at Week I-8 than the <40 kg subgroup (21 [72.4%] of 29 participants; 95% CI: 54.30%, 85.30%); however, the CIs overlapped.

During the maintenance period, key efficacy endpoint results were generally similar between the weight subgroups, with the exception of the following:

- A higher proportion of participants <40 kg achieved endoscopic response at Week M-44 than participants ≥40 kg (8 [38.1%] of 21 participants [95% CI: 20.80%, 59.10%] versus 15 [24.2%] of 62 participants [95% CI: 15.20%, 36.20%], respectively); however, the CIs overlapped.

Likewise, in the FASR, while the proportion of participants who achieved clinical response at Week M-8 was generally similar between weight subgroups, the proportion of participants who achieved endoscopic response was numerically higher in participants <40 kg than participants who weighed ≥40 kg.

In addition, while the clinical responders at Week M-0 in the FASRES had generally similar key efficacy endpoint results to those in the FASCR, there were very few participants who were delayed responders at Week M-8 (n=6) limiting conclusions.

**Exposure Optimisation Substudy Efficacy Analyses**

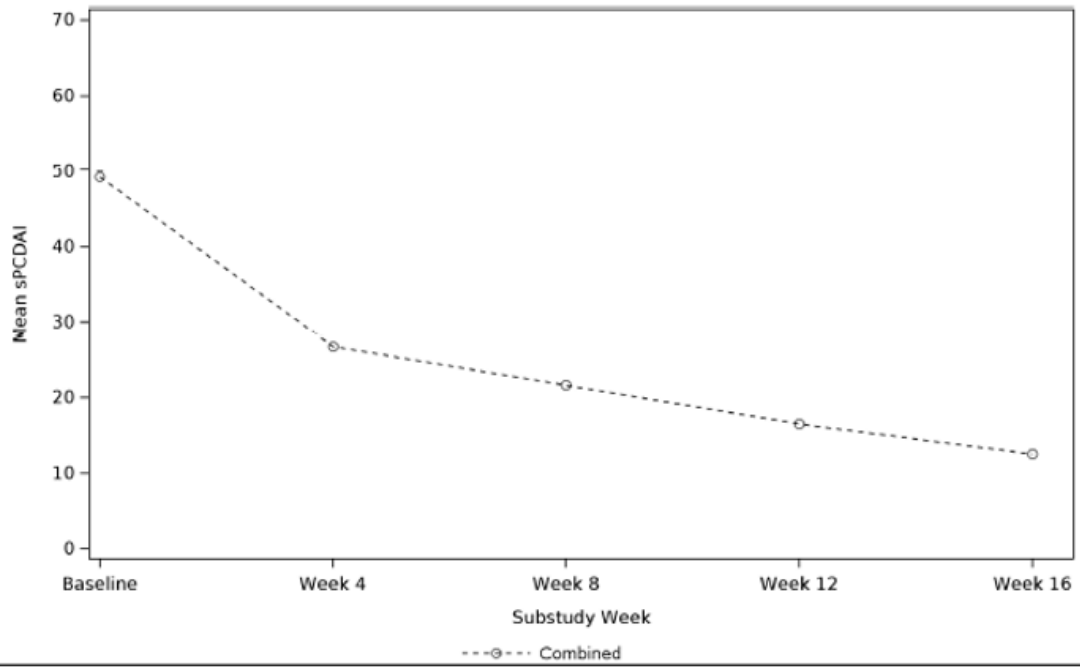
An objective of the EOS was to evaluate the efficacy of ustekinumab administered q4w in participants who had induction nonresponse or LOR and low ustekinumab exposure. Efficacy was evaluated using the sPCDAI, a shorter version of the PCDAI. The sPCDAI is composed of the following 6 PCDAI components: abdominal pain, general well-being, weight, stool, abdominal examination, and extraintestinal manifestations. Unlike the full PCDAI score, the sPCDAI does not include measures of height velocity, perirectal examination, and laboratory data (hematocrit, albumin, and ESR).

A total of 26 participants (11 participants in the q12w treatment group and 15 participants in the q8w treatment group) entered the substudy (see Section 4.7 for details). Prior to or at the time of the

initiation of the q4w dose regimen, the sPCDAI mean (SD) and median scores were 49.2 (14.12) and 52.5, respectively, and the CRP mean (SD) concentration was 20.25 (27.245) mg/L, consistent with moderately to severely active disease. Additionally, a larger proportion of participants in the EOS had a history of biologic failure, with 21 (80.8%) participants compared with 57 (56.4%) participants in the main study.

The overall efficacy results at Substudy Week 16 are summarised briefly below using observed data. EOS participants entered at different timepoints and were allowed to continue study treatment until the end of the original main study maintenance period (and final Week M-44 visit). Therefore, no systematic analysis of q4w efficacy was planned beyond Substudy Week 16 because the duration of the treatment course was variable. A line plot of mean sPCDAI scores from the initiation of the substudy through Substudy Week 16 can be found in Figure 32.

**Figure 32: Line plot of mean sPCDAI score over time up to 16 weeks after entering the substudy; substudy analysis set (Study CNTO1275CRD3004)**




Note: Refer to table TSSEF01.

The proportions of participants who entered the optional EOS and achieved clinical remission and clinical response after 16 weeks on q4w dosing were similar to participants in the main study. At Substudy Week 16:

- Participants in clinical remission: 10 (50.0%) of 20 participants (Table 30).
- Participants in clinical response: 19 (95.0%) of 20 participants (Table 31).
- The mean (SD) and median sPCDAI scores at Substudy Week 16 were 12.5 (13.72) and 10.0, respectively (mean [SD] change from baseline sPCDAI score: -37.5 [21.49]; median score change of -40.0).
- The mean (SD) CRP concentration at Substudy Week 16 was 2.45 (1.728) mg/L (mean [SD] change from baseline: -10.68 [21.936] mg/L).
- The mean (SD) and median baseline ESR was 34.1 (23.45) and 30.0 mm/h, respectively. At Substudy Week 16, the mean (SD) and median ESR was 28.3 (22.52) and 19.5 mm/h,

respectively (mean [SD] change from baseline: -4.4 [16.14] mm/h; median change of -5.0 mm/h).

Additionally, all 3 induction nonresponder participants with low ustekinumab levels who were not in clinical response by Week M-8 achieved response after dose adjustment to q4w and completed study.

**Table 30: Number of subjects in clinical remission through the end of the substudy period; substudy analysis set (Study CNTO1275CRD3004)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | q12w->q4w | q8w->q4w | Combined |
| Analysis set: Substudy | 11 | 15 | 26 |
| Substudy Week 4 | | | |
| N | 11 | 12 | 23 |
| Subjects in clinical remission[a] | 4 (36.4%) | 2 (16.7%) | 6 (26.1%) |
| 95% CI for proportion of subjects in clinical remission[b] | (15.2%, 64.6%) | (4.7%, 44.8%) | (12.5%, 46.5%) |
| Substudy Week 8 | | | |
| N | 11 | 14 | 25 |
| Subjects in clinical remission[a] | 3 (27.3%) | 4 (28.6%) | 7 (28.0%) |
| 95% CI for proportion of subjects in clinical remission[b] | (9.7%, 56.6%) | (11.7%, 54.6%) | (14.3%, 47.6%) |
| Substudy Week 12 | | | |
| N | 9 | 14 | 23 |
| Subjects in clinical remission[a] | 4 (44.4%) | 6 (42.9%) | 10 (43.5%) |
| 95% CI for proportion of subjects in clinical remission[b] | (18.9%, 73.3%) | (21.4%, 67.4%) | (25.6%, 63.2%) |
| Substudy Week 16 | | | |
| N | 8 | 12 | 20 |
| Subjects in clinical remission[a] | 3 (37.5%) | 7 (58.3%) | 10 (50.0%) |
| 95% CI for proportion of subjects in clinical remission[b] | (13.7%, 69.4%) | (32.0%, 80.7%) | (29.9%, 70.1%) |

Note: Observed data are used.
[a] Clinical remission is defined as sPCDAI score ≤10 points.
[b] The confidence intervals are based on the Wilson statistic.

**Table 31: Number of subjects in clinical response through the end of the substudy period; substudy analysis set (Study CNTO1275CRD3004)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | q12w->q4w | q8w->q4w | Combined |
| Analysis set: Substudy | 11 | 15 | 26 |
| Substudy Week 4 | | | |
| N | 11 | 12 | 23 |
| Subjects in clinical response[a] | 10 (90.9%) | 11 (91.7%) | 21 (91.3%) |
| 95% CI for proportion of subjects in clinical response[b] | (62.3%, 98.4%) | (64.6%, 98.5%) | (73.2%, 97.6%) |
| Substudy Week 8 | | | |
| N | 11 | 14 | 25 |
| Subjects in clinical response[a] | 11 (100.0%) | 12 (85.7%) | 23 (92.0%) |
| 95% CI for proportion of subjects in clinical response[b] | (74.1%, 100.0%) | (60.1%, 96.0%) | (75.0%, 97.8%) |
| Substudy Week 12 | | | |
| N | 9 | 14 | 23 |
| Subjects in clinical response[a] | 8 (88.9%) | 13 (92.9%) | 21 (91.3%) |
| 95% CI for proportion of subjects in clinical response[b] | (56.5%, 98.0%) | (68.5%, 98.7%) | (73.2%, 97.6%) |
| Substudy Week 16 | | | |
| N | 8 | 12 | 20 |
| Subjects in clinical response[a] | 8 (100.0%) | 11 (91.7%) | 19 (95.0%) |
| 95% CI for proportion of subjects in clinical response[b] | (67.6%, 100.0%) | (64.6%, 98.5%) | (76.4%, 99.1%) |

Note: Observed data are used.
[a] Clinical response is defined as a reduction from baseline in the sPCDAI score of ≥10.
[b] The confidence intervals are based on the Wilson statistic.

## *Summary of main study(ies)*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 32: Summary of Efficacy for Study CNTO1275CRD3004**

| | |
|---|---|
| **Title:** A Phase 3 Study of the Efficacy, Safety, and Pharmacokinetics of Ustekinumab as Open label Intravenous Induction Treatment Followed by Randomised Double blind Subcutaneous Ustekinumab Maintenance in Paediatric Participants with Moderately to Severely Active Crohn's Disease | |
| Study identifier | Study CNTO1275CRD3004 |
| Design | This was a Phase 3, multicenter interventional study that consisted of an open-label induction period with a single IV ustekinumab induction dose followed by a maintenance period with a randomised, double-blind, parallel-group, 2-arm study design, exploring 2 different SC ustekinumab maintenance dose regimens. Participants were 2 to <18 years of age 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. |

| | | | |
|---|---|---|---|
| | Duration of main phase:<br><br>Duration of Run-in phase:<br><br>Duration of Extension phase: | | 52 weeks (8 weeks induction, 44 weeks maintenance)<br>6 weeks screening period<br><br>LTE, Variable |
| Hypothesis | Ustekinumab is an effective therapy in paediatric participants with moderately to severely active CD. A determination of the efficacy of ustekinumab is based on totality of evidence from primary and secondary endpoints | | |
| Treatment group induction phase | Single IV dose of Ustekinumab at Week I-0 | | |
| Treatments groups maintenance phase | Ustekinumab q12w | | Ustekinumab 90 mg q12w, 44 weeks, 49 participants randomised at Week I-8 |
| | Ustekinumab q8w | | Ustekinumab 90 mg q8w, 44 weeks, 48 participants randomised at Week I-8 |
| Endpoints and definitions | Primary Efficacy Endpoint | Clinical Remission I-8 | The primary endpoint is clinical remission at Week I-8 (PCDAI score ≤10 points). |
| | Secondary Efficacy Endpoint | Clinical Remission I-6 | Clinical Remission at Week I-6 as assessed by sPCDAI (sPCDAI score ≤10 points). |
| | Secondary Efficacy Endpoint | Clinical Response I-8 | Clinical response at Week I-8. A reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30. |
| | Secondary Efficacy Endpoint | Clinical Response I-6 | Clinical response at Week I-6 as assessed by sPCDAI (a reduction from baseline in the sPCDAI score of ≥10 points). |
| | Secondary Efficacy Endpoint | Endoscopic response M-8 | Endoscopic response at Week M-8* as assessed by SES-CD. |
| | Secondary Efficacy Endpoint | Clinical response M-8 | Clinical response at Week M-8.* |
| | Secondary Efficacy Endpoint | Clinical remission M-44 | Clinical remission at Week M-44, evaluated among participants who were in clinical response at Week I-8. |
| | Secondary Efficacy Endpoint | Endoscopic response M-44 | Endoscopic response at Week M-44 as 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). |
| | Secondary Efficacy Endpoint | Clinical response M-44 | Clinical response at Week M-44, evaluated among participants who were in clinical response at Week I-8. |
| | Secondary Efficacy Endpoint | C-free clinical remission M-44 | Corticosteroid-free clinical remission at Week M-44 (PCDAI score of ≤10 points and did not receive corticosteroids for at least 90 days prior to Week M-44), evaluated among participants who were in clinical response at Week I-8. |

| | | | |
|---|---|---|---|
| | Secondary Efficacy Endpoint | Clinical remission M-44 (I-8) | Clinical remission at Week M-44 for participants who were in clinical remission at Week I-8. |
| *These endpoints were evaluated 8 weeks after the start of the maintenance period; however, the objective was to evaluate response due to induction. | | | |
| Database lock | 06 January 2025 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | Population: All participants who received an administration of study intervention in induction at Week I-0.<br>Timepoint: Week I-8 | | |
| Descriptive statistics and estimate variability | Treatment group | Ustekinumab IV | |
| | Number of subjects | 101 | |
| | **Primary Efficacy Endpoint** | | |
| | Clinical Remission I-8<br>(95% CI) | 47/101 (46.5%)<br>(37.1%, 56.2%) | |
| | **Results of Secondary Endpoint Analyses through Week M-8** | | |
| | Clinical Remission I-6<br>(95% CI) | 46/101 (45.5%)<br>(36.2%, 55.2%) | |
| | Clinical Response I-8<br>(95% CI) | 85/101 (84.2%)<br>(75.8%, 90.0%) | |
| | Clinical Response I-6<br>(95% CI) | 90/101 (89.1%)<br>(81.5%, 93.8%) | |
| | Endoscopic Response M-8<br>(95% CI) | 34/94 (36.2%)<br>(27.2%, 46.2%) | |
| | Clinical Response M-8<br>(95% CI) | 83/97 (85.6%)<br>(77.2%, 91.2%) | |
| | **Results of Secondary Endpoint Analyses through Week M-44** | | |
| | Treatment group | Ustekinumab q12w | Ustekinumab q8w |
| | Number of subjects | 44 | 41 |
| | Clinical Remission M-44<br>(95% CI) | 26/44 (59.1%)<br>(44.4%, 72.3%) | 20/41 (48.8%)<br>(34.3%, 63.5%) |
| | Endoscopic Response M-44<br>(95% CI) | 13/43 (30.2%)<br>(18.6%, 45.1%) | 10/40 (25.0%)<br>(14.2%, 40.2%) |
| | Clinical Response M-44<br>(95% CI) | 28/44 (63.6%)<br>(48.9%, 76.2%) | 23/41 (56.1%)<br>(41.0%, 70.1%) |
| | C-Free Clinical Remission M-44<br>(95% CI) | 26/44 (59.1%)<br>(44.4%, 72.3%) | 19/41 (46.3%)<br>(32.1%, 61.3%) |

| | | | |
|---|---|---|---|
| | Clinical Remission M-44 (I-8)<br>(95% CI) | 15/24 (62.5%)<br>(42.7%, 78.8%) | 17/23 (73.9%)<br>(53.5%, 87.5%) |
| Effect estimate per comparison | Primary endpoint and all secondary endpoints at Week I-8 and M-8 | Comparison group | Ustekinumab IV |
| | | Proportion | See above |
| | | Confidence Interval | See above |
| | | P-value | NA |
| | All secondary endpoints at Week M-44 | Comparison groups | Ustekinumab q12w and Ustekinumab q8w |
| | | Proportion | see above |
| | | Confidence Interval | see above |
| | | P-value | NA |

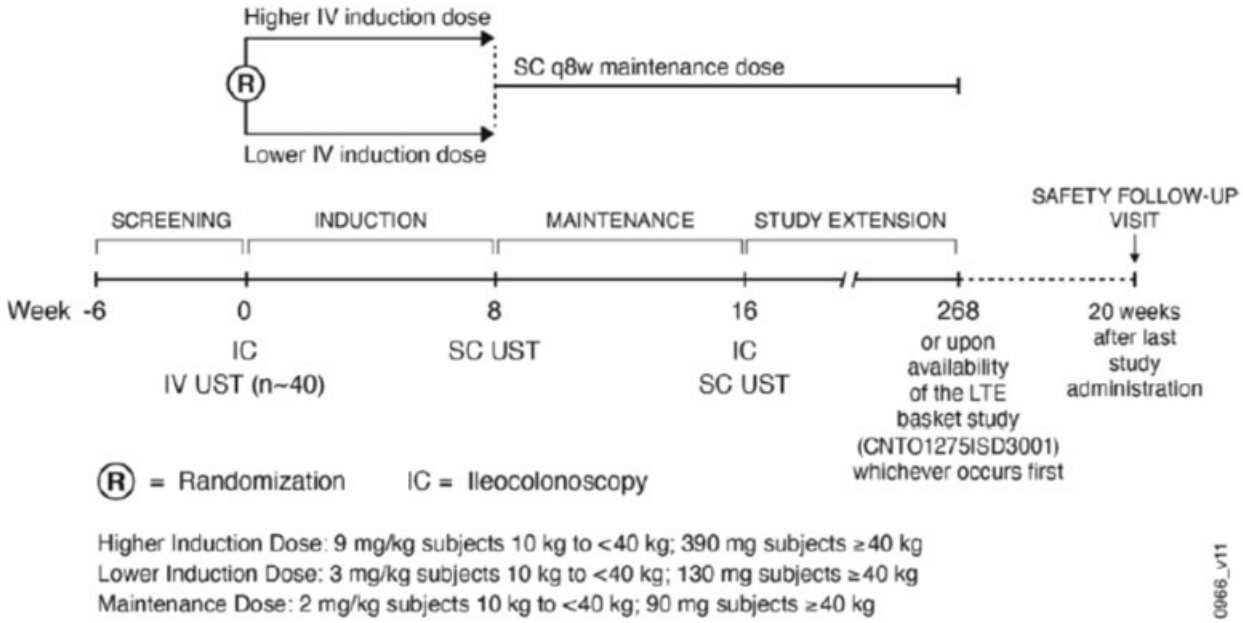
## 2.5.2. Study CRD1001 + LTE, phase 1

**Title of Study:** A Randomised Double-blind Pharmacokinetic Study of Ustekinumab in Paediatric Subjects with Moderately to Severely Active Crohn's Disease

**Study Number:** CNTO1275CRD1001

This study has been assessed in the application EMEA/H/C/000958/II/108 and will be summarised here for completeness.

**Figure 33: Study design overview**




### *Results*

Summaries of efficacy were based on all randomised subjects who received at least 1 administration of study agent (i.e., the efficacy analysis set).

**Clinical Response and remission**

Clinical response is defined as a reduction from baseline in the PCDAI score of ≥15 points. At Week 8, the proportions of subjects in the low-induction dose group and in the high-induction dose group in clinical response were 47.8% and 47.6%, respectively (Table 33). The proportions of subjects in clinical response at Week 16 were similar to those at Week 8. At the earlier timepoint of Week 3, the proportions of subjects in clinical response were numerically higher in the high-induction dose group than in the low-induction dose group.

**Table 33: Number of subjects in clinical response through week 16; efficacy analysis set (Study CNTO1275CRD1001)**

| | Ustekinumab | | |
|---|---|---|---|
| | 3 mg/kg IV or 130 mg IV → 2 mg/kg SC or 90 mg SC | 9 mg/kg IV or 390 mg IV → 2 mg/kg SC or 90 mg SC | Combined |
| Analysis set: Efficacy analysis set | 23 | 21 | 44 |
| Week 3 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical response[a, b] | 10 (43.5%) | 12 (57.1%) | 22 (50.0%) |
| Week 6 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical response[a, b] | 13 (56.5%) | 12 (57.1%) | 25 (56.8%) |
| Week 8 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical response[a, b] | 11 (47.8%) | 10 (47.6%) | 21 (47.7%) |
| Week 12 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical response[a, b] | 10 (43.5%) | 13 (61.9%) | 23 (52.3%) |
| Week 16 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical response[a, b] | 12 (52.2%) | 11 (52.4%) | 23 (52.3%) |

[a] Subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening CD or due to lack of efficacy or had prohibited concomitant medication changes are considered not to be in clinical response.
[b] Subjects who had insufficient data to calculate the PCDAI score at that visit are considered not to be in clinical response.

[TEFCRES01A.RTF] [/OPT/ZFS002/PRD/JANSS241117/STATS/PRIMARY/PROG/TABLES/TEFCRES01A.SAS] 19APR2019,10:03:29 AM

Clinical remission is defined as a PCDAI score ≤10 points. In general, there was a pattern for the proportion of subjects in clinical remission to be numerically greater in the high-induction dose group than in the low-induction dose group, particularly at the earlier timepoints (i.e., Week 3 and Week 6) (Table 34).

**Table 34: Number of subjects in clinical remission through week 16; efficacy analysis set (Study CNTO1275CRD1001)**

| | Ustekinumab | | |
|---|---|---|---|
| | 3 mg/kg IV or 130 mg IV → 2 mg/kg SC or 90 mg SC | 9 mg/kg IV or 390 mg IV → 2 mg/kg SC or 90 mg SC | Combined |
| Analysis set: Efficacy analysis set | 23 | 21 | 44 |
| Week 3 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical remission[a, b] | 3 (13.0%) | 5 (23.8%) | 8 (18.2%) |
| Week 6 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical remission[a, b] | 4 (17.4%) | 6 (28.6%) | 10 (22.7%) |
| Week 8 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical remission[a, b] | 5 (21.7%) | 4 (19.0%) | 9 (20.5%) |
| Week 12 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical remission[a, b] | 5 (21.7%) | 5 (23.8%) | 10 (22.7%) |
| Week 16 | | | |
| N | 23 | 21 | 44 |
| Subjects in clinical remission[a, b] | 5 (21.7%) | 6 (28.6%) | 11 (25.0%) |

[a] Subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening CD or due to lack of efficacy or had prohibited concomitant medication changes are considered not to be in clinical remission.
[b] Subjects who had insufficient data to calculate the PCDAI score at that visit are considered not to be in clinical remission.

Two sensitivity analyses were performed for clinical response and clinical remission at Week 8. Both sensitivity analyses did not show results that would alter the conclusions.

- Sensitivity Analysis 1: Subjects not meeting the inclusion criteria for baseline PCDAI score of >30 were excluded.
- Sensitivity Analysis 2: The PCDAI calculation was performed based on the average of each of the sub-scores for the history recall component for the past week, instead of the worst of the sub-scores for the past week, as specified for the primary analysis.

Subgroup analyses were performed to examine the consistency of clinical response at Week 8 and clinical remission at Week 8. The effect of ustekinumab was generally consistent with that observed in the overall study population, although the small sample sizes within the subgroups limit the interpretation of these analyses.

Among the subjects in clinical response at Week 8 (47.7%, Table 33) the proportion of subjects who maintained clinical response and achieved clinical remission at Week 16 was 81.0% and 38.1%, respectively, in the combined ustekinumab group. Among the subjects in clinical remission at Week 8 (20.5%, Table 34) the proportion of subjects who maintained clinical remission at Week 16 was 88.9% in the combined ustekinumab group.

Based on the post-hoc analysis of all subjects who entered the **LTE**, more than half (58.8%) of the subjects were in clinical response at Week 48 (Table 35). Clinical response according to the alternative definition was defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30. Similar to the clinical response results based on the primary definition, the proportions of subjects in clinical response remained high throughout the LTE period among those subjects who remained in the study.

Based on the post-hoc analysis of all subjects who entered the LTE, 41.2% of the subjects were in clinical remission at Week 48 (Table 35). Based on the post-hoc analysis of all subjects who entered the LTE, 38.2% of the subjects were in corticosteroid-free clinical remission at Week 48. Based on that same

analysis, 90.0% of the subjects who were in clinical remission at Week 8 were still in clinical remission at Week 48 (Table 35).

**Table 35: Post-hoc analysis of clinical response and clinical remission endpoints at week 48; efficacy analysis set (Study CNTO1275CRD1001)**

| | |
|---|---|
| Analysis set: Efficacy Analysis Set | 34 |
| N | 34 |
| Subjects in clinical response[a,b] | 20 (58.8%) |
| Subjects in clinical remission[a,b] | 14 (41.2%) |
| Subjects in corticosteroid-free clinical remission[a,b] | 13 (38.2%) |
| Subjects in clinical remission at Week 8[a,b] | |
| N | 10 |
| Subjects in clinical remission at week 48[a,b] | 9 (90.0%) |

[a] Subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening Crohn's disease or due to lack of efficacy or had prohibited concomitant medication changes are considered not to be response/remission.
[b] Subjects who had insufficient data to calculate the PCDAI score at that visit are considered not to be in response/remission.

**Change From baseline in the PCDAI Score**

The median baseline PCDAI score in both the low-induction dose group and in the high induction dose group was 42.50. A decrease in the PCDAI score from baseline was observed at Weeks 3, 6, 8, 12, and 16 in the low-induction dose group and in the high-induction dose group. At Week 8 and at Week 16, the median decrease in PCDAI score was 15.00 in the low-induction dose group and 16.25 in the high-induction dose group.

The effect of ustekinumab observed during the randomised, double-blind period was maintained during the LTE period for those subjects who remained in the study. The median (range) baseline PCDAI score was 42.50 (12.5; 60.0) (study extension efficacy analysis set). The median (range) PCDAI score at Week 48 was lower than that at baseline, with a median (range) change from baseline of -25.00 (-45.0; 15.0). Although numbers of remaining subjects at the subsequent visits were small, the reductions were maintained after the Week 48 visit in subjects who continued to participate in the study. Improvement was seen for all components (of PCDAI).

**Fistula Response**

A fistula response is defined as a ≥50% reduction in the number of draining fistulas. Three subjects in the low-induction dose group, and 1 subject in the high-induction dose group had 1 or more fistulas at baseline. At Week 8 and Week 16, none of the subjects with fistulas at baseline in the low-induction dose group had a fistula response. The subject with a fistula at baseline in the high-induction dose group did not have a fistula response at Week 8 but did have a fistula response at Week 16.

**Height and Weight Status**

The height z-score is a measure of the deviation of the subject's height from the expected height for a population of the same age and gender. Consistent with the growth inhibition seen in patients with Crohn's disease, the median (mean) z-scores at baseline for height status were -0.75 (-0.63) and -0.78 (-0.49) for the low-induction dose group and high-induction dose group, respectively. At Week 16, the median (mean) change from baseline in z-scores for height status were -0.05 (-0.04) and -0.01 (-0.04) for the low-induction dose group and high-induction dose group, respectively suggesting catch-up growth

in both treatment groups. Consistent with the risk of growth inhibition seen in patients with Crohn's disease, the median (range) z-score at baseline for height status was -0.83 (-1.54; 0.08) (study extension efficacy analysis set). For those subjects who remained in the study, improvements observed through Week 16 were maintained during the LTE period.

The weight z-score is a measure of the deviation of the subject's weight from the expected weight for a population of the same age and gender. Consistent with the growth inhibition seen in patients with Crohn's disease, the median (mean) z-scores at baseline for weight status were -0.33 (-0.38) and -0.67 (-0.48) for the low-induction dose group and high-induction dose group, respectively. At Week 16, the median (mean) change from baseline in z-scores for weight status were 0.11 (0.10) and 0.13 (0.02) for the low-induction dose group and high-induction dose group, respectively, consistent with catch-up growth and clinical improvement in both treatment groups. The median (range) z-score at baseline for weight status was -0.48 (-1.24; 0.05) (study extension efficacy analysis set). For those subjects who remained in the study, improvements observed through Week 16 were maintained during the LTE period.

The BMI z-score is a measure of the deviation of the subject's BMI from the expected BMI for a reference population of the same age and gender. The median (range) z-score at baseline for BMI status was -0.47 (-1.06; 0.09) (study extension efficacy analysis set). For those subjects who remained in the study, median actual z-scores improved at Week 48 and improvements were maintained over time during the LTE period.

**Inflammatory Markers**

**Table 36: Post-hoc summary of baseline, postbaseline, and change from baseline in inflammatory marker levels at week 48; efficacy analysis set (Study CNTO1275CRD1001)**

| | |
|---|---|
| Analysis set: Efficacy Analysis Set | 34 |
| C-reactive Protein | |
| Baseline | |
| N | 34 |
| Mean (SD) | 17.73 (23.008) |
| Median | 10.43 |
| IQ range | (2.36; 19.90) |
| Range | (0.1; 91.6) |
| Week 48[c,d] | |
| N | 34 |
| Mean (SD) | 11.61 (17.911) |
| Median | 4.87 |
| IQ range | (1.06; 12.50) |
| Range | (0.1; 84.1) |
| Change from baseline | |
| Week 48[c,d] | |
| N | 34 |
| Mean (SD) | -6.11 (15.574) |
| Median | -0.46 |
| IQ range | (-9.35; 0.00) |
| Range | (-61.3; 19.5) |
| Fecal Lactoferrin | |
| Baseline | |
| N | 34 |
| Mean (SD) | 252.83 (249.215) |
| Median | 163.54 |
| IQ range | (63.04; 290.91) |
| Range | (2.1; 1000.0) |
| Week 48[c,d] | |
| N | 34 |
| Mean (SD) | 180.15 (269.106) |
| Median | 61.76 |
| IQ range | (11.79; 188.22) |
| Range | (0.4; 1000.0) |
| Change from baseline | |

| | |
|---|---|
| Week 48[c,d] | |
| N | 34 |
| Mean (SD) | -72.69 (271.029) |
| Median | -48.44 |
| IQ range | (-161.77; 14.42) |
| Range | (-988.2; 539.5) |
| Fecal Calprotectin | |
| Baseline | |
| N | 34 |
| Mean (SD) | 4160.53 (6875.930) |
| Median | 2026.00 |
| IQ range | (710.00; 3796.00) |
| Range | (15.0; 36000.0) |
| Week 48[c,d] | |
| N | 34 |
| Mean (SD) | 1505.38 (1662.070) |
| Median | 1267.00 |
| IQ range | (101.00; 2076.00) |
| Range | (15.0; 6376.0) |
| Change from baseline | |
| Week 48[c,d] | |
| N | 34 |
| Mean (SD) | -2655.15 (6764.344) |
| Median | -805.00 |
| IQ range | (-2098.00; 0.00) |
| Range | (-34786.0; 2382.0) |

[c] Subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening Crohn's disease or due to lack of efficacy or had prohibited concomitant medication changes had their baseline value carried forward.
[d] Subjects who had insufficient data at the designated analysis timepoint had their last value carried forward.

**Endoscopic Endpoints**

Endoscopic analyses were conducted for the patients having eligible SES -CD score of ≥3 at baseline. Endoscopic response was defined as a reduction from induction baseline in SES-CD score ≥50%. At Week 16, the proportions of subjects in the low-induction dose group and in the high induction dose group in endoscopic response were 31.6% (6 subjects) and 27.8% (5 subjects), respectively (Table 37).

**Table 37: Number of subjects in endoscopic response at week 16; efficacy analysis set with eligible SES-CD score at baseline (Study CNTO1275CRD1001)**

| | Ustekinumab | | |
|---|---|---|---|
| | 3 mg/kg IV or 130 mg IV → 2 mg/kg SC or 90 mg SC | 9 mg/kg IV or 390 mg IV → 2 mg/kg SC or 90 mg SC | Combined |
| Analysis set: Efficacy analysis set with eligible SES-CD score at baseline | 19 | 18 | 37 |
| Week 16 | | | |
| N | 19 | 18 | 37 |
| Subjects with endoscopic response[a, b] | 6 (31.6%) | 5 (27.8%) | 11 (29.7%) |

[a] Subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening CD or due to lack of efficacy or had prohibited concomitant medication changes are considered not to be in endoscopic response.
[b] Subjects with missing segments at the designated analysis timepoint had their baseline score for the missing segment(s) carried forward.

Endoscopic remission was defined as SES-CD score ≤2. At Week 16, the proportions of subjects in the low-induction dose group and in the high induction dose group in endoscopic remission were 15.8% (3 subjects) and 11.1% (2 subjects), respectively (Table 38).

**Table 38: Number of subjects in endoscopic remission at week 16; efficacy analysis set with eligible SES-CD score at baseline (Study CNTO1275CRD1001)**

| | Ustekinumab | | |
|---|---|---|---|
| | 3 mg/kg IV or 130 mg IV → 2 mg/kg SC or 90 mg SC | 9 mg/kg IV or 390 mg IV → 2 mg/kg SC or 90 mg SC | Combined |
| Analysis set: Efficacy analysis set with eligible SES-CD score at baseline | 19 | 18 | 37 |
| Week 16 | | | |
| N | 19 | 18 | 37 |
| Subjects with endoscopic remission[a, b] | 3 (15.8%) | 2 (11.1%) | 5 (13.5%) |

[a] Subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening CD or due to lack of efficacy or had prohibited concomitant medication changes are considered not to be in endoscopic remission.
[b] Subjects with missing segments at the designated analysis timepoint had their baseline score for the missing segment(s) carried forward.

The median (mean) SES-CD score at baseline was 18.0 (16.9) and 14.5 (17.3) for subjects in the low-induction dose group and the high-induction dose group, respectively (Table 39). The median (mean) change from baseline at Week 16 was -2.0 (-4.4) and -0.5 (-2.7) for subjects in the low-induction dose group and the high-induction dose group, respectively.

**Table 39: Summary of baseline, postbaseline and change from baseline in SES-CD score at week 16; efficacy analysis set with eligible SES-CD score at baseline (Study CNTO1275CRD1001)**

| | Ustekinumab | | |
|---|---|---|---|
| | 3 mg/kg IV or 130 mg IV →2 mg/kg SC or 90 mg SC | 9 mg/kg IV or 390 mg IV →2 mg/kg SC or 90 mg SC | Combined |
| Analysis set: Efficacy analysis set with eligible SES-CD score at baseline | 19 | 18 | 37 |
| Baseline | | | |
| N | 19 | 18 | 37 |
| Mean (SD) | 16.9 (10.03) | 17.3 (8.51) | 17.1 (9.19) |
| Median | 18.0 | 14.5 | 15.0 |
| IQ range | (8.0; 23.0) | (13.0; 19.0) | (11.0; 23.0) |
| Range | (3; 37) | (3; 37) | (3; 37) |
| Week 16[a, b] | | | |
| N | 19 | 18 | 37 |
| Mean (SD) | 12.5 (9.34) | 14.6 (9.82) | 13.5 (9.49) |
| Median | 10.0 | 14.0 | 13.0 |
| IQ range | (3.0; 19.0) | (9.0; 19.0) | (8.0; 19.0) |
| Range | (0; 33) | (0; 40) | (0; 40) |
| Change from baseline | | | |
| Week 16[a, b] | | | |
| N | 19 | 18 | 37 |
| Mean (SD) | -4.4 (8.34) | -2.7 (7.23) | -3.6 (7.76) |
| Median | -2.0 | -0.5 | -1.0 |
| IQ range | (-11.0; 0.0) | (-8.0; 0.0) | (-8.0; 0.0) |
| Range | (-21; 10) | (-21; 9) | (-21; 10) |

[a]Subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening CD or due to lack of efficacy or had prohibited concomitant medication changes had their baseline value carried forward.
[b]Subjects with missing segments at the designated analysis timepoint had their baseline score for the missing segment(s) carried forward.

Clinically meaningful endoscopic improvement is defined as a reduction in SES-CD of ≥3 points from baseline. At Week 16, the proportions of subjects in the low-induction dose group and in the high induction dose group with a clinically meaningful endoscopic improvement were 42.1% (8 subject) and 33.3% (6 subjects), respectively (data not shown).

Endoscopic healing is defined as the complete absence of any mucosal ulcerations among subjects who presented with ulceration in at least 1 ileocolonic segment at baseline. At Week 16, the proportions of subjects in the low-induction dose group and in the high induction dose group with endoscopic healing were 15.8% (3 subjects) and 11.1% (2 subjects), respectively (data not shown).

**Medical resource utilisation**

The impact of ustekinumab treatment on medical resource utilisation was assessed by measuring subjects disease-related hospitalisations and surgeries. Through Week 16, more subjects (6 subjects, 26.1%) in the low-induction dose group were hospitalised compared to subjects (1 subject, 4.8%) in the high-induction dose group (Table 40).

**Table 40: Number of subjects with a Crohn's disease-related hospitalisation or surgery through week 16; efficacy analysis set (Study CNTO1275CRD1001)**

| | Ustekinumab | | |
|---|---|---|---|
| | 3 mg/kg IV or 130 mg IV →2 mg/kg SC or 90 mg SC | 9 mg/kg IV or 390 mg IV →2 mg/kg SC or 90 mg SC | Combined |
| Analysis set: Efficacy analysis set | 23 | 21 | 44 |
| Hospitalization | | | |
| N | 23 | 21 | 44 |
| Subjects with Crohn's disease-related hospitalizations Through Week 16 | 6 (26.1%) | 1 (4.8%) | 7 (15.9%) |
| Surgery | | | |
| N | 23 | 21 | 44 |
| Subjects with Crohn's disease-related surgeries Through Week 16 | 2 (8.7%) | 0 | 2 (4.5%) |

**IMPACT-III**

The median (mean) IMPACT-III score at baseline was 111.5 (111.0) and 102.0 (105.5) for subjects in the low-induction dose group and the high-induction dose group, respectively. The median (mean) change from baseline at Week 8 and Week 16 was 0.0 (11.1) and 12.5 (14.9), respectively, for subjects in the low-induction dose group and 3.0 (8.8) and 4.0 (12.2), respectively, for subjects in the high-induction dose group.

During the LTE period, IMPACT-III was only collected at Week 48. The mean (SD) IMPACT-III score at baseline (study extension efficacy analysis set) was 107.9 (17.16). The positive effect of ustekinumab on HRQOL was maintained during the LTE period, with a mean (SD) change from baseline of 23.9 (25.41) at Week 48.

**Key Efficacy Endpoints by Subgroups**

To evaluate the potential impact of baseline age, body weight, and history of TNF -antagonist exposure on the efficacy of ustekinumab through Week 16, key efficacy endpoints were further analysed by baseline age, body weight, and history of TNF-antagonist baseline exposure subgroups. Note that the small sample sizes within the subgroups limits the interpretation of these subgroup analyses. In addition, post-hoc analyses were conducted to evaluate the potential impact of baseline BSA and PCDAI severity on clinical response or clinical remission at Week 8. Overall results by age groups were generally consistent with the overall population. Overall results by body weight groups were generally consistent with the overall population. No definite conclusion can be drawn due to small numbers in the subgroup of subjects not exposed to anti-TNF therapy. Overall, there were no differences in clinical response or clinical remission by baseline median BSA. Although interpretations are limited by the small sample size, subjects appeared to show clinical response and clinical remission at Week 8 across baseline severity categories including severe disease.

**Table 41: Number of subjects in clinical response through week 16 by weight; efficacy analysis set (Study CNTO1275CRD1001)**

| | Weight < 40 kg | | | Weight >=40 kg | | |
|---|---|---|---|---|---|---|
| | 3 mg/kg IV → 2 mg/kg SC | 9 mg/kg IV → 2 mg/kg SC | Combined | 130 mg IV → 90 mg SC | 390 mg IV → 90 mg SC | Combined |
| Analysis set: Efficacy analysis set | 10 | 8 | 18 | 13 | 13 | 26 |
| Week 3 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical response[a, b] | 5 (50.0%) | 4 (50.0%) | 9 (50.0%) | 5 (38.5%) | 8 (61.5%) | 13 (50.0%) |
| Week 6 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical response[a, b] | 5 (50.0%) | 3 (37.5%) | 8 (44.4%) | 8 (61.5%) | 9 (69.2%) | 17 (65.4%) |
| Week 8 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical response[a, b] | 5 (50.0%) | 3 (37.5%) | 8 (44.4%) | 6 (46.2%) | 7 (53.8%) | 13 (50.0%) |
| Week 12 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical response[a, b] | 5 (50.0%) | 4 (50.0%) | 9 (50.0%) | 5 (38.5%) | 9 (69.2%) | 14 (53.8%) |
| Week 16 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical response[a, b] | 7 (70.0%) | 3 (37.5%) | 10 (55.6%) | 5 (38.5%) | 8 (61.5%) | 13 (50.0%) |

[a] Subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening CD or due to lack of efficacy or had prohibited concomitant medication changes are considered not to be in clinical response.
[b] Subjects who had insufficient data to calculate the PCDAI score at that visit are considered not to be in clinical response.

**Table 42: Number of subjects in clinical remission through week 16 by weight; efficacy analysis set (Study CNTO1275CRD1001)**

| | Weight < 40 kg | | | Weight >=40 kg | | |
|---|---|---|---|---|---|---|
| | 3 mg/kg IV → 2 mg/kg SC | 9 mg/kg IV → 2 mg/kg SC | Combined | 130 mg IV → 90 mg SC | 390 mg IV → 90 mg SC | Combined |
| Analysis set: Efficacy analysis set | 10 | 8 | 18 | 13 | 13 | 26 |
| Week 3 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical remission[a, b] | 1 (10.0%) | 1 (12.5%) | 2 (11.1%) | 2 (15.4%) | 4 (30.8%) | 6 (23.1%) |
| Week 6 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical remission[a, b] | 2 (20.0%) | 2 (25.0%) | 4 (22.2%) | 2 (15.4%) | 4 (30.8%) | 6 (23.1%) |
| Week 8 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical remission[a, b] | 3 (30.0%) | 1 (12.5%) | 4 (22.2%) | 2 (15.4%) | 3 (23.1%) | 5 (19.2%) |
| Week 12 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical remission[a, b] | 3 (30.0%) | 1 (12.5%) | 4 (22.2%) | 2 (15.4%) | 4 (30.8%) | 6 (23.1%) |
| Week 16 | | | | | | |
| N | 10 | 8 | 18 | 13 | 13 | 26 |
| Subjects in clinical remission[a, b] | 3 (30.0%) | 2 (25.0%) | 5 (27.8%) | 2 (15.4%) | 4 (30.8%) | 6 (23.1%) |

[a] Subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening CD or due to lack of efficacy or had prohibited concomitant medication changes are considered not to be in clinical remission.
[b] Subjects who had insufficient data to calculate the PCDAI score at that visit are considered not to be in clinical remission.

## 2.5.3. Study 3010, RWE observational study

**Title of Study:** Real-world Evidence for the Effectiveness and Safety of Ustekinumab Treatment in Paediatric Patients with Crohn's Disease: A Retrospective Cohort Study Using the ImproveCareNow Registry Data - REALITI

**Study Number:** CNTO1275CRD3010

This study has been assessed in the application EMEA/H/C/000958/II/108 and will be summarised here for completeness.

### *Methods*

Study CNTO1275CRD3010 (hereafter referred to as CRD3010) is a retrospective, single arm, non-interventional, observational study designed to provide evidence for the effectiveness and safety of ustekinumab treatment in Paediatric Patients (Primary Cohort) (aged 2 to <18 years) and young adults (ages 18 to <26 years) with moderately to severely active Crohn's disease using the ICN registry (Protocol CNTO1275CRD3010; IND 011632 SN 0560). Patients in this study were diagnosed with Crohn's disease and enrolled in the ICN paediatric IBD patient registry prior to initiating treatment with ustekinumab. Health care services, including Crohn's disease-related therapies, were provided to the patients and data collection occurred prospectively during routine clinical practice. The treatment decision to prescribe ustekinumab was made outside the context of this study as a part of routine clinical care.

## Study participants

Inclusion Criteria

- Having at least one ICN visit with documented new use of ustekinumab.
- Age ≥2 to <26 years at initial treatment with ustekinumab.
- Patients with a documented Crohn' s disease diagnosis at the time ustekinumab was initiated (i.e., Baseline); If diagnosis at Baseline is missing, then the diagnosis from previous visit within study window will be utilised.
- Having at least one ICN visit prior to or at the time of the ICN visit when ustekinumab is first documented.
- Having at least one record in the ICN registry database after ustekinumab initiation.
- Having received first dose of ustekinumab on or before 22 June 2019.
- Having provided informed consent for use of ICN data for research purposes.

Exclusion Criteria

- Documented exposure to ustekinumab before enrolment in ICN (by chart review).

In addition to the primary and major secondary populations, various cohorts of patients were also examined (Table 43).

**Table 43: Study populations**

| Cohort | Population | Referred to in the document as | Baseline inclusion criteria from ICN | Age (years) |
|---|---|---|---|---|
| 1 | Primary, moderate-severe, ≥40 kg | Pediatric Patients (Primary Cohort) | All CD patients treated with ustekinumab and body weight ≥40 kg and sPCDAI ≥30 at Baseline | ≥2 to <18 |
| 2 | Moderate-severe, <40 kg | Moderate-severe, <40 kg | All CD patients treated with ustekinumab and body weight <40 kg, and sPCDAI ≥30 at Baseline | ≥2 to <18 |
| 3 | Moderate-severe, pediatric | Moderate-severe, pediatric | All CD patients treated with ustekinumab sPCDAI ≥ 30 at Baseline | ≥2 to <18 |
| 4 | Active disease, ≥40 kg | Pediatric Patients (Active disease) | All CD patients treated with ustekinumab and body weight ≥40 kg, and sPCDAI >10 or corticosteroid use at Baseline | ≥2 to <18 |
| 5 | Active disease, <40 kg | Active disease, <40 kg | All CD patients treated with ustekinumab and body weight <40 kg with sPCDAI >10 or corticosteroid use at Baseline | ≥2 to <18 |
| 6 | All pediatric treated with ustekinumab | All Pediatric Patients Treated (Cohort 6) | All CD patients treated with ustekinumab, regardless of sPCDAI or corticosteroid use at Baseline | ≥2 to <18 |
| 7 | Young adults, moderate-severe | Young Adults (Reference; Cohort 7) | All CD patients treated with ustekinumab and body weight ≥40 kg and sPCDAI ≥30 at Baseline | ≥18 to <26 |
| 8 | Young adults, active disease | Young Adults (Reference, active disease) | All CD patients treated with ustekinumab and body weight ≥40 kg, and sPCDAI >10 or corticosteroids at Baseline | ≥18 to <26 |
| 9 | All young adults treated with ustekinumab | All Young Adults Treated (Reference; Cohort 9) | All CD patients treated with ustekinumab, regardless of sPCDAI or corticosteroid use at Baseline | ≥18 to <26 |

Note:

- Moderately to severely active Crohn's disease is defined as a sPCDAI ≥30 at baseline. The baseline visit is defined as up to 12 weeks before and 2 weeks after the date of the first ustekinumab dose.
- Active Crohn's disease is defined as sPCDAI >10 at baseline and/or corticosteroid use for the treatment of Crohn's disease.

## Treatments

Induction and maintenance dose bands were derived to approximate exposures similar, lower, and higher than that studied in the adult Phase 3 Crohn's disease program. Induction, initial maintenance, and final maintenance dose bands were determined by chart review and defined as follows.

**Table 44: Induction Dose Bands**

| Induction Dose Bands | |
|---|---|
| **Adult Equivalent Dose Range** | **Study Dose Band[a]** |
| Less than 130 mg equivalent dose | <0.2 mg/kg/week |
| Approximately 130 mg equivalent dose | 0.2 to <0.5 mg/kg/week |
| Approximately 6 mg/kg dose (260 – 520 mg) | 0.5 to <1.65 mg/kg/week |
| Greater than 520 mg equivalent dose | ≥1.65 mg/kg/week |

[a] Dose in mg/kg/week = dose(mg) /weight(kg)/dose period (week) is calculated for each patient based on the last non-missing weight prior to or on the induction dose date and a dose period of 8 weeks

Note: An induction dose was calculated as the sum of all documented ustekinumab doses from IV ustekinumab initiation until the end of the induction phase, Week 8 after initiation. If a patient received SC dosing during this interval, the dose was adjusted by 70% to account for the bioavailability of ustekinumab.

**Table 45: Maintenance Dose Bands**

| Maintenance Dose Bands | |
|---|---|
| **Adult Equivalent Dose Range** | **Study Dose Band[a]** |
| Less than 90 mg q12w | <0.08 mg/kg/week |
| Approximately 90 mg q12w or 90 mg q8w | 0.08 to 0.28 mg/kg/week |
| Greater than 90 mg q8w | >0.28 mg/kg/week |
| [a] Dose in mg/kg/week=dose(mg) /weight(kg)/frequency(week) is calculated for each patient based on the last non-missing weight prior to or on the maintenance dose date and the dose frequency for that maintenance dose | |
| Note: An initial maintenance dose was defined as the first SC dose of ustekinumab beginning at 8 weeks after ustekinumab initiation based on the chart review. A final maintenance dose at Week 52 was defined as the last dose prior to one year after the ustekinumab initiation for patients who received ustekinumab beyond one year, or the last dose prior to discontinuation for patients who discontinued ustekinumab prior to one year after ustekinumab initiation based on the chart review. More frequent initial and final dosing (eg, q4w) was summarized by converting it to an equivalent total dose during an 8-week period and if greater than 90 mg q8w, was captured as a separate band. | |

## Objectives

**Table 46: Objectives and Endpoints**

| Objective | Endpoint |
|---|---|
| **Primary Objective**<br>To evaluate the effectiveness of ustekinumab in achieving clinical remission in pediatric patients (≥2 to <18 years and weight ≥40 kg at Baseline) | The primary endpoint is clinical remission at Week 52 |
| **Major Secondary Objective**<br>To evaluate the effectiveness of ustekinumab in achieving clinical remission in young adults (≥18 to <26 years at Baseline) | The major secondary endpoint is clinical remission at Week 52 |
| Note: The definition of clinical remission (unless otherwise stated) is sPCDAI ≤ 10 at Week 52 without intercurrent events (ICEs) prior to Week 52. | |

## Other Endpoints

- Corticosteroid-free remission at Week 52.
- Clinical remission based on PGA at Week 52.
- Change from baseline at Week 52 in growth parameters including age-gender-specific z-scores for weight, height, and BMI.
- Endoscopic remission at Week 52.
- Change from baseline at Week 52 in SEMA-CD score.
- Clinical remission by full PCDAI at Week 52.

## Data source

The study analysis was based on the ICN registry data collected from 10 January 2010, until 29 February 2020, and the data from the retrospective chart reviews that were conducted for the same time period. A cut-off date of 29 February 2020 was chosen to avoid the potential confounding effects of COVID-19 on patient visits and assessments. The primary data source for this study was the medical record of each eligible patient who provided a signed participation agreement/ICF from the ICN registry data. The ICN registry is a secure database that collects data at outpatient IBD medical encounters. The registry

includes detailed demographic (e.g., age, gender, race, and ethnicity) and clinical characteristics (e.g., phenotype and extent of disease [Paris classification]) and concomitant medication usage. The database also collects serial measures of disease activity and efficacy endpoints (sPCDAI) data components, PGA of current disease status, serum markers of inflammation and safety outcomes such as laboratory assessments, serious infections, IBD surgeries, and hospitalizations. The ICN registry currently houses data from over 35,000 paediatric patients, 350,000 visits, and 130,000 patient-years along with data collected from over 900 paediatric patients treated with Ustekinumab off-label for Crohn's disease.

## Sample size

As part of the totality of evidence, a criterion for comparison was utilised in this study. If the lower limit of the 2-sided 95% CI for the proportion of Paediatric Patients (Primary Cohort) in clinical remission at Week 52 is greater than the pre-defined threshold established from the upper limit of the 2-sided 95% CI for the adult placebo remission rate based on the meta-analysis of placebo patients in similar adult clinical studies, then it suggests the effectiveness of ustekinumab in treating paediatrics patients with Crohn's disease. Power analyses were performed to examine the probability of meeting the comparison criterion for various assumed scenarios. For a sample size of 105 patients and a pre-specified threshold of 20%, the probability to meet the criterion is approximately 93% if the paediatric ustekinumab remission rate is 36% (i.e., the same as the adult remission rate), close to 100% if the paediatric ustekinumab remission rate is 45% (which is 125% of the adult remission rate), and 31% if the paediatric ustekinumab remission rate is 27% (which is preserving 75% of the adult remission rate).

## Randomisation/Blinding (masking)

NA

## Statistical methods

All patients in the FAS (defined as all enrolled patients who met the study eligibility criteria) of the Primary Cohort were included in the efficacy and safety analysis. The similar analyses were performed in the FAS of the reference Young Adults cohort (Reference Cohort 7, age ≥18 and <26, weighing ≥40 kg; sPCDAI ≥30 at baseline) and seven alternative study cohorts. Descriptive statistics, e.g., mean, median, standard deviation, interquartile range, minimum, and maximum, were used to summarise continuous variables. Counts and percentages were used to summarise categorical variables. For the dichotomised endpoints, the 95% CIs were provided as appropriate. The Kaplan-Meier method was used to analyse the time to discontinuation of ustekinumab.

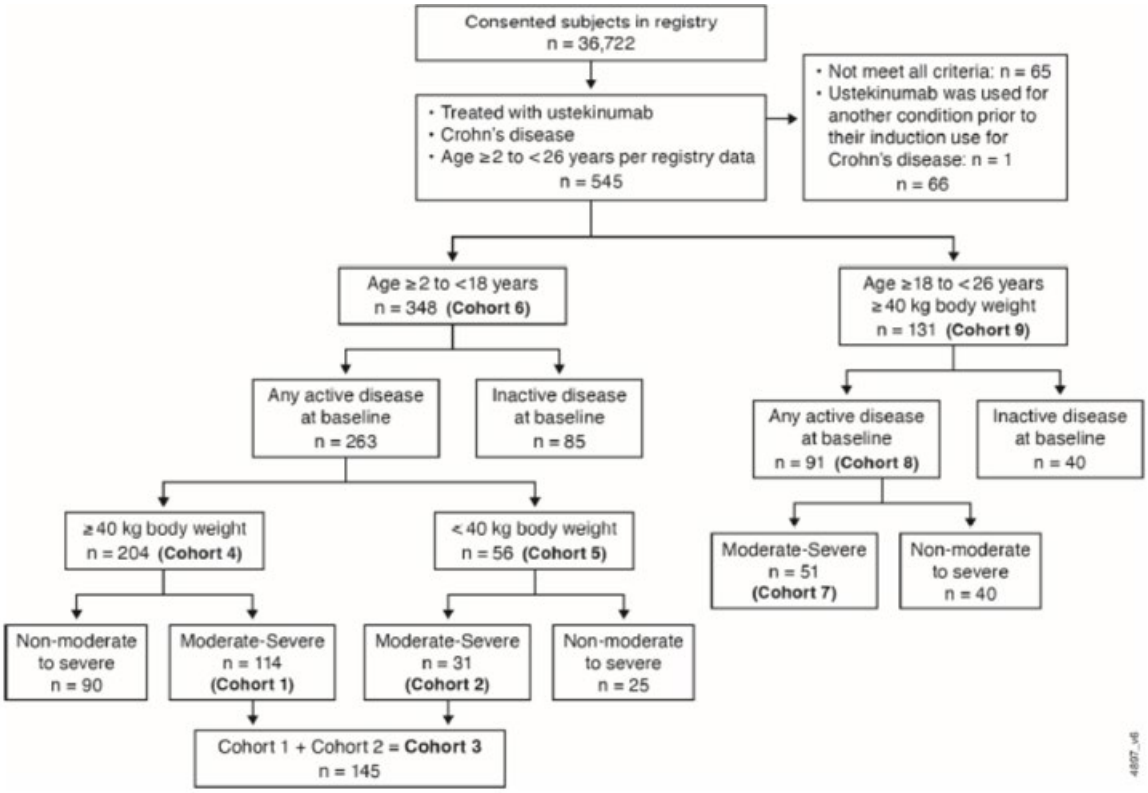
The evaluation of the effectiveness of ustekinumab in the Paediatric Patients (Primary Cohort) was based on the totality of evidence. The lower limit of the 2-sided 95% CI for the paediatric clinical remission rate at Week 52 was compared with the upper limit of the 2-sided 95% CI for the adult placebo remission rate that was established from (1) an updated meta-analysis of adult placebo data using a revised study selection criteria and (2) an analysis of the placebo data from the adult ustekinumab Crohn's disease Study CNTO1275CRD3003. In addition, (3) the paediatric clinical remission rate at Week 52 in Paediatric Patients (Primary Cohort) was descriptively compared with Young Adults (Reference; Cohort 7).

## Results

## Participant flow

A total of 479 patients treated with ustekinumab were included in the analysis cohort in this study. Of these 479 patients, 196 had moderately to severely active disease at baseline, in which, Paediatric Patients (Primary Cohort) had 114 patients (23.8%) and there were 51 (10.6%) patients in the Young Adults (Reference; Cohort 7), and 31 in paediatric patients weighing <40 kg cohort (Cohort 2).

**Figure 34: Study population flowchart**




- Active Crohn's disease is defined as sPCDAI >10 or corticosteroid use at baseline.
- Non-moderately to severely active Crohn's disease is defined as 10<sPCDAI<30 or corticosteroid use at baseline.
- Moderately to severely active Crohn's disease is defined as sPCDAI ≥30 at baseline.
- Three patients from Cohort 6 (All Pediatric Patients Treated) who had active Crohn's disease at baseline were excluded due to missing weight at baseline.
- Cohort 3: All moderately to severely active Crohn's disease patients treated with sPCDAI≥ 30 at baseline.

**Treatment Discontinuation**

For all eligible patients, all data collected in the ICN registry and by chart review through the earlier date of Week 76 from first dose of ustekinumab or 29 February 2020 were included. Following initiation, the absence of documented ustekinumab treatment was considered treatment discontinuation when there was a treatment gap of ≥6 months since the last administration, or ≥2 visits, at least 4 weeks apart without documented ustekinumab treatment. The majority of the paediatric and young adult patients (approximately 80%) had no treatment discontinuation event and continued their treatment with ustekinumab through Week 52. For the Paediatric Patients (Primary Cohort), 29 (25.4%) of 114 patients discontinued treatment with ustekinumab prior to Week 52. Paediatric Cohort 3 consisted of all paediatric patients (<40 kg and ≥40 kg) with moderately to severely active CD (145 patients). Young Adult Cohort 7 consisted of young adults with moderately to severely active CD and a body weight of ≥40 kg (51

patients) (Table 47). The most common reason for discontinuation of ustekinumab treatment before Week 52 (18 [15.8%] of 114 patients) was being assessed as a "Primary non-responder."

Approximately 25% of patients in each cohort (Paediatric Primary Cohort 1, Paediatric Cohort 3, and Young Adult Cohort 7) discontinued treatment with ustekinumab prior to Week 52 (Table 47). The rate of treatment discontinuation over time was similar between the young adult reference cohort and the paediatric cohorts.

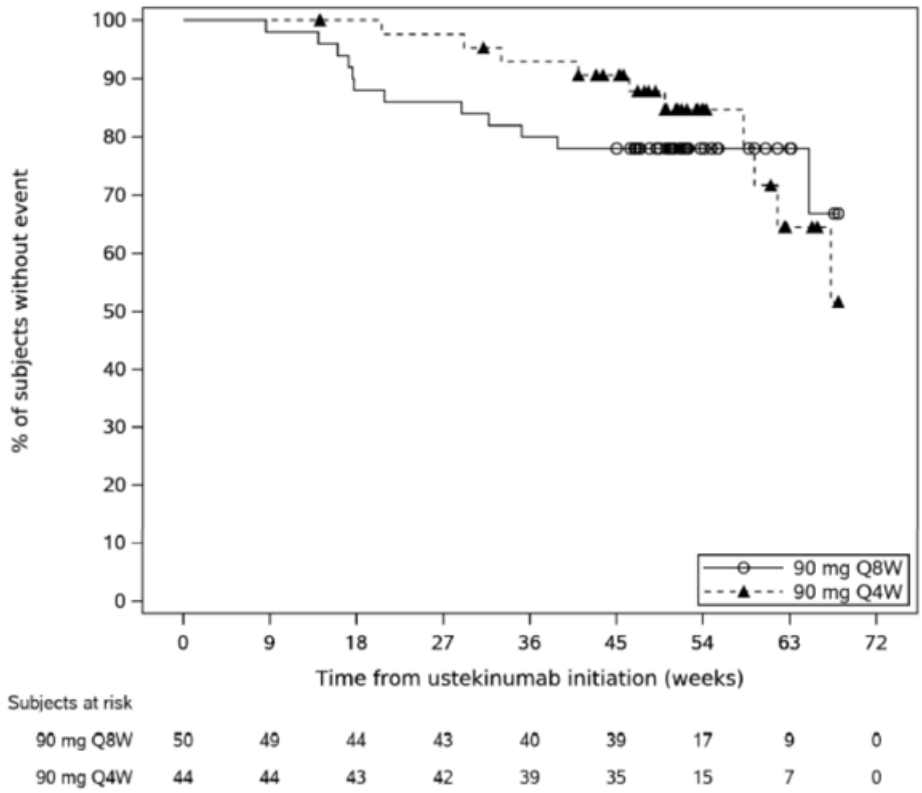
**Table 47: Number of subjects who discontinued ustekinumab treatment through week 52; primary cohort, cohort 3, and cohort 7; full analysis set (Study CNTO1275CRD3010)**

| | Pediatric patients (Primary Cohort) | Pediatric Patients (Cohort 3) | Young Adults Reference Cohort (Cohort 7) |
|---|---|---|---|
| Analysis set: | | | |
| N | 114 | 145 | 51 |
| Subjects who discontinued ustekinumab | 29 (25.4%) | 35 (24.1%) | 13 (25.5%) |
| Reason for treatment discontinuation | | | |
| Primary non-responder[a] | 18 (15.8%) | 20 (13.8%) | 5 (9.8%) |
| Secondary failure (worsening of Crohn's disease)[b] | 6 (5.3%) | 7 (4.8%) | 5 (9.8%) |
| Intolerant[c] | 1 (0.9%) | 1 (0.7%) | 0 |
| Serious adverse event | 0 | 0 | 0 |
| | Pediatric patients (Primary Cohort) | Pediatric Patients (Cohort 3) | Young Adults Reference Cohort (Cohort 7) |
| Insurance or other financial concerns | 0 | 0 | 0 |
| Other | 1 (0.9%) | 3 (2.1%) | 3 (5.9%) |
| Unknown/not reported | 3 (2.6%) | 4 (2.8%) | 0 |

[a] Primary non-responder: ustekinumab was never effective or the initial response was inadequate.
[b] Secondary failure: ustekinumab was initially effective, then lost effectiveness, e.g., worsening of Crohn's disease.
[c] Intolerant: Includes acute reactions after administration of medication and delayed administration reactions.
Note: N is the number of subjects who initiated ustekinumab.
Note: Primary cohort includes pediatric subjects (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30 at baseline) and body weight ≥40 kg at baseline.
Note: Cohort 7 includes young adult subjects (age ≥18 to <26 years) treated with ustekinumab, with moderately-severely active CD (sPCDAI ≥30) and body weight ≥40 kg at baseline.
Note: Cohort 3 includes pediatric patients (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30) at baseline.
Adapted from (Mod5.3.5.4/CNTO1275CRD3010/TEFTRTDC01, TEFTRTDC01A, TEFTRTDC01C).

A Kaplan-Meier plot of time to event (ustekinumab treatment discontinuation) by final ustekinumab dose and frequency for the Paediatric Patients (Primary Cohort) through Week 52 is provided in Figure 35.

**Figure 35: Ad-hoc analysis: Kaplan-Meier plot of time to ustekinumab treatment discontinuation by ustekinumab final maintenance dose and frequency; primary cohort full analysis set (Study CNTO1275CRD3010)**




Subjects at risk

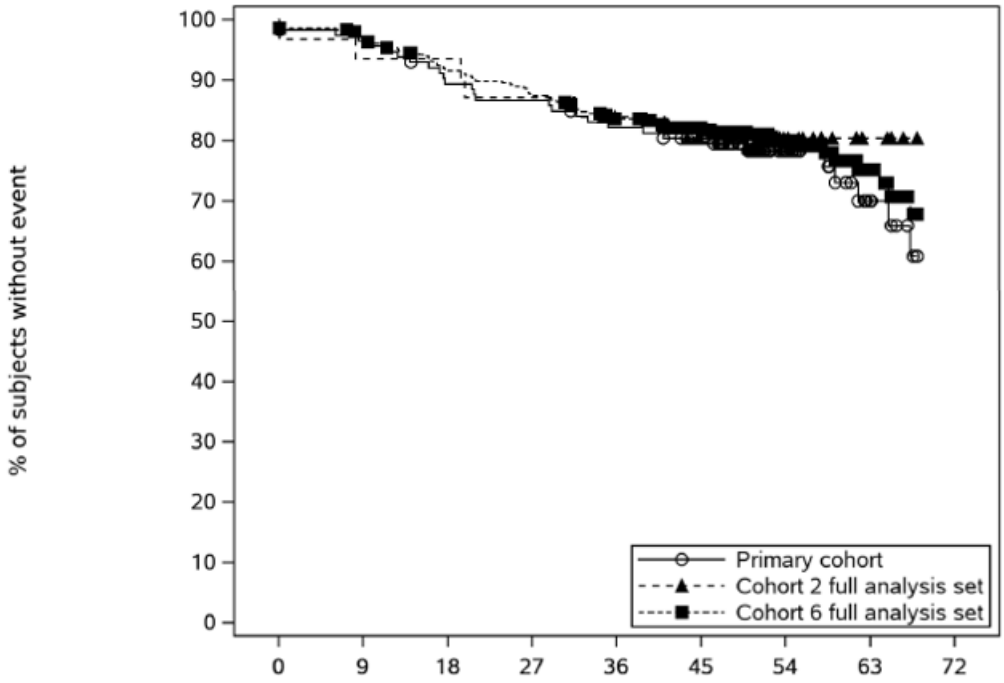
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 90 mg Q8W | 50 | 49 | 44 | 43 | 40 | 39 | 17 | 9 | 0 |
| 90 mg Q4W | 44 | 44 | 43 | 42 | 39 | 35 | 15 | 7 | 0 |

Note: Subjects who discontinue ustekinumab will be considered an 'Event' and their date of ustekinumab discontinuation will be used in the time to event calculation. Subjects who did not have an event (ie, ustekinumab discontinuation) are censored at the date of last dose of ustekinumab or the end date of the Week 52 window (ie, Week 52 + 16 weeks), whichever comes first.
Note: The survival curves are estimated using the Kaplan-Meier method.
Note: Final maintenance dose at Week 52 is defined as the last subcutaneous dose prior to one year after the date of the first ustekinumab dose for subjects who received ustekinumab beyond one year, or the last dose prior to discontinuation for subjects who discontinued ustekinumab prior to one year after the date of the first ustekinumab dose.
Note: Primary cohort includes pediatric subjects (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30 at baseline) and body weight ≥40 kg at baseline.

Through Week 52, a slightly higher proportion of patients receiving 90 mg q4w dosing did not discontinue treatment compared with patients receiving the 90 mg q8w dosing. After Week 52, a greater proportion of patients in the q4w group who discontinued treatment with ustekinumab than in the q8w group is observed among a few patients who had data available at a later time within the Week 52 window (i.e., Week 52 ± 16 weeks).

The Kaplan-Meier plots of time to event (ustekinumab treatment discontinuation) for patients weighing <40 kg with moderately to severely active Crohn's disease at baseline (Cohort 2) and All Paediatric Patients Treated (Cohort 6) were similar to those for the Paediatric Patients (Primary Cohort) (Figure 36).

**Figure 36: Ad-hoc analysis: Kaplan-Meier plot of time to ustekinumab treatment discontinuation by cohort; primary, cohort 2 and cohort 6 full analysis set (Study CNTO1275CRD3010)**




| Subjects at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Primary cohort | 114 | 109 | 100 | 97 | 91 | 86 | 40 | 19 | 0 |
| Cohort 2 full analysis set | 31 | 29 | 29 | 27 | 24 | 20 | 13 | 5 | 0 |
| Cohort 6 full analysis set | 348 | 335 | 312 | 299 | 277 | 257 | 112 | 40 | 0 |

Note: Subjects who discontinue ustekinumab will be considered an 'Event' and their date of ustekinumab discontinuation will be used in the time to event calculation. Subjects who did not have an event (ie, ustekinumab discontinuation) are censored at the date of last dose of ustekinumab or the end date of the Week 52 window (ie, Week 52 + 16 weeks), whichever comes first.
Note: The survival curves are estimated using the Kaplan-Meier method.
Note: Primary cohort includes pediatric subjects (age ≥2 to <18 years) treated with ustekinumab along with moderately-severely active Crohn's disease (sPCDAI ≥30 at baseline) and body weight ≥40 kg at baseline; Cohort 2 includes pediatric subjects (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30) and body weight <40 kg at baseline; Cohort 6 includes pediatric subjects (age ≥2 to <18 years) treated with ustekinumab regardless of sPCDAI or corticosteroid use at baseline.

## Baseline data

Baseline demographics and disease characteristics in Paediatric Cohorts 1 and 3 were consistent with a population of children with moderate to severely active CD. Most ICN paediatric patients previously failed other biologics, representing a refractory population. Baseline characteristics in the young adult cohort were similar to the paediatric cohorts with the exception that participants in the paediatric cohorts were younger and had a shorter disease duration (Table 48).

**Table 48: Summary of baseline demographics and Crohn's disease characteristics; paediatric patients (primary cohort and cohort 3) vs. young adults (cohort 7); full analysis set (Study CNTO1275CRD3010)**

| | Pediatric patients (Primary Cohort) | Pediatric patients (Cohort 3) | Young Adults (Cohort 7) |
|---|---|---|---|
| Analysis set: Full Analysis Set | 114 | 145 | 51 |
| Age, years | | | |
| N | 114 | 145 | 51 |
| Mean (SD) | 15.4 (1.52) | 14.6 (2.53) | 19.0 (1.22) |
| Median | 16.0 | 15.0 | 19.0 |
| Range | (11; 17) | (4; 17) | (18; 23) |
| IQ range | (15.0; 16.0) | (14.0; 16.0) | (18.0; 19.0) |
| ≥2-<12 years | 4 (3.5%) | 15 (10.3%) | 0 |
| ≥12-<18 years | 110 (96.5%) | 130 (89.7%) | 0 |
| ≥18 years | 0 | 0 | 51 (100.0%) |
| Sex | | | |
| N | 114 | 145 | 51 |
| Female | 58 (50.9%) | 76 (52.4%) | 32 (62.7%) |
| Race | | | |
| N | 114 | 145 | 51 |
| Black or African American | 9 (7.9%) | 13 (9.0%) | 3 (5.9%) |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| White | 93 (81.6%) | 115 (79.3%) | 43 (84.3%) |
| Weight, (kg) | | | |
| N | 114 | 145 | 51 |
| Mean (SD) | 57.6 (14.38) | 52.0 (16.96) | 61.6 (14.48) |
| Median | 54.6 | 51.6 | 58.6 |
| Range | (40; 129) | (16; 129) | (41; 115) |
| IQ range | (45.6; 64.3) | (41.4; 60.5) | (51.2; 69.8) |
| <40 kg | 0 | 31 (21.4%) | 0 |
| ≥40 kg | 114 (100.0%) | 114 (78.6%) | 51 (100.0%) |
| Body mass index, kg/m$^2$ | | | |
| N | 112 | 143 | 51 |
| Mean (SD) | 21.1 (4.52) | 19.9 (4.62) | 22.1 (5.17) |
| Median | 20.1 | 18.6 | 20.5 |
| Range | (13; 39) | (13; 39) | (16; 43) |
| IQ range | (18.0; 23.2) | (16.8; 21.9) | (18.7; 25.0) |
| Underweight <18.5 | 39 (34.8%) | 70 (49.0%) | 10 (19.6%) |
| Normal 18.5-<25 | 56 (50.0%) | 56 (39.2%) | 28 (54.9%) |
| Overweight 25-<30 | 11 (9.8%) | 11 (7.7%) | 11 (21.6%) |
| Obese ≥30 | 6 (5.4%) | 6 (4.2%) | 2 (3.9%) |
| Age at diagnosis, years | | | |
| N | 106 | 136 | 47 |
| Mean (SD) | 11.1 (2.83) | 10.4 (3.17) | 12.0 (3.95) |
| Median | 11.0 | 11.0 | 12.0 |
| Range | (4; 17) | (1; 17) | (0; 18) |
| IQ range | (9.0; 13.0) | (9.0; 12.5) | (9.0; 15.0) |
| CD disease duration, years | | | |
| N | 105 | 135 | 47 |
| Mean (SD) | 4.25 (2.441) | 4.11 (2.405) | 6.84 (4.363) |
| Median | 3.99 | 3.72 | 6.20 |
| Range | (0.1; 10.2) | (0.1; 11.4) | (0.8; 20.3) |
| IQ range | (2.42; 5.79) | (2.16; 5.68) | (3.56; 9.75) |

| | | | |
|---|---|---|---|
| Lower GI (Ileocolonic) disease | | | |
| N | 114 | 145 | 51 |
| Ileum only | 13 (11.4%) | 15 (10.3%) | 5 (9.8%) |
| Colon only | 24 (21.1%) | 32 (22.1%) | 7 (13.7%) |
| Ileocolonic | 76 (66.7%) | 97 (66.9%) | 39 (76.5%) |
| None | 1 (0.9%) | 1 (0.7%) | 0 |
| PCDAI Score | | | |
| N | 30 | 37 | 10 |
| Mean (SD) | 33.2 (13.86) | 33.6 (13.78) | 25.3 (11.21) |
| Median | 35.0 | 35.0 | 26.3 |
| Range | (10; 60) | (10; 60) | (10; 48) |
| IQ range | (22.5; 42.5) | (22.5; 42.5) | (20.0; 32.5) |
| Remission or mild ≤30 | 12 (40.0%) | 15 (40.5%) | 7 (70.0%) |
| Moderate >30-≤40 | 10 (33.3%) | 10 (27.0%) | 2 (20.0%) |
| Severe >40 | 8 (26.7%) | 12 (32.4%) | 1 (10.0%) |
| sPCDAI Score | | | |
| N | 114 | 145 | 51 |
| Mean (SD) | 44.4 (12.14) | 45.3 (12.16) | 44.0 (12.17) |
| Median | 40.0 | 45.0 | 45.0 |
| Range | (30; 75) | (30; 75) | (30; 70) |
| IQ range | (35.0; 50.0) | (35.0; 55.0) | (30.0; 55.0) |
| Remission or mild ≤30 | 24 (21.1%) | 28 (19.3%) | 15 (29.4%) |
| Moderate >30-≤40 | 35 (30.7%) | 43 (29.7%) | 9 (17.6%) |
| Severe >40 | 55 (48.2%) | 74 (51.0%) | 27 (52.9%) |
| SEMA-CD score at baseline | | | |
| N | 38 | 48 | 22 |
| Mean (SD) | 8.8 (4.62) | 8.7 (4.66) | 6.5 (4.83) |
| Median | 8.5 | 8.0 | 6.5 |
| Range | (0; 18) | (0; 18) | (0; 15) |
| IQ range | (5.0; 13.0) | (5.0; 13.5) | (3.0; 9.0) |
| Receiving corticosteroids at baseline | | | |
| No | 46 (40.4%) | 55 (37.9%) | 18 (35.3%) |
| Yes | 68 (59.6%) | 90 (62.1%) | 33 (64.7%) |
| Number of prior biologics used: | | | |
| N | 114 | 145 | 51 |
| none | 1 (0.9%) | 1 (0.7%) | 2 (3.9%) |
| 1 | 43 (37.7%) | 55 (37.9%) | 21 (41.2%) |
| 2 | 46 (40.4%) | 56 (38.6%) | 12 (23.5%) |
| ≥3 | 24 (21.1%) | 33 (22.8%) | 16 (31.4%) |

Key: IQ = interquartile.
Note: N's for each parameter reflect non-missing values.
Note: Primary cohort includes pediatric subjects (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30 at baseline) and body weight ≥40 kg at baseline. Cohort 3 includes pediatric subjects (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30) at baseline. Cohort 7 includes young adult subjects (age ≥18 to <26 years) treated with ustekinumab, with moderately-severely active CD (sPCDAI ≥30) and body weight ≥40 kg at baseline.
Adapted from (Mod5.3.5.4/CNTO1275CRD3010/AttTSIDEM02, AttTSIDEM02A, AttTSIDEM02C).

**Dosing**

The route of the first induction dose for the Paediatric Patients (cohort 3) for 139 (95.9%) of 145 patients was IV. A majority of the patients (129 [93.5%] of 138) received an induction dose in the range of 0.5 to <1.65 mg/kg/week (equivalent to IV dose of 260 to 520 mg). The majority of patients received the weight-based induction dosage recommended in the approved prescribing information for adult Crohn's disease; ≤55 kg 260 mg; >55 kg to ≤85 kg 390 mg; >85 kg/520 mg, equivalent to approximately 6 mg/kg.

The proportion of Young Adults (Reference; Cohort 7) receiving their first induction dose IV was 48 (94.1%) of 51. A total of 43 (93.5%) of 46 patients received an induction dose in the range of 0.5 to <1.65 mg/kg/week (equivalent to IV dose of 260 to 520 mg), with the weight base dosing generally aligning to the adult posology. The dosing regimen for the Young Adults (Reference: Cohort 7), was similar to that of patients in the Paediatric Patients (Cohort 3).

The majority of patients <40 kg with moderate to severe Crohn's disease (Cohort 2) received an induction dose of 260 mg, which is consistent with 92.6% of these patients receiving an induction dose in the range of 0.5 to <1.65 mg/kg/week, which is expected to provide equivalent exposure to the reference cohort).

A total of 112 (86.2%) of 130 patients in the Paediatric Patients (cohort 3) received an initial maintenance dose of ustekinumab of 90 mg q8w. A majority of the patients (103 [79.2%] of 130) received an initial maintenance dose in the range of 0.08 to ≤0.28 mg/kg/week is equivalent to approximately 90 mg q12w or 90 mg q8w. A majority of the patients (42 [85.7%] of 49) in the Young Adults (Reference; Cohort 7) received an initial maintenance dose in the range of 0.08 to ≤0.28 mg/kg/week is equivalent to approximately 90 mg q12w or 90 mg q8w. A slightly smaller proportion, 40 (81.6%) of 49 patients in the Young Adults (Reference; Cohort 7) received an initial maintenance dose of 90 mg q8w.

A total of 64 (49.2 %) of 130 patients in the Paediatric Patients (cohort 3) received a final maintenance dose of ustekinumab of 90 mg q8w. Approximately half of the patients (66 [50.8%] of 130) received a final maintenance dose in the range of 0.08 to ≤0.28 mg/kg/week, equivalent to approximately 90 mg q12w or 90 mg q8w. The proportion of Young Adults (Reference; Cohort 7) receiving their final maintenance dose of ustekinumab of 90 mg q8w was 33 (70.2%) of 47. A majority of patients (39 [83.0%] of 47) received a final maintenance dose in the range of 0.08 to ≤0.28 mg/kg/week, equivalent to approximately 90 mg q12w or 90 mg q8w.

## Outcomes and estimation

In CNTO1275CRD3010, the evaluation of the effectiveness of ustekinumab in a real-world setting was based on the totality of evidence through the 3 comparisons outlined below.

1. Young Adult Cohort 7 from CNTO1275CRD3010.

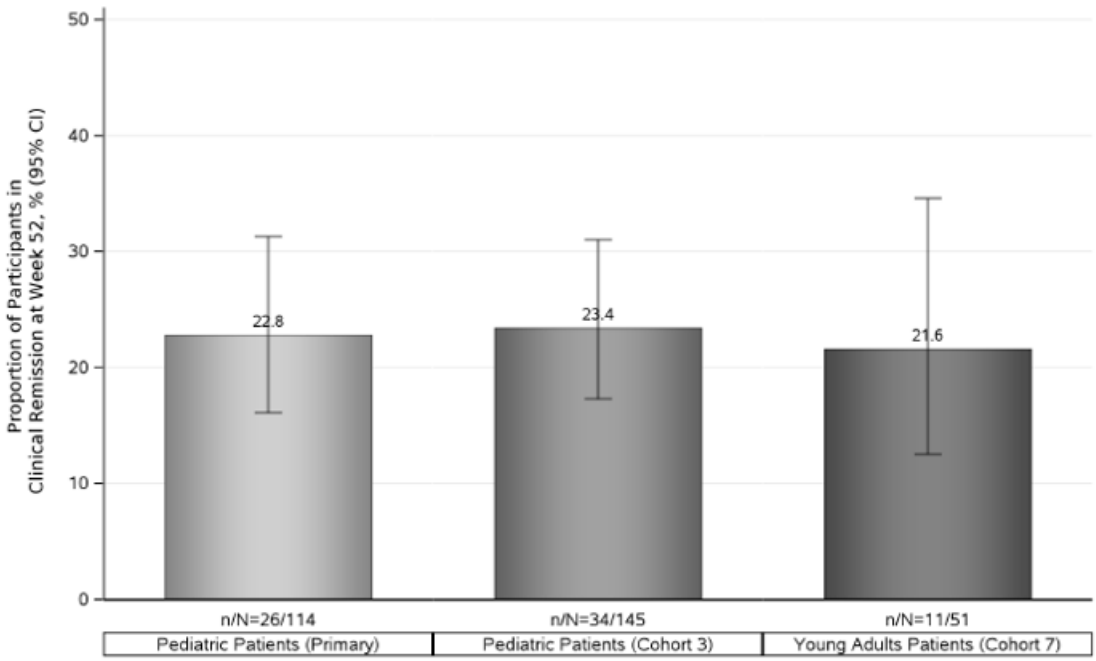
2. Placebo group of the adult studies CNTO1275CRD3001 and CNTO1275CRD3003.

3. The upper 95% confidence bound of a meta-analysis of the placebo group from selected adult historical studies.

Along with the Primary Paediatric Cohort 1 (patients between the ages of 2 years and <18 years, weighing ≥40 kg with an sPCDAI of ≥30 at baseline), the results from Paediatric Cohort 3 (between the ages of 2 years and <18 years, with an sPCDAI of ≥30 at baseline, regardless of weight) are presented comprehensively, as this population is most comparable to the study population in CNTO1275CRD3004 and is assessed using the same comparisons.

Comparison 1: At Week 52, the proportions of participants who were in sPCDAI clinical remission was similar among the paediatric patients (23.4% [95% CI: 17.3%, 31.0%] in Paediatric Cohort 3 and 22.8% [95% CI: 16.1%, 31.3%] in Paediatric Primary Cohort 1 compared with participants in Young Adult Cohort 7 (21.6% [95% CI: 12.5%, 34.6%]), with overlapping 95% CIs (Figure 37). The proportions of participants in clinical remission were also similar across baseline medication subgroups, and numerically lower in those who had received ≥3 prior biologics.

**Figure 37: Comparison of clinical remission achieved at week 52 in primary cohort, cohort 3 and cohort 7; full analysis set (Study CNTO1275CRD3010)**




Key: CD = Crohn's disease; sPCDAI = short pediatric Crohn's disease activity index.
Note: Primary cohort includes pediatric patients (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30) at baseline and body weight ≥40 kg at baseline. Cohort 3 includes pediatric patients (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30) at baseline. Cohort 7 includes young adult patients (age ≥18 to <26 years) treated with ustekinumab, with moderately-severely active CD (sPCDAI ≥30) and body weight ≥40 kg at baseline.
Note: Clinical remission is defined as sPCDAI ≤ 10.
Note: Subjects who had intercurrent events (ICEs) are considered not to be in clinical remission: (a) an IBD-related surgery with the exception of minor procedures such as ostomy revision, drainage of a superficial abscess or seton placement, (b) discontinuation of study agent due to worsening Crohn's disease or due to lack of effectiveness as assessed by chart review, (c) increase above baseline in prednisone, budesonide, or methyl-prednisolone dosage or new use of corticosteroids within 90 days prior to Week 52 endpoint assessment date, (d) initiation of AZA, 6-MP, or MTX within 90 days prior to Week 52 endpoint assessment date, or (e) initiation of cyclosporine, tacrolimus, or biologic agents prior to the date of Week 52 endpoint assessment or the ustekinumab discontinuation date.
Not: After accounting for ICEs, subjects who had missing clinical remission status at Week 52 are considered not to be in clinical remission.
Note: N is the number of subjects who initiated ustekinumab.
Note: The Week 52 value for the endpoint is defined as the non-missing measurement closest to Week 52 within the Week 52 window (ie, the time period from -16 to +16 weeks from Week 52). Week 52 is calculated as the date of the first dose of ustekinumab +365.
Note: The confidence intervals are based on the Wilson statistic.
Adapted from (Mod5.3.5.4/CNTO1275CRD3010/AttTEFCREM01, AttTEFCREM01A, AttTEFCREM01).

**Totality of Evidence Comparison 2: CRD3001/CRD3003 Adult Placebo Clinical Remission Rate**

Comparison 2: At Week 52, greater proportions of paediatric patients with moderately to severely active CD achieved clinical remission (23.4% of participants in Paediatric Cohort 3 and 22.8% of participants in Primary Paediatric Cohort 1) compared with the proportion of adults with moderately to severely active CD on placebo participating in CNTO1275CRD3001 and CNTO1275CRD3003 (19 [7.7%] of 247 patients). Additionally, the lower bound of the 95% CI for the proportions of paediatric participants in Paediatric Cohort 3 and Paediatric Cohort 1 in clinical remission at Week 52 (17.3% and 16.1%, respectively) were higher than the upper bound of the 95% CI of the placebo participants in the CNTO1275CRD3001 adult study (95% CI: 5.0%, 11.7%), indicating superiority of ustekinumab over placebo.

**Totality of Evidence Comparison 3: Data from Meta-analysis**

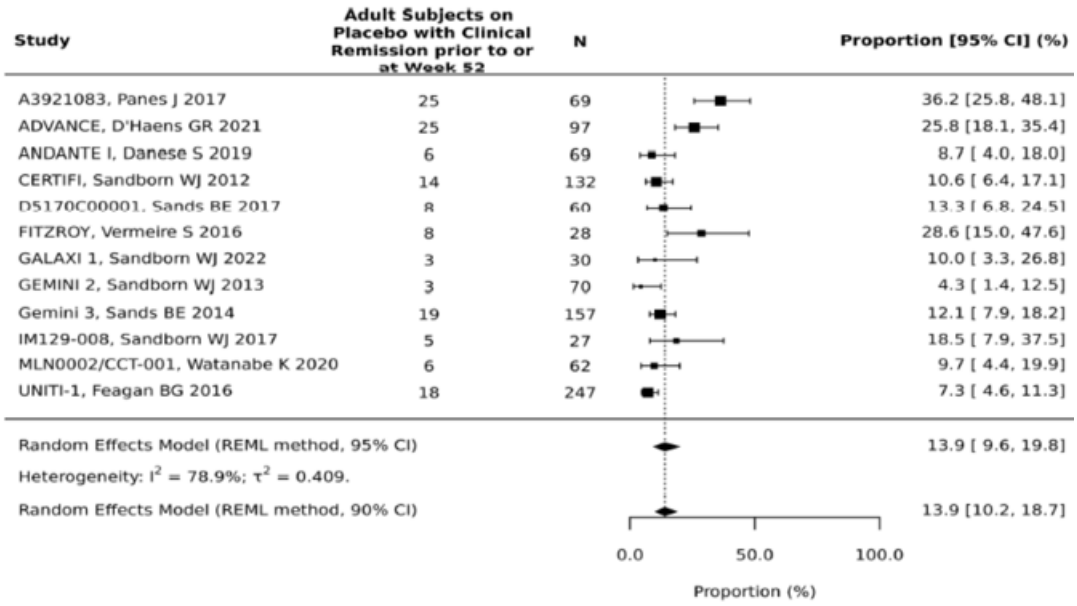
The meta-analysis conducted using more expansive inclusion criteria for study selection identified 12 studies with the appropriate biologic-failure populations.

There were major limitations with the meta-analysis. Specifically, the studies included in the meta-analysis reported the proportion of placebo participants in clinical remission after induction therapy (after only 6 to 12 weeks of treatment) and this estimated placebo clinical remission rate was compared with clinical remission after approximately 52 weeks of treatment in CNTO1275CRD3010.

The meta-analysis was conducted first with a full set of 12 studies and secondly, using a subset of 10 studies, excluding 2 influential studies (these studies had unusually high placebo clinical remission rates that could be attributed to multiple documented limitations of the studies). Of note, none of the adult studies included in the meta-analysis had placebo data beyond 12 weeks. The pooled proportion of adult patients on placebo in clinical remission at Week 52 based on a random effects model using the restricted maximum-likelihood method with sample size as weights was 13.9% (95% CI: 9.6%, 19.8%) (Figure 38). The meta-analysis estimate based on the revised selection criteria with 10 studies (removing the 2 influential studies) resulted in a lower estimate of the proportion of patients in clinical remission of 11.2% (95% CI: 8.4%, 14.7%).

The lower limit of the 2-sided 95% CI for the proportion of paediatric patients in Paediatric Cohort 3 achieving clinical remission at Week 52 (17.3%) did not exceed the upper limit of the 2-sided 95% CI for the first meta-analysis (19.8%), but did exceed the upper limit of the 2-sided 95% CI for the meta-analysis estimated remission rate using 10 studies (14.7%). Results comparing the lower limit of the 2-sided 95% CI from patients in Paediatric Cohort 1 were nearly identical.

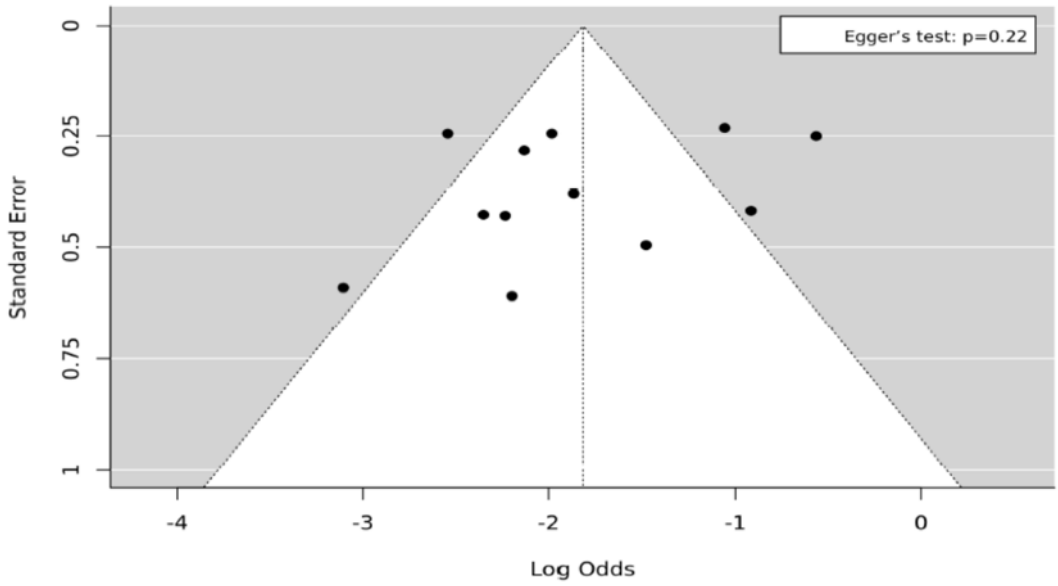
**Figure 38: Forest plot of number of adult subjects on placebo in clinical remission prior to or at week 52 by meta-analysis; (Study CNTO1275CRD3010)**




Visual inspection of the funnel plot (Figure 39) shows some extent of asymmetry of the included studies. There are more studies that are located on the left-side than the right-side of the vertical line (i.e., the overall estimate of the clinical remission), and among the 5 studies that are outside the triangular 95% confidence region, 2 studies (A3921083 and ADVANCE) on the right side are located towards the top of

the pyramid, and relatively far from the 95% CI borders and other studies. This indicates the existence of heterogeneity (small sample size) and potential bias.

**Figure 39: Funnel plot of studies used in the meta-analysis; (Study CNTO1275CRD3010)**




**Treatment Discontinuation, Clinical Response, Corticosteroid-free Remission, and PGA Remission**

**Treatment Discontinuation**

The majority of paediatric and young adult patients (approximately 80%) continued their treatment with ustekinumab through Week 52, with treatment discontinuation defined as a gap of ≥6 months without documented ustekinumab treatment or ≥2 visits, at least 4 weeks apart without documented ustekinumab treatment. The most frequent reason for early discontinuation of ustekinumab in both Paediatric Cohort 3 and Paediatric Primary Cohort 1 was being classified as a primary nonresponder (20 [13.8%] and 18 [15.8%] of 114 patients, respectively), followed by secondary failure (worsening of Crohn's disease; 7 [4.8%] and 6 [5.3%] patients, respectively). Based on an ad hoc analysis in the Paediatric Primary Cohort 1, through Week 52, a slightly higher proportion of patients receiving the 90 mg q4w regimen did not discontinue treatment compared with patients receiving the 90 mg q8w regimen, suggesting that a subgroup of patients may benefit from escalation to the 90 mg q4w regimen.

**sPCDAI Clinical Response and Remission, PGA Remission, and Corticosteroid-free Remission**

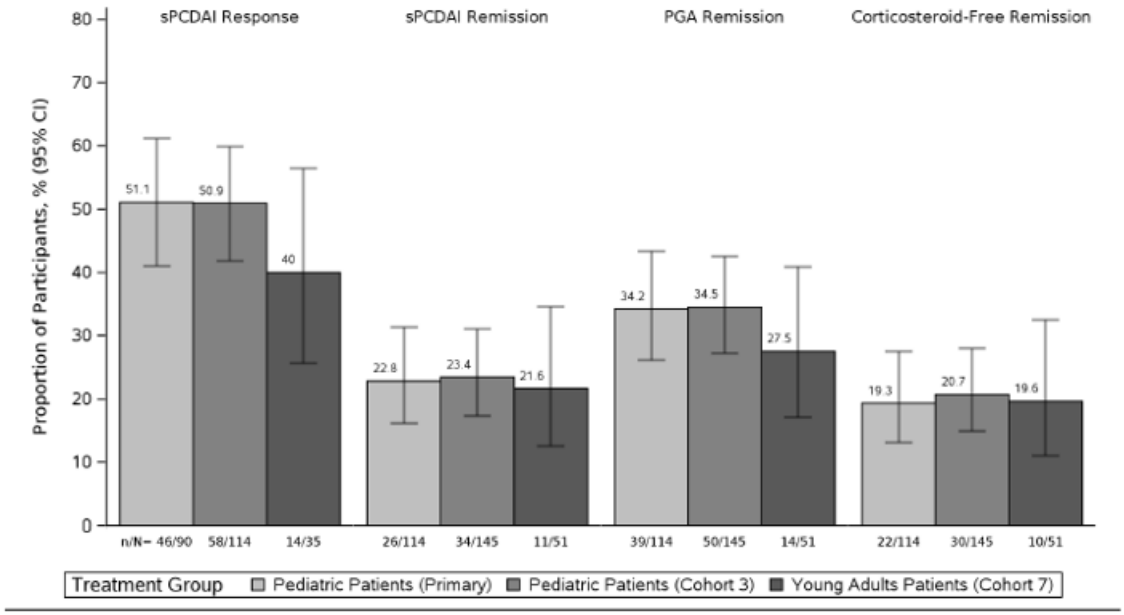
At Week 52, the proportions of participants in sPCDAI clinical response and in PGA remission were numerically higher (with overlapping 95% CIs) in the paediatric cohorts than in Young Adult Cohort 7 (Figure 40). The proportions of participants in sPCDAI clinical remission and corticosteroid-free remission were similar between the paediatric patients in Paediatric Primary Cohort 1, Paediatric Cohort 3, and Young Adult Cohort 7.

**sPCDAI Clinical Response and Remission, PGA Remission, and Corticosteroid-free Remission**

At Week 52, the proportions of participants in sPCDAI clinical response and in PGA remission were numerically higher (with overlapping 95% CIs) in the paediatric cohorts than in Young Adult Cohort 7 (Figure 40). The proportions of participants in sPCDAI clinical remission and corticosteroid-free remission

were similar between the paediatric patients in Paediatric Primary Cohort 1, Paediatric Cohort 3, and Young Adult Cohort 7.

**Figure 40: Key efficacy endpoints at week 52 in primary cohort, cohort 3 and cohort 7; full analysis set (Study CNTO1275CRD3010)**




Key: CD = Crohn's disease; sPCDAI = short pediatric Crohn's disease activity index.
Note: Primary cohort includes pediatric patients (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30) at baseline and body weight ≥40 kg at baseline. Cohort 3 includes pediatric patients (age ≥2 to <18 years) treated with ustekinumab, with moderately-severely active Crohn's disease (sPCDAI ≥30) at baseline. Cohort 7 includes young adult patients (age ≥18 to <26 years) treated with ustekinumab, with moderately-severely active CD (sPCDAI ≥30) and body weight ≥40 kg at baseline."
Note: sPCDAI response is defined as a reduction from baseline in the sPCDAI score of ≥10. sPCDAI remission is defined as sPCDAI ≤ 10. PGA (physician's global assessment) remission is defined as having a PGA rating of quiescent. Corticosteroid-free clinical remission was defined as sPCDAI ≤ 10 without use of corticosteroids within 90 days prior to Week 52 endpoint assessment.
Note: Subjects who had intercurrent events (ICEs) are considered not to be in clinical remission: (a) an IBD-related surgery with the exception of minor procedures such as ostomy revision, drainage of a superficial abscess or seton placement, (b) discontinuation of study agent due to worsening Crohn's disease or due to lack of effectiveness as assessed by chart review, (c) increase above baseline in prednisone, budesonide, or methyl-prednisolone dosage or new use of corticosteroids within 90 days prior to Week 52 endpoint assessment date, (d) initiation of AZA, 6-MP, or MTX within 90 days prior to Week 52 endpoint assessment date, or (e) initiation of cyclosporine, tacrolimus, or biologic agents prior to the date of Week 52 endpoint assessment or the ustekinumab discontinuation date.
Note: After accounting for ICEs, subjects who had missing clinical remission status at Week 52 are considered not to be in clinical remission. Subjects who had missing clinical response status at Week 52 after accounting for ICEs are excluded.
Note: N is the number of subjects who initiated ustekinumab.
Note: The Week 52 value for the endpoint is defined as the non-missing measurement closest to Week 52 within the Week 52 window (ie, the time period from -16 to +16 weeks from Week 52). Week 52 is calculated as the date of the first dose of ustekinumab +365.
Adapted from (Mod5.3.5.4/CNTO1275CRD3010/AttTEFCREM01, AttTEFCREM01A, AttTEFCREM01C, AttTEFPGA01, AttTEFPGA01A, AttTEFPGA01C, AttTEFCORT01, AttTEFCORT01A, AttTEFCORT01C; and AttADTEFCRES01, AttADTEFCRES01A, AttADTEFCRES01C).

**Dose Escalation to q4w Regimen**

At Week 52, 47 (35.6%) of 134 patients in Paediatric Cohort 3 and 42 (39.6%) of 108 patients in Paediatric Primary Cohort 1 dose escalated to the q4w dose regimen. Of those whose final maintenance dose regimen was q4w, 9 (17.6%) of 51 patients in Paediatric Cohort 3 and 8 (18.2%) of 44 patients in Paediatric Primary Cohort 1 were in clinical remission at Week 52.

Of note, a lower proportion of young adults (18.8% in Young Adult Cohort 7) dose escalated to q4w compared with paediatric patients. However, the dosing of the Young Adult Cohort 7 was possibly constrained by the approved labeled dose, while the paediatric cohorts had no such constraints.

**Growth Parameters**

In Paediatric Cohort 3, the median (range) in BMI z-score changed from -0.32 (-5.2, 2.7) at baseline to 0.04 (-3.7; 2.7) at Week 52. However, there was no evidence of improvement in height z-score or catch-up growth. In paediatric patients in Paediatric Primary Cohort 1, a positive median change from baseline in BMI z-score was shown, suggestive of an improvement in growth status for at least 50% of patients.

For example, the median (range) in BMI z-score changed from 0.02 (-5.2, 2.7) at baseline, to 0.15 (-3.4; 2.7) at Week 52. This is a noteworthy shift from an extremely low z-score range, indicative of severe underweight/malnutrition status, to a narrower (but still substantial) range, suggesting growth recovery and possible catch-up group in some patients.

In Young Adult Cohort 7, a positive median change from baseline in BMI z-score was shown, suggestive of an improvement in growth status. For example, the median (range) in BMI z-score changed from -0.36 (-4.2, 2.3) at baseline to -0.20 (-2.9; 2.2) at Week 52. The positive median change from baseline in BMI z-score reflects a pattern of normal growth among patients in Young Adult Cohort 7.

**Endoscopy Assessments**

Because endoscopic videos are not part of the ICN registry, computing an SES-CD score was not possible. Therefore, endoscopic outcomes in this RWE study were assessed using the SEMA-CD, a reliable and valid assessment used to evaluate and record endoscopic disease severity in paediatric CD by clinicians in real-world settings (different from the SES-CD derived from prospective videos in clinical studies).

At Week 52, the proportions of the paediatric patients achieving endoscopic remission (without undergoing a colonic or ileal resection surgery) were similar in the paediatric cohorts (5 [23.8%] of 21 patients in Paediatric Cohort 3 and 4 [20%] of 20 patients in Paediatric Primary Cohort 1. Only 3 patients in Young Adult Cohort 7 had endoscopic outcome data, therefore making it impossible to make a comparison between young adult and paediatric patients.

A total of 23 patients were evaluable for change in baseline SEMA-CD scores at Week 52. The median (interquartile range) value for the change from baseline in SEMA-CD scores for paediatric patients with moderately to severely active CD (Paediatric Cohort 3) (n=23) was -2.00 (-4.00; -2.00). The small number of young adults (n=3) precludes any comparisons.

**Clinical Remission as Determined by full PCDAI at Week 52**

Full PCDAI was calculated in those participants who had laboratory evaluations available. Full PCDAI was calculated in 26 paediatric patients in Paediatric Cohort 3, with 6 (23.1% [95% CI: 11.0%, 42.1%]) patients in PCDAI clinical remission at Week 52. Of the 21 paediatric patients (Paediatric Primary Cohort 1) who had nonmissing PCDAI assessments at Week 52, 5 (23.8% [95% CI: 10.6%, 45.1%]) patients were in PCDAI clinical remission at Week 52. Despite the small sample size with a full PCDAI score, these results are consistent with those seen with sPCDAI.

Of the 9 patients in Young Adult Cohort 7 who had nonmissing PCDAI assessment at Week 52, 4 (44.4% [95% CI: 18.9%, 73.3%]) patients were in full PCDAI clinical remission at Week 52.

## Analysis performed across trials (pooled analyses and meta-analysis)

***Comparison of studies CRD3004 and CRD1001***

CNTO1275CRD3004 was a Phase 3 pivotal study of efficacy, safety, and PK, and CNTO1275CRD1001 was a Phase 1 PK study. A majority of participants in CNTO1275CRD1001 had a history of intolerance or failure to biologics. Additionally, participants in CNTO1275CRD1001 with LOR and low exposure during the study did not have the option to dose adjust, unlike participants in CNTO1275CRD3004. Due to the many differences in the study design and participant characteristics, efficacy outcomes from these 2 studies are not pooled and are presented side by side, with a focus on results from the Phase 3 pivotal study, CNTO1275CRD3004.

**Study Participants**

**Disposition**

**Induction (Through Week I-8)**

All participants in CNTO1275CRD3004 and CNTO1275CRD1001 received study intervention at Week 0. One participant in each study terminated study participation prematurely through Week I-8/Week 8. In CNTO1275CRD1001, 21 participants received dosing that was equivalent to the IV dosing in CNTO1275CRD3004 (9 mg/kg for participants <40 kg or 390 mg for participants ≥40 kg). Three participants in each study discontinued study intervention early. For CNTO1275CRD1001, 2 (9.1%) of 22 participants who were clinical responders did not enter the LTE study at Week 16.

**Maintenance (Through Week M-44/Week 48)**

All participants who received study intervention at Week I-0/Week 0 and were clinical responders were randomised and received treatment at Week M-0 in CNTO1275CRD3004 and received the first SC maintenance dose at Week 8 in CNTO1275CRD1001. A total of 9 participants in CNTO1275CRD3004 (6 [13.6%] of 44 participants in the q12w treatment group and 3 [7.3%] of 41 participants in the q8w treatment group) and 3 (13.6%) of 22 participants in CNTO1275CRD1001 terminated study participation early through Week M-44/Week 48. The proportions of participants who discontinued study intervention through Week M-44/Week 48 ere low and similar between CNTO1275CRD3004 (5 [11.4%] of 44 participants in the q12w treatment group and 5 [12.2%] of 41 participants in the q8w treatment group) and CNTO1275CRD1001 (3 [13.6%] of 22 participants).

**Demographic and Baseline Clinical Characteristics**

The demographic characteristics in the FAS across the paediatric CNTO1275CRD3004 and CNTO1275CRD1001 studies were generally similar overall with the exception of participants in CNTO1275CRD1001 who had lower height, weight, and BMI z-scores, and a lower percentage of male participants enrolled:

- In CNTO1275CRD3004, the median age was 14.0 years, and in CNTO1275CRD1001, the median age was 13.0 years.
- Most participants were white (88 [87.1%] of 101 participants in CNTO1275CRD3004, and 17 [81.0%] of 21 participants in CNTO1275CRD1001).
- A greater percentage of male participants (60 [59.4%] of 101 participants in CNTO1275CRD3004, and 12 [57.1%] of 21 participants in CNTO1275CRD1001) than female participants (41 [40.6%] participants in CNTO1275CRD3004, and 9 [42.9%] participants in CNTO1275CRD1001) were enrolled.
- The median body weight was numerically lower in CNTO1275CRD1001 (42.6 kg) than in CNTO1275CRD3004 (47.2 kg).

- BMI z-scores were higher in CNTO1275CRD3004 than in CNTO1275CRD1001 (mean [SD: -0.17 [0.963] versus -0.44 [1.295]). Additionally, a higher proportion of participants in CNTO1275CRD1001 were classified as underweight (15 [71.4%] participants versus 57 [56.4%] participants in CNTO1275CRD3004).
- Participants in CNTO1275CRD3004 had higher height z-scores than participants in CNTO1275CRD1001 (mean [SD]: 0.27 [1.152] versus -0.49 [1.191]).

Demographic and baseline disease characteristics were generally similar in the FASCR to the FAS.

**Crohn's Disease Baseline Characteristics**

Crohn's disease characteristics at baseline across studies CNTO1275CRD3004 and CNTO1275CRD1001 were representative of a population of paediatric participants with moderately to severely active CD. In the CNTO1275CRD3004 and CNTO1275CRD1001 induction treated participants:

- The mean age at diagnosis was older in CNTO1275CRD3004 (10.9 years) than in CNTO1275CRD1001 (8.8 years).
- The median duration of CD was shorter in CNTO1275CRD3004 (2.0 years) than in CNTO1275CRD1001 (3.5 years).
- A higher percentage of participants in CNTO1275CRD3004 had extraintestinal manifestations (59 [58.4%] of 101 participants) than in CNTO1275CRD1001 (9 [42.9%] of 21 participants).
- A lower number of participants had a PCDAI score of "severe" (>40) in CNTO1275CRD3004 (44 [43.6%] of 101 participants) than in CNTO1275CRD1001 (12 [60.0%] of 20 participants).
- The majority of participants in both studies had an endoscopic disease severity score (SES-CD score) of moderate (44 [44.0%] of 100 participants in CNTO1275CRD3004 and 11 [52.4%] of 21 participants in CNTO1275CRD1001) or severe (31 [31.0%] in CNTO1275CRD3004 and 6 [28.6%] participants in CNTO1275CRD1001).
- A total of 7 (6.9%) of 101 participants in CNTO1275CRD3004 and 1 (4.8%) of 21 participants in CNTO1275CRD1001 had a fistula.
- The majority of participants in both studies had abnormal CRP serum concentrations (>3 mg/L); 72 (71.3%) of 101 participants in CNTO1275CRD3004 and 14 (66.7%) of 21 participants in CNTO1275CRD1001.
- The majority of participants in both studies had abnormal fecal calprotectin concentrations (>250 mg/kg) (92 [92.9%] of 99 participants in CNTO1275CRD3004 and 17 [85.0%] of 20 participants in CNTO1275CRD1001).

**Concomitant Medications for Crohn's Disease**

The proportion of participants in the FAS who were taking at least 1 CD-related concomitant medication at baseline was numerically higher for participants in CNTO1275CRD3004 than participants in CNTO1275CRD1001 (Table 49).

**Table 49: Summary of Crohn's disease-related concomitant medications at baseline among subjects receiving higher induction ustekinumab IV in CRD1001 and subjects in CDR3004; full analysis set (Study CNTO1275CRD1001 and (Study CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Full Analysis Set | 21 | 101 |
| Any CD-related concomitant medication at baseline | 13 (61.9%) | 72 (71.3%) |
| Antibiotic | 0 | 6 (5.9%) |
| Oral corticosteroid use | 7 (33.3%) | 25 (24.8%) |
| Corticosteroid use (excl. budesonide and beclomethasone dipropionate ) | 7 (33.3%) | 10 (9.9%) |
| Budesonide | 0 | 15 (14.9%) |
| Beclomethasone dipropionate | 0 | 1 (1.0%) |
| Immunomodulatory drugs | 10 (47.6%) | 43 (42.6%) |
| 6-Mercaptopurine/ Azathioprine | 6 (28.6%) | 37 (36.6%) |
| Methotrexate | 4 (19.0%) | 6 (5.9%) |
| 5-Aminosalicylate (5-ASA) | 5 (23.8%) | 32 (31.7%) |

Note: Subjects may appear in more than one category.

Crohn's disease-related concomitant medications at baseline were generally similar in the FASCR to the FAS.

**Medication History for Crohn's Disease**

Across CNTO1275CRD3004 and CNTO1275CRD1001, the medication history for participants with CD was representative of a population of participants with moderately to severely active CD. A greater proportion of participants in CNTO1275CRD1001 (19 [90.5%] of 21 participants) had a history of biologic failure than participants in CNTO1275CRD3004 (57 [56.4%] of 101 participants), as expected based on the eligibility criteria for CNTO1275CRD1001.

**Extent of Exposure**

All paediatric study participants in both studies received their scheduled ustekinumab infusion at Week 0. All paediatric study participants who were clinical responders in both studies received their first scheduled maintenance dose of ustekinumab at Week M-0/Week 8.

The mean (SD) total duration of ustekinumab exposure was 38.8 (12.31) and 41.1 (12.03) weeks for participants in the q12w and q8w treatment groups, respectively, in CNTO1275CRD3004 and 36.8 (9.63) weeks for participants in CNTO1275CRD1001. The median total duration of ustekinumab exposure was 44.1 and 48.1 weeks for participants in the q12w and q8w treatment groups, respectively, in CNTO1275CRD3004 and 40.1 weeks for participants in CNTO1275CRD1001.

**Efficacy**

CNTO1275CRD3004 was a Phase 3 pivotal study of efficacy, safety, and PK. CNTO1275CRD1001 was a Phase 1 PK study. Due to differences in the study design and participant characteristics, efficacy outcomes from these 2 studies are presented side by side in this section, with a focus on results from the Phase 3 pivotal study, CNTO1275CRD3004.

For the purpose of the descriptive comparisons, a clinical response definition of a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30 points was applied to both CNTO1275CRD3004 and CNTO1275CRD1001.

**Key Efficacy Endpoints**

**Induction (Through Week I-8)**

A summary of the key efficacy endpoints during the induction period across CNTO1275CRD3004 and CNTO1275CRD1001 is presented in Table 50.

**Clinical Remission**

- In CNTO1275CRD3004, 46.5% of participants were in clinical remission at Week I-8; this proportion was numerically higher, with overlapping CIs, than the proportion of participants in CNTO1275CRD1001 in clinical remission at Week 8 (23.8%). This may be partly explained by the higher percentage of biologic failure participants in CNTO1275CRD1001.

**Clinical Response**

- In CNTO1275CRD3004, a numerically higher proportion of participants were in clinical response at Week I-8 than participants in CNTO1275CRD1001 at Week 8 (84.2% versus 52.4% of participants, respectively).

**PCDAI Scores**

- PCDAI scores at Week I-8/Week 8 improved (decreased) in both studies.

**Reduction in Markers of Inflammation**

*C-reactive Protein*

- The mean changes (SD) from baseline of CRP levels at Week I-8/Week 8 were similar between CNTO1275CRD3004 and CNTO1275CRD1001.
- Reductions in mean serum CRP levels over time through Week I-8/Week 8 were similar between CNTO1275CRD3004 and CNTO1275CRD1001.

*Fecal Calprotectin*

- There was a reduction in fecal calprotectin at Week I-8/Week 8 in both paediatric studies.

**Table 50: Summary of key efficacy endpoints at week I-0 (week 0) and week I-8 (week 8) among subjects receiving higher induction ustekinumab IV in CRD1001 and subjects in CRD3004; full analysis set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Full Analysis Set | 21 | 101 |
| Week I-8 (Week 8) | | |
| N | 21 | 101 |
| Subjects in clinical remission[a1,b1,b2] | 5 (23.8%) | 47 (46.5%) |
| 95% CI[c] | (10.6%, 45.1%) | (37.1%, 56.2%) |
| N | 21 | 101 |
| Subjects in clinical response[a2,b1,b2] | 11 (52.4%) | 85 (84.2%) |
| 95% CI[c] | (32.4%, 71.7%) | (75.8%, 90.0%) |
| PCDAI Score | | |
| Baseline | | |
| N | 20 | 101 |
| Mean (SD) | 41.38 (11.135) | 41.16 (7.620) |
| Median | 42.50 | 40.00 |
| Range | (17.5; 57.5) | (20.0; 62.5) |
| Week I-8 (Week 8) | | |
| N | 20 | 100 |
| Mean (SD) | 21.63 (15.692) | 14.05 (11.258) |
| Median | 17.50 | 12.50 |
| Range | (0.0; 57.5) | (0.0; 47.5) |
| Change From Baseline | | |
| N | 20 | 100 |
| Mean (SD) | -19.75 (15.995) | -27.08 (13.442) |
| Median | -16.25 | -27.50 |
| Range | (-50.0; 5.0) | (-52.5; 5.0) |
| C Reactive Protein (mg/L) | | |
| Baseline | | |
| N | 21 | 101 |
| Mean (SD) | 20.12 (29.980) | 19.35 (25.740) |
| Median | 8.00 | 9.10 |
| Range | (0.1; 112.0) | (0.1; 121.6) |
| Week I-8 (Week 8) | | |
| N | 21 | 98 |
| Mean (SD) | 11.43 (17.931) | 10.07 (13.440) |
| Median | 4.78 | 5.35 |
| Range | (0.1; 74.1) | (0.1; 57.4) |
| Change From Baseline | | |
| N | 21 | 98 |
| Mean (SD) | -8.70 (16.514) | -8.71 (20.626) |
| Median | -0.27 | -2.35 |
| Range | (-50.5; 9.1) | (-93.5; 43.3) |

| | | |
|---|---|---|
| Fecal Calprotectin (mg/kg) | | |
| Baseline | | |
| N | 19 | 99 |
| Mean (SD) | 2627.16 (3433.577) | 3138.00 (4560.476) |
| Median | 1814.00 | 1903.00 |
| Range | (93.0; 15365.0) | (15.0; 36000.0) |
| Week I-8 (Week 8) | | |
| N | 19 | 95 |
| Mean (SD) | 1757.11 (2182.326) | 1864.60 (3045.166) |
| Median | 1089.00 | 1233.00 |
| Range | (56.0; 8344.0) | (15.0; 26773.0) |
| Change From Baseline | | |
| N | 19 | 93 |
| Mean (SD) | -870.05 (3907.905) | -1143.06 (4711.036) |
| Median | -37.00 | -594.00 |
| Range | (-14276.0; 4620.0) | (-33975.0; 13300.0) |

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |

[a1] Clinical remission is defined as a PCDAI score ≤10 points.
[a2] 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 points.
[a3] For CRD3004, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3. For CRD1001, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% in subjects with a baseline SES-CD score of ≥3. (Note: Ns of subjects with a baseline SES-CD score ≥3 was selected from full analysis set in CRD1001 and full randomized analysis set in CRD3004.)
[b1] For CRD3004, intercurrent events (ICEs) include: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4. ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 were not considered to have achieved the endpoint at Week I-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint. Subjects who had ICEs 1-3, and 5 prior to a visit are considered to have no change from baseline for that endpoint at that visit and subsequent visit. Subjects with ICE 4 have their data assumed missing after the ICE 4 occurred.
[b2] For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint. Subjects who had insufficient data to calculate the PCDAI score at a visit are considered to not have achieved the endpoint. Subjects who had a prohibited Crohn's disease-related surgery, or discontinued study agent due to an AE of worsening CD or due to lack of efficacy, or had prohibited concomitant medication changes had their baseline value carried forward. Subjects who had insufficient data had their last value carried forward as in the main CRD1001 study.
[c] The confidence intervals are based on the Wilson statistic.
Note: Baseline is defined as the last observation prior to or at the time of the first study intervention.
Note: Observed data were used for weight, height, and BMI z-scores.

**Growth Parameters**

In both studies at Week I-8/Week 8, weight and BMI z-scores increased from baseline for both male and female participants:

- The mean (SD) changes from baseline in weight z-scores for male and female participants in CNTO1275CRD3004 were 0.09 (0.238) and 0.14 (0.243), respectively, and in CNTO1275CRD1001 were 0.09 (0.203) and 0.06 (0.177), respectively.
- The mean (SD) changes from baseline in BMI z-scores for male and female participants in CNTO1275CRD3004 were 0.14 (0.289) and 0.18 (0.327), respectively, and in CNTO1275CRD1001 were 0.20 (0.346) and 0.10 (0.207), respectively.

**Maintenance (Through Week M-44/Week 48)**

A summary of the key efficacy endpoints during the maintenance period across CNTO1275CRD3004 and CNTO1275CRD1001 is presented in Table 51.

Of note, the CNTO1275CRD1001 study was designed to have its first database lock after the Week 16 visit, and therefore, the study protocol designated visits after Week 16 as "study extension" visits (LTE). For the purposes of this SCE, all data collected in CNTO1275CRD1001 after the participants received their first SC maintenance dose of ustekinumab at the Week 8 visit through Week 48 (±10 days) are considered occurring during the maintenance period of the study.

This was done to align with the phases of the Phase 3 CNTO1275CRD3004 study for reporting 1 year efficacy and safety. Additionally, treatment failure rules were applied to the clinical remission and clinical response endpoints at Week 48 of the CNTO1275CRD1001 study to align CNTO1275CRD1001 with CNTO1275CRD3004. Specifically, the treatment failure rules were participants who had a prohibited CD-related surgery, discontinued study intervention due to an AE of worsening Crohn's disease or due to lack of efficacy, or had prohibited concomitant medication changes were considered to not have achieved the endpoint at Week 48.

**Table 51: Summary of key efficacy endpoints at week M-44/week 48 among subjects in CRD1001 and subjects in CRD3004; full clinical responder analysis set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | q8w | | q12w | |
| | CRD1001 | CRD3004 | CRD3004 | CRD3004 Combined |
| Analysis set: Full Clinical Responder | 22 | 41 | 44 | 85 |
| Week M-44/Week 48 | | | | |
| N | 22 | 41 | 44 | 85 |
| Subjects in clinical remission[a1,b1,b2] | 13 (59.1%) | 20 (48.8%) | 26 (59.1%) | 46 (54.1%) |
| 95% CI[d] | (38.7%, 76.7%) | (34.3%, 63.5%) | (44.4%, 72.3%) | (43.6%, 64.3%) |
| N | 22 | 41 | 44 | 85 |
| Subjects in clinical response[a2,b1,b2] | 16 (72.7%) | 23 (56.1%) | 28 (63.6%) | 51 (60.0%) |
| 95% CI[d] | (51.8%, 86.8%) | (41.0%, 70.1%) | (48.9%, 76.2%) | (49.4%, 69.8%) |
| N | 22 | 41 | 44 | 85 |
| Subjects in corticosteroid-free clinical remission[c] | 12 (54.5%) | 19 (46.3%) | 26 (59.1%) | 45 (52.9%) |
| 95% CI[d] | (34.7%, 73.1%) | (32.1%, 61.3%) | (44.4%, 72.3%) | (42.4%, 63.2%) |

| | | | | |
|---|---|---|---|---|
| PCDAI | | | | |
| N | 18 | 41 | 43 | 84 |
| Mean (SD) | 9.72 (10.877) | 20.98 (19.469) | 18.43 (20.325) | 19.67 (19.833) |
| Median | 7.50 | 12.50 | 7.50 | 7.50 |
| Range | (0.0; 45.0) | (0.0; 60.0) | (0.0; 55.0) | (0.0; 60.0) |
| PCDAI Change from Baseline | | | | |
| N | 18 | 41 | 43 | 84 |
| Mean (SD) | -27.64 (13.297) | -20.49 (19.245) | -23.49 (18.380) | -22.02 (18.754) |
| Median | -28.75 | -30.00 | -30.00 | -30.00 |
| Range | (-45.0; 0.0) | (-52.5; 0.0) | (-57.5; 0.0) | (-57.5; 0.0) |
| Change from Baseline of C Reactive Protein (mg/L) | | | | |
| N | 18 | 41 | 43 | 84 |
| Mean (SD) | -8.56 (13.892) | -6.00 (14.475) | -7.28 (21.999) | -6.65 (18.609) |
| Median | -1.10 | 0.00 | 0.00 | 0.00 |
| Range | (-54.5; 4.9) | (-64.4; 9.2) | (-102.5; 11.6) | (-102.5; 11.6) |
| Change from Baseline of Fecal Calprotectin (mg/kg) | | | | |
| N | 13 | 37 | 40 | 77 |
| Mean (SD) | -2692.46 (4787.412) | -893.00 (3538.401) | -554.05 (1239.296) | -716.92 (2597.662) |
| Median | -1476.00 | 0.00 | 0.00 | 0.00 |
| Range | (-16882.0; 2382.0) | (-20878.0; 1205.0) | (-6030.0; 858.0) | (-20878.0; 1205.0) |

[a1] Clinical remission is defined as a PCDAI score ≤10 points.
[a2] 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 points.
[b1] For CRD3004, intercurrent events (ICEs) include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6. ICEs strategies: Subjects who had ICEs 1-5, and 7 prior to a visit are considered to have no change from baseline for PCDAI, CRP, and fecal calprotectin at that visit and subsequent visit. Subjects with ICE 6 have their data assumed missing after the ICE 6 occurred. Subjects that have ICEs 1-5, and 7 prior to Week M-44 are not considered to be in clinical remission or clinical response at Week M-44 (ie. composite strategy). Subjects with ICE 6 prior to Week M-44 are considered to have missing clinical remission or clinical response data from the time of the event onward (ie. hypothetical strategy). After accounting for the ICEs, subjects who have missing clinical remission or clinical response data are considered not to be in clinical remission or clinical response at Week M-44.
[b2] For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint. Subjects who had insufficient data to calculate the PCDAI score at a visit are considered to not have achieved the endpoint. Subjects who had a prohibited Crohn's disease-related surgery, or discontinued study agent due to an AE of worsening CD or due to lack of efficacy or had prohibited concomitant medication changes had their baseline value carried forward. Subjects who had insufficient data were not imputed as in the LTE of the CRD1001 study.
[c] For CRD1001, corticosteroid-free clinical remission is defined as PCDAI score ≤10 points and not receiving corticosteroids 30 days prior to the visit during the LTE. For CRD3004, corticosteroid-free clinical remission is defined as PCDAI score ≤10 points and not receiving corticosteroids for at least 90 days prior to Week M-44 and at least 30 days prior to other visits.
[d] The confidence intervals are based on the Wilson statistic.
Note: Baseline is defined as the last observation prior to or at the time of the first study intervention.
Note: Observed data were used for weight, height, and BMI z-scores.
Adapted from [tefkey08b.rtf] [PROD/cnto1275/z_sce/dbr_2025_01/re_2025_01/tefkey08b.sas] 29APR2025, 22:25

**Growth Parameters**

At Week M-44, height, weight, and BMI z-scores were similar to baseline or improved for male and female participants in CNTO1275CRD3004 (Table 52). In CNTO1275CRD1001 at Week 48, all z-scores similarly remained stable or improved, with the exception of height z-scores for male participants.

**Table 52: Summary of change from baseline in tertiary Endpoints at Week M-44/Week 48 among subjects in CRD1001 and subjects in CRD3004; full clinical responder analysis set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | q8w | | q12w | |
| | CRD1001 | CRD3004 | CRD3004 | CRD3004 Combined |
| Analysis set: Full Clinical Responder | 22 | 41 | 44 | 85 |
| Height Z score | | | | |
| Change from baseline[b,c] | | | | |
| N | 18 | 36 | 40 | 76 |
| Mean (SD) | 0.05 (0.327) | -0.01 (0.260) | 0.04 (0.285) | 0.02 (0.272) |
| Median | -0.05 | 0.00 | 0.03 | 0.01 |
| Range | (-0.3; 0.8) | (-0.4; 0.8) | (-0.5; 0.8) | (-0.5; 0.8) |
| IQ range | (-0.20; 0.24) | (-0.23; 0.16) | (-0.12; 0.19) | (-0.14; 0.18) |
| Female | | | | |
| N | 10 | 12 | 16 | 28 |
| Mean (SD) | 0.16 (0.331) | 0.03 (0.318) | -0.01 (0.222) | 0.00 (0.263) |
| Median | 0.00 | -0.01 | 0.04 | 0.01 |
| Range | (-0.2; 0.8) | (-0.4; 0.8) | (-0.5; 0.3) | (-0.5; 0.8) |
| IQ range | (-0.09; 0.36) | (-0.14; 0.16) | (-0.13; 0.15) | (-0.13; 0.16) |
| Male | | | | |
| N | 8 | 24 | 24 | 48 |
| Mean (SD) | -0.08 (0.287) | -0.02 (0.231) | 0.07 (0.320) | 0.02 (0.280) |
| Median | -0.20 | 0.02 | 0.00 | 0.01 |
| Range | (-0.3; 0.5) | (-0.4; 0.4) | (-0.4; 0.8) | (-0.4; 0.8) |
| IQ range | (-0.26; 0.04) | (-0.25; 0.14) | (-0.11; 0.19) | (-0.17; 0.18) |
| Weight Z score | | | | |
| Change from baseline[b,c] | | | | |
| N | 18 | 36 | 40 | 76 |
| Mean (SD) | 0.14 (0.310) | 0.09 (0.450) | 0.22 (0.458) | 0.16 (0.456) |
| Median | 0.14 | 0.18 | 0.12 | 0.15 |
| Range | (-0.4; 0.7) | (-1.2; 0.8) | (-0.6; 1.7) | (-1.2; 1.7) |
| IQ range | (-0.07; 0.36) | (-0.22; 0.45) | (-0.09; 0.45) | (-0.11; 0.45) |
| Female | | | | |
| N | 10 | 12 | 16 | 28 |
| Mean (SD) | 0.25 (0.288) | 0.30 (0.289) | 0.22 (0.478) | 0.26 (0.403) |
| Median | 0.20 | 0.33 | 0.19 | 0.26 |
| Range | (-0.2; 0.7) | (-0.4; 0.7) | (-0.6; 1.2) | (-0.6; 1.2) |
| IQ range | (-0.01; 0.52) | (0.18; 0.47) | (-0.12; 0.46) | (0.01; 0.47) |
| Male | | | | |
| N | 8 | 24 | 24 | 48 |
| Mean (SD) | 0.00 (0.299) | -0.01 (0.485) | 0.22 (0.455) | 0.10 (0.480) |
| Median | 0.04 | -0.04 | 0.11 | 0.06 |
| Range | (-0.4; 0.4) | (-1.2; 0.8) | (-0.5; 1.7) | (-1.2; 1.7) |
| IQ range | (-0.25; 0.24) | (-0.35; 0.40) | (-0.06; 0.45) | (-0.15; 0.42) |

| | | | | |
|---|---|---|---|---|
| BMI Z score | | | | |
| Change from baseline[b,c] | | | | |
| N | 18 | 36 | 40 | 76 |
| Mean (SD) | 0.16 (0.392) | 0.11 (0.561) | 0.25 (0.546) | 0.18 (0.553) |
| Median | 0.22 | 0.18 | 0.15 | 0.16 |
| Range | (-0.8; 0.7) | (-1.7; 1.3) | (-1.1; 1.8) | (-1.7; 1.8) |
| IQ range | (-0.10; 0.45) | (-0.28; 0.48) | (-0.13; 0.49) | (-0.15; 0.48) |
| Female | | | | |
| N | 10 | 12 | 16 | 28 |
| Mean (SD) | 0.21 (0.316) | 0.31 (0.342) | 0.26 (0.646) | 0.28 (0.529) |
| Median | 0.24 | 0.27 | 0.23 | 0.27 |
| Range | (-0.4; 0.6) | (-0.5; 0.8) | (-1.1; 1.8) | (-1.1; 1.8) |
| IQ range | (0.03; 0.45) | (0.18; 0.49) | (-0.09; 0.50) | (0.05; 0.49) |
| Male | | | | |
| N | 8 | 24 | 24 | 48 |
| Mean (SD) | 0.09 (0.486) | 0.01 (0.627) | 0.23 (0.482) | 0.12 (0.564) |
| Median | 0.19 | 0.01 | 0.12 | 0.09 |
| Range | (-0.8; 0.7) | (-1.7; 1.3) | (-0.4; 1.6) | (-1.7; 1.6) |
| IQ range | (-0.22; 0.44) | (-0.39; 0.44) | (-0.15; 0.49) | (-0.23; 0.46) |

Note: Baseline is defined as the last observation prior to or at the time of the first study intervention.
Note: Data from the time of substudy onward are not included.
[a] For CRD3004, clinical remission is defined as a PCDAI score ≤10 points. For CRD1001, 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 points.
[b] For CRD3004, ICEs include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6. For CRD1001, subjects who had a prohibited Crohn's disease-related surgery or discontinued study agent due to an AE of worsening CD or due to lack of efficacy or had prohibited concomitant medication changes had their baseline value carried forward.
[c] For CRD3004, ICEs strategies: Subjects that have ICEs 1-5, and 7 prior to Week M-44 are not considered to be in clinical remission at Week M-44 (ie. composite strategy). Subjects with ICE 6 prior to Week M-44 are considered to have missing clinical remission data from the time of the event onward (ie. hypothetical strategy). After accounting for the ICEs, subjects who have missing clinical remission data are considered not to be in clinical remission at Week M-44. Subjects that have ICEs 1-5, and 7 prior to a visit are considered to have no change from baseline for that endpoint at that visit and subsequent visit. Subjects with ICE 6 have their data assumed missing after the ICE 6 occurred. For CRD1001, missing values for subjects who had insufficient data at the designated analysis timepoint were not imputed.
[d] The confidence intervals are based on the Wilson statistic.
[e] For CRD3004, corticosteroid-free clinical remission is defined as PCDAI score ≤10 points and not receiving corticosteroids for at least 30 days prior to the visit. For CRD1001, corticosteroid-free clinical remission is defined as PCDAI score ≤10 points and not receiving corticosteroids 30 days prior to the visit during the LTE.
Adapted from [tefcomb01.rtf] [PROD/cnto1275/z_sce/dbr_2025_01/re_2025_01/tefcomb01.sas] 08APR2025, 01:53

**Endoscopic Response**

For CNTO1275CRD3004, endoscopic response was defined as a reduction from baseline in an SES-CD score ≥50% of, or an SES-CD score of ≤2, in participants with a baseline SES-CD score of ≥3. For CNTO1275CRD1001, endoscopic response was defined as a reduction from baseline in the SES-CD score of ≥50% in participants with a baseline SES-CD score of ≥3. Because it was anticipated that mucosal healing might not occur at Week I-8, the endpoint was measured 8 weeks later, at Week M-8/Week 16 instead of Week I-8/Week 8.

The majority of participants in both CNTO1275CRD3004 (94 of 97 participants) and CNTO1275CRD1001 (18 of 21 participants) had SES-CD scores ≥3 at baseline. At Week M-8/Week 16, 36.2% of participants in CNTO1275CRD3004 and 27.8% of participants in CNTO1275CRD1001 were in endoscopic response (Table 53).

**Table 53: Summary of subjects in Endoscopic response at Week M-44/Week 48 among subjects in CRD1001 and subjects in CRD3004; full analysis set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Full Analysis Set (Study CNTO1275CRD1001) Full Randomized Analysis Set (Study CNTO1275CRD3004) | 21 | 97 |
| Subjects with baseline SES-CD score ≥3 | 18 | 94 |
| Week M-8 (Week 16) | | |
| N | 18 | 94 |
| Subjects in endoscopic response[a1,a2,b1,b2] | 5 (27.8%) | 34 (36.2%) |
| 95% CI[c] | (12.5%, 50.9%) | (27.2%, 46.2%) |

[a1] For CRD3004, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3.
[a2] For CRD1001, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% in subjects with a baseline SES-CD score of ≥3.
[b1] For CRD3004, intercurrent events (ICEs) include: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4. ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 are considered to not have achieved the endpoint at Week M-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint.
[b2] For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint. Subjects with missing segments at the designated analysis timepoint had their baseline score for the missing segment(s) carried forward.
[c] The confidence intervals are based on the Wilson statistic.

**Health-related Quality of Life**

At Week M-44/Week 48, an overall clinically meaningful (using distribution-based methodology) improvement in IMPACT-III total scores was seen in both CNTO1275CRD3004 and CNTO1275CRD1001; these changes were similar across the studies (Table 54). Specifically, by treatment group, the mean (SD) changes from baseline were 20.4 (30.69) in the q8w treatment group in CNTO1275CRD3004 and 26.2 (24.07) in the q8w treatment group in CNTO1275CRD1001.

**Table 54: Summary of from baseline in IMAPCT-III scores at Week M-44/Week 48 among subjects in CRD1001 and subjects in CRD3004; full clinical set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**

| | Ustekinumab | | |
|---|---|---|---|
| | q8w | | q12w |
| | CRD1001 | CRD3004 | CRD3004 |
| Analysis set: Full Analysis Set | 44 | 48 | 49 |
| Subjects ≥10 years of age at Week I-0/Week 0 | 41 (93.2%) | 45 (93.8%) | 42 (85.7%) |
| Baseline[a] | | | |
| N | 36 | 38 | 36 |
| Mean (SD) | 108.0 (16.49) | 101.7 (23.37) | 102.8 (25.06) |
| Median | 103.5 | 100.0 | 102.0 |
| Range | (74; 144) | (53; 142) | (40; 143) |
| Week M-44/Week 48[b1,b2,c,d] | | | |
| N | 18 | 34 | 34 |
| Mean (SD) | 132.4 (22.70) | 120.9 (23.93) | 121.5 (27.61) |
| Median | 137.0 | 123.5 | 128.0 |
| Range | (85; 164) | (67; 161) | (40; 159) |
| Change from baseline[b1,b2,c,d] | | | |
| N | 18 | 31 | 32 |
| Mean (SD) | 26.2 (24.07) | 20.4 (30.69) | 15.7 (24.31) |
| Median | 31.0 | 0.0 | 0.0 |
| Range | (-29; 62) | (0; 96) | (-10; 87) |

[a] Baseline is defined as the last observation prior to or at the time of the first study intervention.
[b1] For CRD3004, intercurrent events (ICEs) include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6. ICEs strategies: Subjects who had ICEs 1-5, and 7 prior to a visit are considered to have no change from baseline for that endpoint at that visit and subsequent visit. Subjects with ICE 6 have their data assumed missing after the ICE 6 occurred.
[b2] For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, or discontinued study agent due to an AE of worsening CD or due to lack of efficacy, or had prohibited concomitant medication changes had their baseline value carried forward. Missing values for subjects who had insufficient data at the designated analysis timepoint were not imputed.
[c] The endpoint was measured at Week M-44 (Week 52) for the CRD3004 study and at Week 48 for the CRD1001 study.
Note: For CRD1001, subjects who entered the long-term extension study were included.
Note: N at baseline and at a postbaseline timepoint is the number of subjects with a non-missing value at the specified time point. N for change from baseline is the number of subjects with non-missing values at both baseline and the postbaseline time point.

**Supplementary Analyses of Efficacy Endpoints Using PCDAI Diary Data**

Clinical remission and clinical response in paediatric participants with CD were also evaluated using daily PCDAI diary data. Instead of a recall period of 1 week, participants used a take-home electronic diary to prospectively record stool frequency, abdominal pain, and general well-being symptoms during the 7 days prior to the scheduled visits. Of note, the home electronic diary devices used in each study were different, thus limiting the interpretation of the comparisons of PCDAI diary data between the 2 paediatric studies.

At Week I-8/Week 8, 37 (36.6%) of 101 participants in CNTO1275CRD3004 and 5 (23.8%) of 21 participants in CNTO1275CRD1001 achieved clinical remission (PCDAI score of ≤10 points) using daily PCDAI diary data. Clinical response was achieved by 69 (68.3%) participants and 11 (52.4%) participants in CNTO1275CRD3004 and CNTO1275CRD1001, respectively (Table 55).

At Week M-44, the proportions of participants in the q8w treatment group who achieved clinical remission and clinical response using daily diary data were numerically higher in CNTO1275CRD1001 (13 [59.1%] and 16 [72.7%] of 22 participants, respectively) than the proportion of participants in the q8w treatment group who achieved clinical remission and clinical response in CNTO1275CRD3004 (18 [43.9%] and (21 [51.2%] of 44 participants, respectively); however, all CIs overlapped.

**Table 55: Number of patients in key efficacy endpoints using PCDAI score at Week I-8 (Week 8) among subjects receiving higher induction ustekinumab IV in CRD1001 and subjects in CRD3004; full analysis set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**

| | Ustekinumab | | |
|---|---|---|---|
| | CRD1001 Diary Data | CRD3004 Diary Data | CRD3004 Recall Data |
| Analysis set: Full Analysis Set | 21 | 101 | 101 |
| Week I-8 (Week 8) | | | |
| PCDAI Score Change from Baseline | | | |
| N | 20 | 93 | 100 |
| Mean (SD) | -19.75 (15.995) | -22.40 (13.614) | -27.08 (13.442) |
| Median | -16.25 | -22.10 | -27.50 |
| Range | (-50.0; 5.0) | (-51.3; 0.4) | (-52.5; 5.0) |
| IQ range | (-31.25; -7.50) | (-33.40; -11.50) | (-36.25; -18.75) |
| N | 21 | 101 | 101 |
| Subjects in clinical remission[a1,b1,b2] | 5 (23.8%) | 37 (36.6%) | 47 (46.5%) |
| 95% CI[c] | (10.6%, 45.1%) | (27.9%, 46.4%) | (37.1%, 56.2%) |
| N | 21 | 101 | 101 |
| Subjects in clinical response[a2,b1,b2] | 11 (52.4%) | 69 (68.3%) | 85 (84.2%) |
| 95% CI[c] | (32.4%, 71.7%) | (58.7%, 76.6%) | (75.8%, 90.0%) |

[a1] Clinical remission is defined as a PCDAI score ≤10 points.
[a2] 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 points.
[b1] For CRD3004, intercurrent events (ICEs) include: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4. ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 were not considered to have achieved the endpoint at Week I-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint.
[b2] For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint. Subjects who had insufficient data to calculate the PCDAI score at a visit are considered to not have achieved the endpoint.
[c] The confidence intervals are based on the Wilson statistic.
[tefkey01a.rtf] [PROD/cnto1275/z_sce/dbr_2025_01/re_2025_01/tefkey01a.sas] 08APR2025, 01:53

**Subpopulation Efficacy**

**Age**

In CNTO1275CRD3004, participants ranged in age from 2 to 17 years. A total of 2 (2.0%) of 101 participants were aged 2 to 6 years, 18 (17.8%) were between 6 and 11 years old, and the majority (80.2%) were aged 12 to 17 years. Overall, there were no major differences in the proportions of participants who achieved clinical response and clinical remission in induction and maintenance across the age subgroups (2 to 11 years and 12 to 17 years) with the exception of the following:

- A numerically higher proportion of participants in the younger age subgroup (14 [70.0%] of 20 participants; 95% CI: 48.1%, 85.5%) versus the older age subgroup (32 [39.5%] of 81

participants; 95% CI: 29.6%, 50.4%) achieved clinical remission at Week I-6; however, the CIs overlapped.

- Similarly, a numerically higher proportion of participants in the younger age subgroup (13 [65.0%] participants; 95% CI: 43.3%, 81.9%) versus the older age subgroup (34 [42.0%] participants; 95% CI: 31.8%, 52.8%) achieved clinical remission at Week I-8; however, the CIs overlapped.

During the maintenance period, generally similar trends were observed between the 2 to 11 years and 12 to 17 years of age subgroups.

Additionally, the number of paediatric participants in the 2 to 11 years age group in CNTO1275CRD1001 was very small (n=4) limiting comparisons with the 12 to 17 years age group.

**Sex**

Overall, there were no remarkable differences in the proportions of participants who achieved clinical response and clinical remission in induction and maintenance between sexes in CNTO1275CRD3004 and CNTO1275CRD1001.

**Body Weight**

A summary of key clinical endpoints by body weight for both paediatric studies for Week I-8/Week 8 and Week M-44/Week 48 are presented in Table 56. Overall, there were no remarkable differences in the proportions of participants who achieved clinical remission and clinical response in induction and maintenance among body weight groups in CNTO1275CRD3004 and CNTO1275CRD1001. In CNTO1275CRD3004, body weight ranged from 13 kg to 88 kg, with approximately one-quarter of the participants weighing <40 kg. This subgroup included 11 participants (10.9%) who weighed less than 30 kg.

In CNTO1275CRD3004, the proportions of participants ≥40 kg who achieved clinical remission and clinical response in the final analysis were similar to those reported in the interim analysis.

**Table 56: Number of key efficacy endpoints by weight group among subjects receiving higher induction ustekinumab IV in CRD1001 and subjects in CRD3004; full analysis set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Full Analysis Set | 21 | 101 |
| Weight Group | | |
| <30 kg | | |
| Week I-8 (Week 8) | | |
| N | 5 | 11 |
| Subjects in clinical remission[a1,b1,b2] | 2 (40.0%) | 6 (54.5%) |
| 95% CI[c] | (11.8%, 76.9%) | (28.0%, 78.7%) |
| N | 5 | 11 |
| Subjects in clinical response[a2,b1,b2] | 3 (60.0%) | 9 (81.8%) |
| 95% CI[c] | (23.1%, 88.2%) | (52.3%, 94.9%) |
| Week M-8 (Week 16) | | |
| Subjects with a baseline SES-CD score ≥3 | 5 | 11 |
| N | 5 | 11 |
| Subjects in endoscopic response as assessed by SES-CD[a3,b1,b2] | 0 | 6 (54.5%) |
| 95% CI[c] | (0.0%, 43.4%) | (28.0%, 78.7%) |
| >=30 - <40 kg | | |
| Week I-8 (Week 8) | | |
| N | 3 | 18 |
| Subjects in clinical remission[a1,b1,b2] | 0 | 5 (27.8%) |
| 95% CI[c] | (0.0%, 56.1%) | (12.5%, 50.9%) |
| N | 3 | 18 |
| Subjects in clinical response[a2,b1,b2] | 1 (33.3%) | 12 (66.7%) |
| 95% CI[c] | (6.1%, 79.2%) | (43.7%, 83.7%) |
| Week M-8 (Week 16) | | |
| Subjects with a baseline SES-CD score ≥3 | 3 | 15 |
| N | 3 | 15 |
| Subjects in endoscopic response as assessed by SES-CD[a3,b1,b2] | 0 | 6 (40.0%) |
| 95% CI[c] | (0.0%, 56.1%) | (19.8%, 64.3%) |
| <40 kg | | |
| Week I-8 (Week 8) | | |
| N | 8 | 29 |
| Subjects in clinical remission[a1,b1,b2] | 2 (25.0%) | 11 (37.9%) |
| 95% CI[c] | (7.1%, 59.1%) | (22.7%, 56.0%) |
| N | 8 | 29 |
| Subjects in clinical response[a2,b1,b2] | 4 (50.0%) | 21 (72.4%) |
| 95% CI[c] | (21.5%, 78.5%) | (54.3%, 85.3%) |
| Week M-8 (Week 16) | | |
| Subjects with a baseline SES-CD score ≥3 | 8 | 26 |
| N | 8 | 26 |
| Subjects in endoscopic response as assessed by SES-CD[a3,b1,b2] | 0 | 12 (46.2%) |
| 95% CI[c] | (0.0%, 32.4%) | (28.8%, 64.5%) |

| | | |
|---|---|---|
| >=40 kg | | |
| Week I-8 (Week 8) | | |
| N | 13 | 72 |
| Subjects in clinical remission[a1,b1,b2] | 3 (23.1%) | 36 (50.0%) |
| 95% CI[c] | (8.2%, 50.3%) | (38.7%, 61.3%) |
| N | 13 | 72 |
| Subjects in clinical response[a2,b1,b2] | 7 (53.8%) | 64 (88.9%) |
| 95% CI[c] | (29.1%, 76.8%) | (79.6%, 94.3%) |
| Week M-8 (Week 16) | | |
| Subjects with a baseline SES-CD score ≥3 | 10 | 68 |
| N | 10 | 68 |
| Subjects in endoscopic response as assessed by SES-CD[a3,b1,b2] | 5 (50.0%) | 22 (32.4%) |
| 95% CI[c] | (23.7%, 76.3%) | (22.4%, 44.2%) |

[a1] Clinical remission is defined as a PCDAI score ≤10 points.
[a2] 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 points.
[a3] For CRD3004, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3. For CRD1001, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% in subjects with a baseline SES-CD score of ≥3.
[b1] For CRD3004, intercurrent events (ICEs) include: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4. ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 were not considered to have achieved the endpoint at Week I-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint.
[b2] For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint. Subjects who had insufficient data to calculate the PCDAI score at a visit are considered to not have achieved the endpoint.
[c] The confidence intervals are based on the Wilson statistic.
Note: Ns of subjects with a baseline SES-CD score ≥3 was selected from full analysis set in CNTO1275CRD1001 and full randomized analysis set in CNTO1275CRD3004.

**Prior Biologic Failure Status**

**Induction (at Week I-8/Week 8)**

Numerically higher proportions of participants in the non-biologic failure groups in CNTO1275CRD3004 and CNTO1275CRD1001 were in clinical remission and clinical response versus those in the biologic failure subgroup (Table 57). For the biologic failure subgroup:

- At Week I-8/Week 8, similar proportions of participants in CNTO1275CRD3004 (31.6%) and CNTO1275CRD1001 (21.1%) were in clinical remission. A greater proportion of participants were in clinical response in CNTO1275CRD3004 (78.9%) versus CNTO1275CRD1001 (52.6%); however, the CIs overlapped.
- At Week M-8 (Week 16), 34.0% and 25.0% of participants in CNTO1275CRD3004 and CNTO1275CRD1001, respectively, were in endoscopic response as assessed by SES-CD.

For the non-biologic failure subgroups, the small sample size in CNTO12751001 (n=2) limited comparisons with CNTO1275CRD3004.

**Table 57: Number of subjects in key efficacy endpoints by prior biologic failure status among subjects receiving higher induction ustekinumab IV in CRD1001 and subjects in CRD3004; full analysis set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Full Analysis Set | 21 | 101 |
| Prior biologic failure status | | |
| Biologic failure | | |
| Week I-8 (Week 8) | | |
| N | 19 | 57 |
| Subjects in clinical remission[a1,b1,b2] | 4 (21.1%) | 18 (31.6%) |
| 95% CI[c] | (8.5%, 43.3%) | (21.0%, 44.5%) |
| N | 19 | 57 |
| Subjects in clinical response[a2,b1,b2] | 10 (52.6%) | 45 (78.9%) |
| 95% CI[c] | (31.7%, 72.7%) | (66.7%, 87.5%) |
| Week M-8 (Week 16) | | |
| Subjects with a baseline SES-CD score ≥3 | 16 | 53 |
| N | 16 | 53 |
| Subjects in endoscopic response as assessed by SES-CD[a3,b1,b2] | 4 (25.0%) | 18 (34.0%) |
| 95% CI[c] | (10.2%, 49.5%) | (22.7%, 47.4%) |
| Non Biologic failure | | |
| Week I-8 (Week 8) | | |
| N | 2 | 44 |
| Subjects in clinical remission[a1,b1,b2] | 1 (50.0%) | 29 (65.9%) |
| 95% CI[c] | (9.5%, 90.5%) | (51.1%, 78.1%) |
| N | 2 | 44 |
| Subjects in clinical response[a2,b1,b2] | 1 (50.0%) | 40 (90.9%) |
| 95% CI[c] | (9.5%, 90.5%) | (78.8%, 96.4%) |
| Week M-8 (Week 16) | | |
| Subjects with a baseline SES-CD score ≥3 | 2 | 41 |
| N | 2 | 41 |
| Subjects in endoscopic response as assessed by SES-CD[a3,b1,b2] | 1 (50.0%) | 16 (39.0%) |
| 95% CI[c] | (9.5%, 90.5%) | (25.7%, 54.3%) |

[a1] Clinical remission is defined as a PCDAI score ≤10 points.
[a2] 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 points.
[a3] For CRD3004, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3. For CRD1001, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% in subjects with a baseline SES-CD score of ≥3.
[b1] For CRD3004, intercurrent events (ICEs) include: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4. ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 were not considered to have achieved the endpoint at Week I-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint.

[b2] For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint. Subjects who had insufficient data to calculate the PCDAI score at a visit are considered to not have achieved the endpoint.
[c] The confidence intervals are based on the Wilson statistic.
Note: Ns of subjects with a baseline SES-CD score ≥3 was selected from full analysis set in CNTO1275CRD1001 and full randomized analysis set in CNTO1275CRD3004.

**Maintenance (Through Week M-44/Week 48)**

At Week M-44/Week 48:

- In both paediatric studies, numerically greater proportions of participants in the nonbiologic failure group were in clinical remission, clinical response, and corticosteroid-free clinical remission than the proportions in the biologic failure subgroup.
- For the biologic failure subgroup, among participants who received the q8w dose regimen.
- Numerically lower proportions of participants in CNTO1275CRD3004 were in clinical remission, clinical response, and corticosteroid-free clinical remission (9 [36.0%], 12 [48.0%], and 8 [32.0%] of 25 participants, respectively) than in CNTO1275CRD1001 (11 [55.0%], 14 [70.0%], and 10 [50.0%] of 20 participants, respectively); however, the CIs overlapped.
- Among the participants in the CNTO1275CRD3004 and CNTO1275CRD1001 who were in clinical remission at Week I-8/Week 8, a numerically lower proportion of participants in CTNO1275CRD3004 were in clinical remission at Week M-44/Week 48 compared with CNTO1275CRD1001 (6 [60.0%] of 10 participants vs 7 [87.5%] of 8 participants); however, the CIs overlapped.

For the non-biologic failure subgroup, the small sample size in CNTO12751001 (n=2) prevented meaningful comparisons with CNTO1275CRD3004.

**Relationship Between Efficacy and Pharmacokinetics**

The relationship between serum ustekinumab concentrations and efficacy outcomes were assessed using pooled data from CNTO1275CRD1001 and CNTO1275CRD3004. For short-term efficacy-PK assessments, observed serum ustekinumab concentrations at Week I-8 and Week M-8 participants were categorised into 4 groups based on the respective ustekinumab concentration quartiles at these timepoints, and the proportions of participants achieving efficacy outcomes in each quartile subgroup were summarised. For long-term efficacy-PK assessment, the average steady-state serum ustekinumab concentrations were categorised into 4 groups based on the ustekinumab concentration quartiles and the proportions of participants achieving efficacy outcomes at Week M-44 in each quartile subgroup were summarised. The efficacy and PK assessments were also performed by the respective median ustekinumab concentration subgroups.

***Induction (through Week I-8)***

**Week I-8**

In the pooled CNTO1275CRD1001 and CNTO1275CRD3004 paediatric studies, the proportions of participants who achieved clinical remission or clinical response at Week I-8 were higher in the top 2 ustekinumab concentration quartile subgroups compared with the other quartile subgroups. Median improvement in PCDAI score at Week I-8 tended to increase with increasing serum concentration. When assessed by the median ustekinumab concentration at Week I-8, the proportions of participants in clinical remission or clinical response at Week I-8 were higher among those with ustekinumab concentrations greater or equal to the median compared with those who had concentrations less than the median. Age and weight had no clear effect on the E-R relationship for clinical remission at Week I-8 in paediatric participants.

**Week M-8**

In the pooled CNTO1275CRD3004 and CNTO1275CRD1001 paediatric studies and across both maintenance treatment groups, the proportion of participants in clinical response or endoscopic response at Week M-8 was lower in the lowest ustekinumab concentration subgroup compared to the other quartile

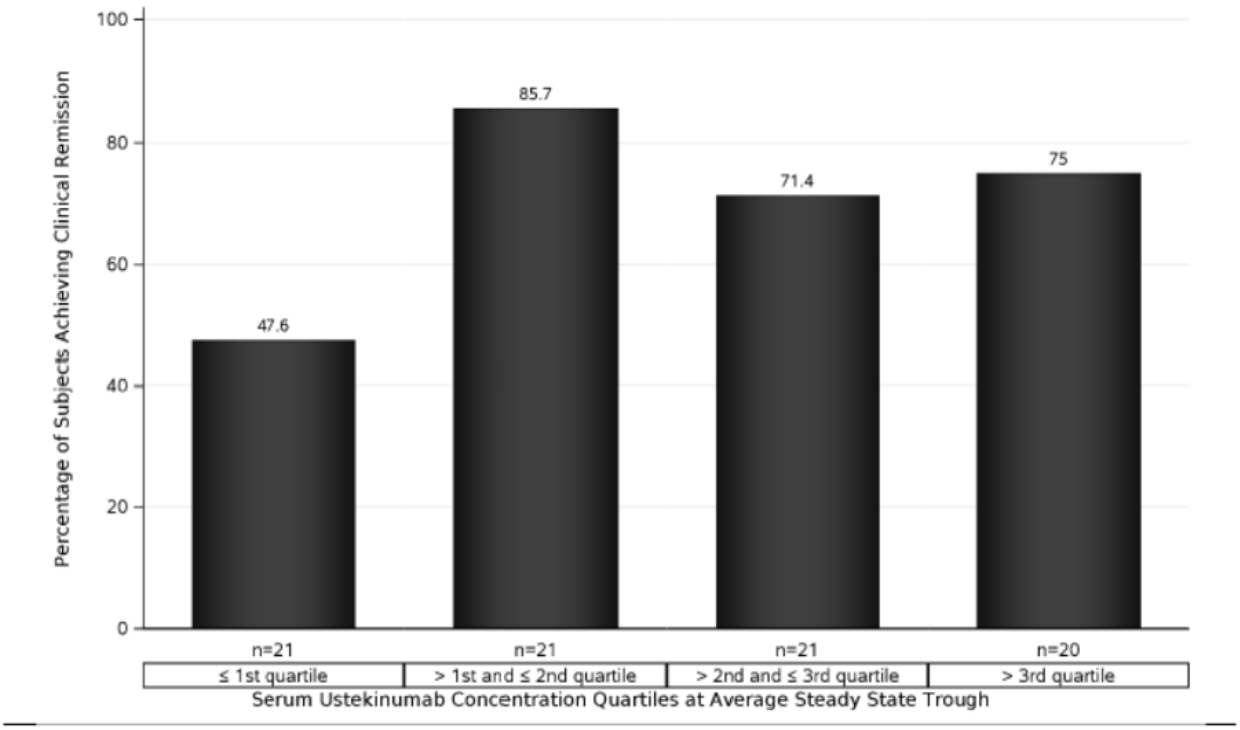
subgroups. Median improvement in PCDAI scores at Week M-8 tended to increase with increasing serum concentration. When assessed by the median ustekinumab concentration at Week M-8, the proportions of participants in clinical response or endoscopic response at Week M-8 were higher among those with ustekinumab concentrations greater or equal to the median compared to those with concentrations less than the median.

**Maintenance (through Week M-44/Week 48)**

In the pooled CNTO1275CRD3004 and CNTO1275CRD1001 paediatric studies and across both maintenance treatment groups, the proportions of participants in clinical remission or clinical response at Week M-44/Week 48 were lower in the lowest ustekinumab concentration subgroup compared to the other quartile subgroups (Figure 41, Table 58). A similar pattern was observed for median improvement in PCDAI at Week M-44/Week 48. When assessed by the median average trough ustekinumab concentration, the proportions of participants in clinical remission or clinical response at Week M-44/Week 48 were numerically higher among those with ustekinumab concentrations greater or equal to the median compared to those with concentrations less than the median.

Age and weight had no clear effect on the E-R relationship for clinical remission at Week M-44 in paediatric participants who were in clinical response at Week I-8 from CNTO1275CRD3004.

**Figure 41: Bar chart of percentage of subjects achieving clinical remission at Week M-44/Week 48 by serum ustekinumab concentration quartiles at average steady state through; PK Clinical Responder analysis set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**



1st quartile=0.41 µg/mL, 2nd quartile=1.21 µg/mL, 3rd quartile=2.15 µg/mL.
Key: n = number of subjects with data.
Note: Clinical remission is defined as PCDAI score ≤10 points.
Note: For CRD3004, intercurrent events (ICEs) include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6. ICEs strategies: Subjects who had ICEs 1-5, and 7 prior to the specified timepoint are considered to not have achieved the endpoint at that timepoint (ie. composite strategy). Subjects with ICE 6 prior to the specified timepoint are considered to have missing endpoint data from the time of the event onward (ie. hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint. For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's Disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint. Subjects who had insufficient data to calculate the PCDAI score at a visit are considered to not have achieved the endpoint.
Note: Subjects in CRD3004 study who dose adjusted are counted in the treatment group they were randomized to at Week M-0, and their data from the time of dose adjustment or substudy onward are not included.
Note: Quartiles are calculated based on ustekinumab concentration at steady state visits for all subjects from CRD3004 and CRD1001 regardless of the induction dosing received. In case of q8w, trough serum ustekinumab concentrations at Week M-24 (Week 32) and Week M-32 (Week 40) are averaged. In case of q12w, trough serum ustekinumab concentrations at Week M-24 and Week M-36 are averaged.

**Table 58: Summary of key efficacy endpoints at Week M-44/Week 48 by average steady state through serum ustekinumab concentration quartiles; PK Clinical Responder analysis set (Studies CNTO1275CRD1001 and Study CNTO1275CRD3004)**

| | Pooled CRD1001 and CRD3004 | | | |
|---|---|---|---|---|
| | Ustekinumab Concentrations at Average Steady State Trough | | | |
| | ≤1st Quartile | >1st Quartile and ≤2nd Quartile | >2nd Quartile and ≤3rd Quartile | >3rd Quartile |
| Analysis set: PK Clinical Responder Analysis Set | 21 | 21 | 21 | 20 |
| Efficacy endpoints at Week M-44/Week 48 | | | | |
| N | 21 | 21 | 21 | 20 |
| Clinical remission at Week M-44/Week 48[a] | 10 (47.6%) | 18 (85.7%) | 15 (71.4%) | 15 (75.0%) |
| Clinical response at Week M-44/Week 48[b] | 14 (66.7%) | 18 (85.7%) | 17 (81.0%) | 17 (85.0%) |

1st quartile=0.41 µg/mL, 2nd quartile=1.21 µg/mL, 3rd quartile=2.15 µg/mL.
[a] Clinical remission is defined as PCDAI score ≤10 points.
[b] 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.
[a,b] For CRD3004, intercurrent events (ICEs) include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6. ICEs strategies: Subjects who had ICEs 1-5, and 7 prior to the specified timepoint are considered to not have achieved the endpoint at that timepoint (ie. composite strategy). Subjects with ICE 6 prior to the specified timepoint are considered to have missing endpoint data from the time of the event onward (ie. hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint. For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's Disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint. Subjects who had insufficient data to calculate the PCDAI score at a visit are considered to not have achieved the endpoint.
Note: Subjects in CRD3004 study who dose adjusted are counted in the treatment group they were randomized to at Week M-0, and their data from the time of dose adjustment or substudy onward are not included.
Note: Quartiles are calculated based on average steady state trough ustekinumab concentration for all subjects in CRD1001 and CRD3004 receiving the q8w or q12w maintenance dosing regardless of the induction dosing. In case of q8w, trough serum ustekinumab concentrations at Week M-24 (Week 32) and Week M-32 (Week 40) are averaged. In case of q12w, trough serum ustekinumab concentrations at Week M-24 and Week M-36 are averaged.

**Relationship Between Efficacy and Immunogenicity**

Using a drug-tolerant assay, the incidence of antibodies to ustekinumab was low during induction and maintenance treatment with ustekinumab. Due to the limited number of participants who were positive for antibodies through Week M44/Week 48 across CNTO1275CRD3004 and CNTO1275CRD1001, no analysis could be made regarding the relationship between antibodies to ustekinumab and efficacy.

***Comparison of studies CRD3004 and adult studies***

Three previously reviewed adult studies for CD are used to support the paediatric extrapolation of ustekinumab. These are:

- CRD3001 (biologic failure participants) - UNITI-1 (NCT01369329) was an 8-week IV induction trial of ustekinumab in participants with moderately to severely active Crohn's disease who failed or were intolerant to TNF$\alpha$ antagonist therapy.
- CRD3002 (conventional medication failure participants) - UNITI-2 (NCT01369342) was an 8-week IV induction trial of ustekinumab in participants with moderately to active Crohn's disease who were anti-TNFα-naïve.
- CRD3003 - IM-UNITI (NCT01369355) was a 44-week maintenance trial of subcutaneous ustekinumab, enrolling participants from UNITI-1 and UNITI-2 who had a clinical response to IV ustekinumab induction.

All comparisons are descriptive only without formal statistical testing. Efficacy results for the ustekinumab IV induction group in the CNTO1275CRD3004 paediatric study were compared descriptively side by side with the 6 mg/kg induction dose utilised in the CNTO1275CRD3001 (anti-TNF therapy failure population) and CNTO1275CRD3002 (conventional treatment failure population) adult induction studies. Additionally, the ustekinumab SC maintenance dose regimens from CNTO1275CRD3004 were compared descriptively with the 90 mg SC maintenance dose regimens in the CNTO1275CRD3003 adult maintenance study. The key efficacy results reported for clinical remission and clinical response were derived from PCDAI scores for participants from CNTO1275CRD3004 and from CDAI scores for participants from the adult Phase 3 CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 studies.

**Baseline Crohn's Disease Characteristics**

Baseline clinical disease characteristics for paediatric participants enrolled in CNTO1275CRD3004 and the 2 pivotal adult Phase 3 studies (CNTO1275CRD3001 and CNTO1275CRD3002) are presented inTable 59. Other than expected differences (eg, notable longer duration of disease in the adult studies) populations were similar except for a numerically higher median CDAI score (353.83) and a numerically higher mean (SD) and median fecal calprotectin concentration in the paediatric CNTO1275CRD3004 study compared with the adult studies, with a greater proportion of participants who had abnormal fecal calprotectin (>250 mg/kg; >90% for both treatment groups) in CNTO1275CRD3004 than in CNTO1275CRD3001 and CNTO1275CRD3002.

**Table 59: Summary of Crohn's disease characteristics across paediatric and adult ustekinumab studies among subjects in CRD3004 and 6 mg/kg ustekinumab group in CRD3001 and CRD3002; Randomised Analysis Set (studies CNTO1275CRD3004, CNTO1275CRD3001, CNTO1275CRD3002)**

| | Pediatric | | | Adult | |
|---|---|---|---|---|---|
| | CRD3004 | | | CRD3001 | CRD3002 |
| | q12w | q8w | Total | Total (6 mg/kg) | Total (6 mg/kg) |
| Total N[a] | 49 | 48 | 97 | 249 | 209 |
| Crohn's Disease Duration (years) | | | | | |
| Mean (SD) | 2.8 (2.51) | 2.6 (1.98) | 2.7 (2.26) | 12.69 (9.246) | 8.68 (8.436) |
| Median | 2.2 | 2.0 | 2.1 | 10.97 | 6.21 |
| CDAI score | | | | | |
| Mean (SD) | 371.50 (105.687) | 359.44 (135.924) | 365.75 (120.236) | 327.6 (62.02) | 302.2 (58.85) |
| Median | 359.22 | 340.00 | 353.83 | 319.0 | 286.0 |
| PCDAI score | | | | | |
| Mean (SD) | 41.48 (7.822) | 40.99 (7.714) | 41.24 (7.732) | NA | NA |
| Median | 40.00 | 40.00 | 40.00 | NA | NA |
| C-reactive protein (CRP), mg/L | | | | | |
| Mean (SD) | 20.45 (26.931) | 18.17 (25.530) | 19.32 (26.136) | 19.50 (25.347) | 17.52 (24.139) |
| Median | 9.10 | 8.05 | 8.30 | 9.93 | 7.82 |
| Abnormal CRP (>3 mg/kg) | 36 (73.5%) | 34 (70.8%) | 70 (72.2%) | 197 (79.1%) | 165 (78.9%) |
| Fecal Calprotectin, mg/kg | | | | | |
| Mean (SD) | 2776.2 (2780.65) | 2818.8 (3577.02) | 2796.9 (3173.96) | 963.03 (1364.250) | 784.20 (1080.701) |
| Median | 1839.0 | 1883.5 | 1839.0 | 530.15 | 523.23 |
| Abnormal Fecal Calprotectin (>250 mg/kg) | 47 (95.9%) | 42 (91.3%) | 89 (93.7%) | 158 (63.5%) | 135 (64.6%) |

[a] For CRD3004, randomized subjects in full analysis set were summarized. For CRD3001 and CRD3002, randomized subjects excluding those enrolled prior to study re-start were summarized.

**Concomitant Medications for Crohn's Disease**

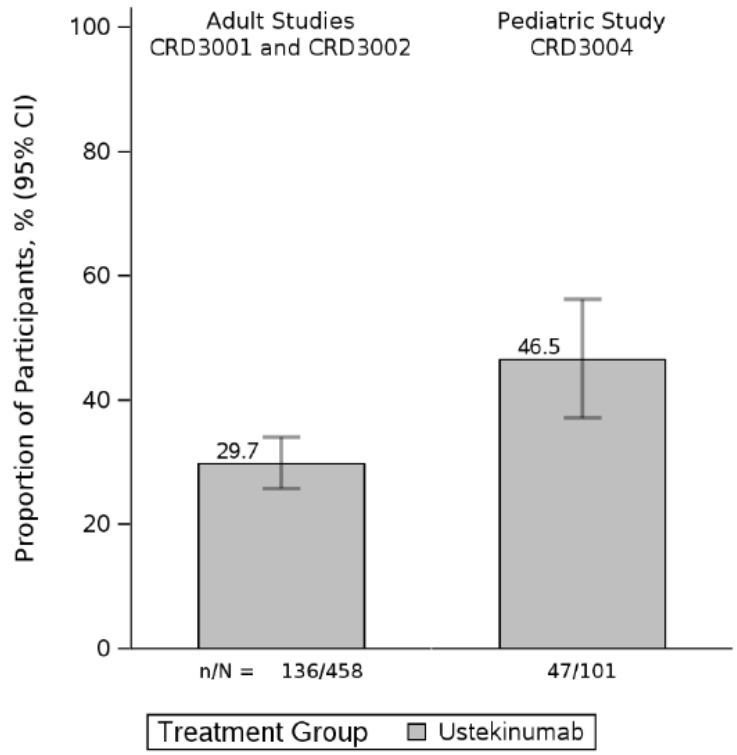
In the CNTO1275CRD3004 paediatric study and the CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 adult studies, a majority (>70%) of participants received 1 or more concomitant medications for CD (eg, corticosteroids [including budesonide and beclomethasone dipropionate], immunomodulators, and/or 5-ASA). In CNTO1275CRD3004, a total of 57 (56.4%) of 101 participants had a history of biologic failure. Enrollment criteria for CNTO1275CRD3001 included a history of biofailure. However, participants may have been categorised initially as a biofailure without definitive documentation, in which case they were subsequently reclassified as a conventional failure. A total of 246 (98.8%) of 249 participants in the 6 mg/kg treatment group in CNTO1275CRD3001 had a history of biologic failure (inadequate initial response, LOR, or intolerance to TNF antagonists). In CNTO1275CRD3002, 65 (100.0%) of 65 participants who received prior TNF antagonist therapy in the 6 mg/kg treatment group had no demonstrated biofailure. While nearly all participants in CNTO1275CRD3001 had a history of biologic failure, and those in CNTO1275CRD3002 did not, the proportion of participants in the adult studies with a prior history of biologic failure combined in the maintenance CNTO1275CRD3003 study (178 [44.8%] of 397 participants) was similar to the CNTO1275CRD3004 paediatric study.

**Efficacy Results - Induction (through Week I-8)**

At Week I-8, ustekinumab induction therapy given to paediatric participants induced a higher proportion of participants who achieved PCDAI clinical remission compared with that of the corresponding CDAI

endpoint in the adult Phase 3 induction studies CNTO1275CRD3001 (TNF failure) and CNTO1275CRD3002 (conventional treatment failure) on IV ustekinumab 6 mg/kg combined (29.7% of adult participants combined; 18.5% of participants in CNTO1275CRD3001 and 34.9% of participants in CNTO1275CRD3002) (Figure 42).

**Figure 42: Primary endpoint, Clinical remission at Week I-8: Studies CNTO1275CRD3004, CNTO1275CRD3001, CNTO1275CRD3002; Full Analysis Set (Study CNTO1275CRD3004)**




**Other Key Induction Efficacy Endpoints**

Overall, the proportions of participants who achieved clinical remission and clinical response were numerically higher after induction in the paediatric CNTO1275CRD3004 study than the corresponding endpoints in the Phase 3 CNTO1275CRD3001 and CNTO1275CRD3002 adult induction studies of ustekinumab at Week I-8/Week 8 (Figure 43 and Table 60). Changes in inflammatory biomarkers (CRP and fecal calprotectin) reflected improvement in both the paediatric and adult populations.

**Clinical Remission**

- Induction therapy given to paediatric participants in CNTO1275CRD3004 induced PCDAI clinical remission in a higher proportion of participants at Week I-6 (45.5% of participants) than participants who achieved CDAI clinical remission at Week 6 in CNTO1275CRD3001 (18.5% of participants) and in CNTO1275CRD3002 (34.9% of participants).

**Clinical Response**

- The proportions of paediatric participants in CNTO1275CRD3004 who achieved PCDAI clinical response at Week I-6 and Week I-8 (89.1% and 84.2% of participants, respectively) were numerically higher than in adults in CNTO1275CRD3001 (33.7% and 37.8% of participants, respectively) and CNTO1275CRD3002 (55.5% and 57.9% of participants, respectively).

**Reduction in Markers of Inflammation**

- The mean changes from baseline in CRP reflected improvement in both paediatric and adult studies.
- The mean changes from baseline in fecal calprotectin reflected improvement in intestinal inflammation in both paediatric and adult studies. However, the magnitude of change was higher in the paediatric study.

**Figure 43: Global descriptive comparison of secondary efficacy endpoints among the paediatric and adult studies on ustekinumab during the induction period; Full Analysis Set (Study CNTO1275CRD3004, CNTO1275CRD3001 and CNTO1275CRD3002)**

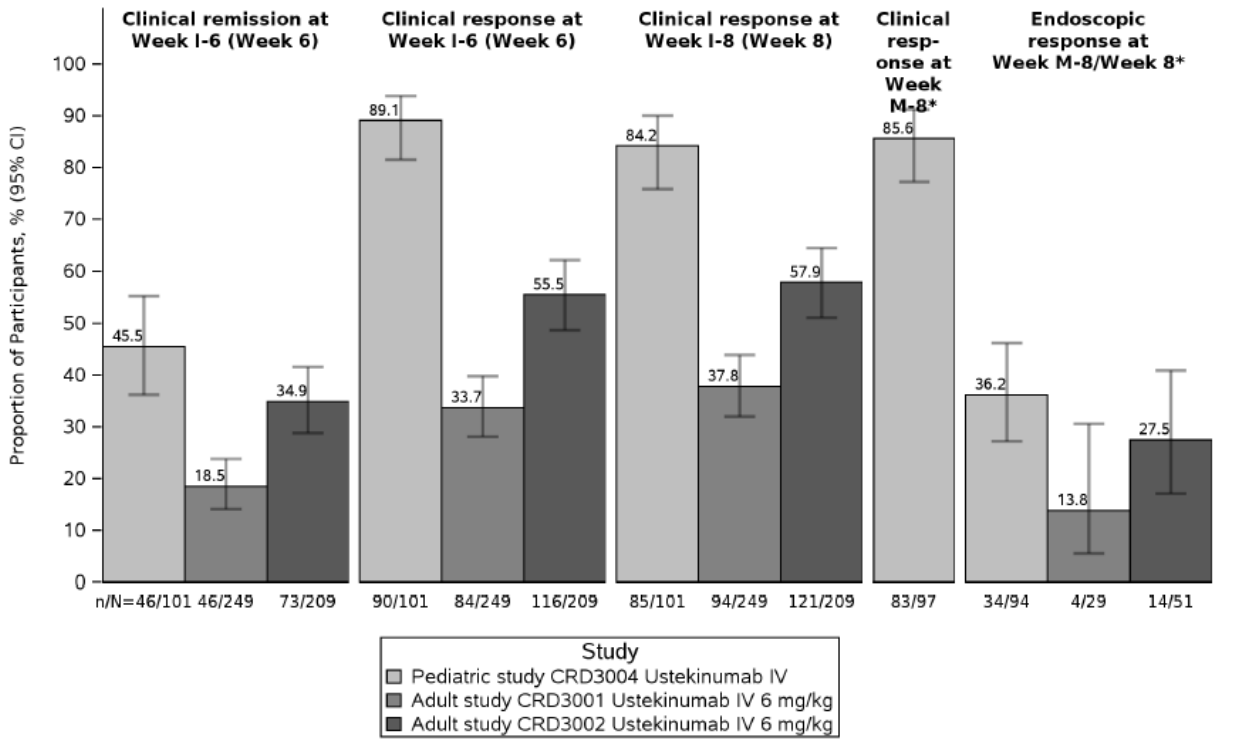


**Table 60: Descriptive comparison of secondary endpoints and key efficacy endpoints among the paediatric and adult studies on ustekinumab during the induction period; Full Analysis Set (Study CNTO1275CRD3004, CNTO1275CRD3001 and CNTO1275CRD3002)**

| | Pediatric | Adult | |
|---|---|---|---|
| | CRD3004 | CRD3001 6 mg/kg | CRD3002 6 mg/kg |
| Analysis Set[a] | 101 | 249 | 209 |
| Clinical Remission[b] | | | |
| Week I-6 (Week 6) | | | |
| N | 46 (45.5%) | 46 (18.5%) | 73 (34.9%) |
| 95% CI | (36.2%, 55.2%) | (14.1%, 23.8%) | (28.8%, 41.6%) |
| Week I-8 (Week 8) | | | |
| N | 47 (46.5%) | 52 (20.9%) | 84 (40.2%) |
| 95% CI | (37.1%, 56.2%) | (16.3%, 26.4%) | (33.8%, 47.0%) |
| Clinical Response[c] | | | |
| Week I-6 (Week 6) | | | |
| N | 90 (89.1%) | 84 (33.7%) | 116 (55.5%) |
| 95% CI | (81.5%, 93.8%) | (28.1%, 39.8%) | (48.7%, 62.1%) |
| Week I-8 (Week 8) | | | |
| N | 85 (84.2%) | 94 (37.8%) | 121 (57.9%) |
| 95% CI | (75.8%, 90.0%) | (32.0%, 43.9%) | (51.1%, 64.4%) |
| Week M-8 | | | |
| N | 83 (85.6%) | - | - |
| 95% CI | (77.2%, 91.2%) | | |
| Subjects with a baseline SES-CD score ≥3 | 94 | 29 | 51 |
| Week M-8/Week 8 | | | |
| N | 94 | 29 | 51 |
| Subjects in endoscopic response as assessed by SES-CD[d] | 34 (36.2%) | 4 (13.8%) | 14 (27.5%) |
| 95% CI | (27.2%, 46.2%) | (5.5%, 30.6%) | (17.1%, 40.9%) |
| Change in CRP from baseline at Week I-8 (Week 8), mg/L | | | |
| N | 98 | 249 | 209 |
| Mean (SD) | -8.71 (20.626) | -5.55 (20.518) | -8.56 (19.596) |
| Median | -2.35 | -2.38 | -2.39 |
| Range | (-93.5; 43.3) | (-122.6; 127.7) | (-128.4; 36.2) |
| IQ range | (-9.50; 0.10) | (-9.86; 0.29) | (-9.42; -0.10) |

| | | | |
|---|---|---|---|
| Change in Fecal Calprotectin from baseline at Week I-8/Week 6, mg/kg | | | |
| N | 93 | 239 | 203 |
| Mean (SD) | -1143.06 (4711.036) | -239.13 (1242.714) | -312.69 (1110.046) |
| Median | -594.00 | -41.25 | -106.32 |
| Range | (-33975.0; 13300.0) | (-6127.3; 9871.0) | (-8057.1; 5449.9) |
| IQ range | (-1221.00; 79.00) | (-382.87; 18.24) | (-471.45; 0.00) |

[a] Analysis set used in CRD3001: Randomized subjects excluding those enrolled prior to study re-start. Analysis set used in CRD3002: Randomized subjects excluding those enrolled prior to study re-start and excluding site 1127. Analysis set used in CRD3004: Full Analysis Set. For clinical response and endoscopic response at week M-8, full randomized analysis set was used for CRD3004.
[b] For CRD3004, clinical remission is defined as a sPCDAI score ≤10 points for Week I-6, and defined as a PCDAI score ≤10 points for Week I-8. For CRD3001 and CRD3002, clinical remission is defined as a CDAI score of <150 points.
[c] For CRD3004, clinical response is defined as a reduction from baseline in the sPCDAI score of ≥10 points for Week I-6, and defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30 points for Week I-8, Week M-8. For CRD3001 and CRD3002, clinical response is defined as a reduction from baseline in the CDAI score of ≥100 points.
[d] For CRD3004, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3. For CRD3001 and CRD3002, endoscopic response was defined as a reduction of ≥50% from induction baseline in SES-CD score.
Note: For CRD3004, intercurrent events (ICEs) include: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4. ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 were not considered to have achieved the endpoint at Week I-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint. Subjects with ICEs 1-3, and 5 prior to a visit are considered to have no change from baseline for that endpoint at that visit and subsequent visits. Subjects with ICE 4 have their data assumed missing after the ICE 4 occurred.
Note: For CRD3001 and CRD3002, subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical remission, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at Week 8 are considered not to be in clinical remission. Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to Week 8 are considered not to be in clinical response, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at Week 8 are considered not to be in clinical response.
Note: Endoscopic response results in studies CRD3001 and CRD3002 were obtained at Week 8. Fecal calprotectin results in studies CRD3001 and CRD3002 were obtained at Week 6.
Note: The confidence intervals are based on the Wilson statistic.

**Endoscopic response**

The endoscopic data from the CNTO1275CRD3001 and CNTO1275CRD3002 adult studies were collected at screening, at the end of the induction study (Week 8 of induction), and Week 44 of maintenance, as part of an optional endoscopic substudy. As a nonrandomised substudy, there is potential for unintentional selection bias that may affect these findings.

In comparing the paediatric and adult endoscopic response rates, consideration should be given to the study's inclusion criteria, timing of endoscopic evaluations, and endpoint definitions. While all studies required evidence of active CD, none of the studies specified a baseline eligibility SES-CD score. Furthermore, in the CNTO1275CRD3004 paediatric study, endoscopic response was a secondary endpoint, defined as either a reduction in the SES-CD score of ≥50% or an SES-CD score of ≤2 in participants with a baseline SES-CD score of ≥3. In the adult endoscopic substudies, the primary endpoint was the change from baseline in the SES-CD score, and endoscopic response was categorised as an exploratory "other endpoint." Endoscopic response was defined in the adult substudies and in the CNTO1275CRD1001 paediatric study similarly as a reduction of at least 50% from the induction baseline in the SES-CD score, applicable to participants with a baseline SES-CD score of ≥3.

During the induction period, the proportion of paediatric participants in CNTO1275CRD3004 who were in endoscopic response at Week M-8 was numerically higher with overlapping CIs than participants in the adult induction studies at Week 8 (36.2% of paediatric participants versus 13.8% and 27.5% of participants in CNTO1275CRD3001 and CNTO1275CRD3002, respectively). The proportion of paediatric participants in CNTO1275CRD1001 who were in endoscopic response at Week 16 was 27.8%. The proportions of clinical responders in endoscopic response at Week M-8/Week 16 were numerically higher (with overlapping CIs) in paediatric participants in CNTO1275CRD3004 and CNTO1275CRD1001 (31 [37.3%] of 83 participants and 5 [45.5%] of 11 participants, respectively) than the proportions of adult participants in the nonrandomised endoscopic substudy from CNTO1275CRD3001 and CNTO1275CRD3002 at Week 8 (18 [21.7%] of 83 participants in the combined 6 mg/kg subgroup.

**Maintenance (through Week M-44/48)**

**Key Efficacy Endpoints**

Overall, clinical remission, clinical response, and changes in inflammatory biomarkers (CRP and fecal calprotectin) compared favorably or were consistently similar between paediatric and adult studies of ustekinumab at Week M-44/Week 44 (Figure 44, Table 61).

Clinical Remission

- The proportion of paediatric participants in PCDAI clinical remission (54.1% of total participants) in CNTO1275CRD3004 was similar to the proportion of adult participants in CDAI clinical remission (51.0% of participants in the combined 90 mg treatment group) in CNTO1275CRD3003.

Clinical Response

- The proportion of paediatric participants in PCDAI clinical response (60.0% of total participants) in CNTO1275CRD3004 was similar to the proportion of adult participants in CDAI clinical response (58.8% of combined participants in the 90 mg treatment group) in CNTO1275CRD3003.

Corticosteroid-free Clinical Remission

- The proportion of paediatric participants in 90-day corticosteroid-free clinical remission (52.9% of total participants) was numerically higher than adult participants (43.2% of participants in the combined 90 mg treatment group); however, the CIs overlapped slightly.

Clinical Remission Among Participants in Clinical Remission at Week I-8/Week 0

- The proportion of paediatric participants who achieved clinical remission at Week M-44 among paediatric participants in clinical remission at Week I-8 was numerically higher than the proportion of adult participants on ustekinumab SC 90 mg who achieved clinical remission at Week 48 among those in clinical remission at Week 0 (68.1% versus 61.5%). The proportions of paediatric and adult participants who achieved clinical remission were numerically lower in the q12w treatment groups than the q8w treatment groups, with overlapping CIs.

Reduction in Markers of Inflammation

- Based on the mean changes from baseline, CRP improved (was reduced compared to baseline) in the paediatric and adult studies.
- Mean changes from baseline in fecal calprotectin reflected improvement in intestinal inflammation in both paediatric and adult studies.

**Figure 44: Global descriptive comparison of secondary efficacy endpoints among the paediatric and adult studies on ustekinumab during at Week M-44; Full Clinical Responder Set (Study CNTO1275CRD3004, CNTO1275CRD3003)**

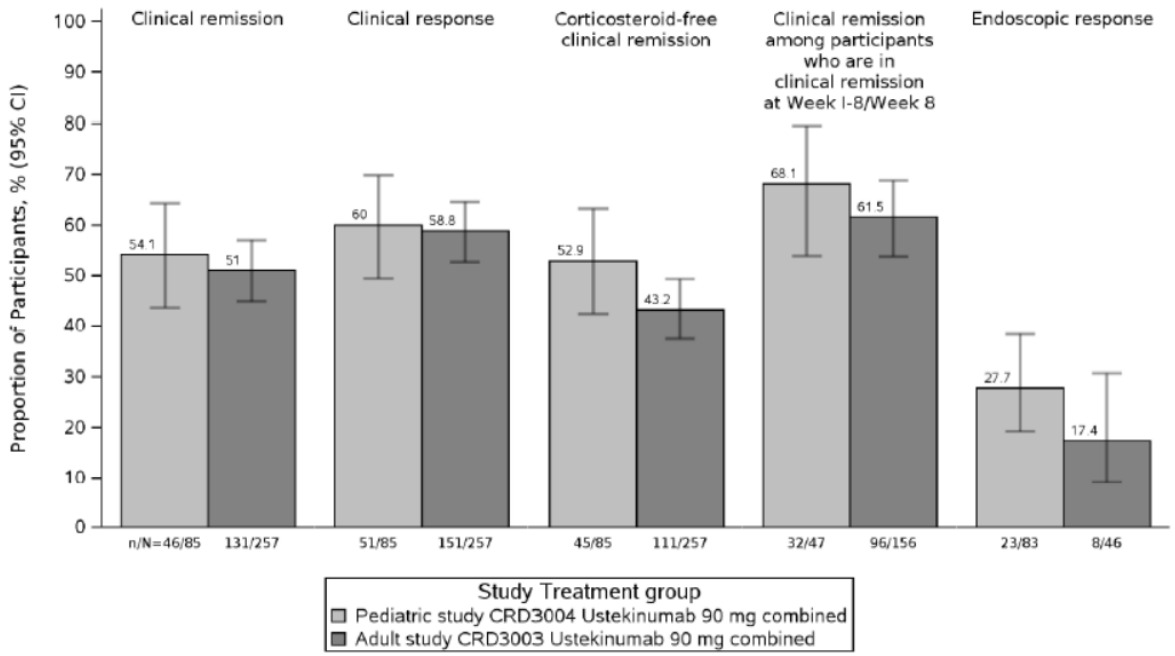



**Table 61: Descriptive comparison of key efficacy endpoints among the paediatric and adult studies at Week M-44; Full Clinical Responder Set (Study CNTO1275CRD3004, CNTO1275CRD3003)**

**Table 20: Descriptive Comparison of Key Efficacy Endpoints Among the Pediatric and Adult Studies at Week M-44 (Week 44); Full Clinical Responder Set (Studies CNTO1275CRD3004, CNTO1275CRD3003)**

| | Pediatric CRD3004 | | | Adult CRD3003 | | | |
|---|---|---|---|---|---|---|---|
| | q8w | q12w | Total | Placebo | q8w, 90 mg | q12w, 90 mg | Combined, 90 mg |
| Analysis set[a] | 41 | 44 | 85 | 131 | 128 | 129 | 257 |
| Week M-44 (Week 44) | | | | | | | |
| N | 41 | 44 | 85 | 131 | 128 | 129 | 257 |
| Subjects in clinical remission[b] | 20 (48.8%) | 26 (59.1%) | 46 (54.1%) | 47 (35.9%) | 68 (53.1%) | 63 (48.8%) | 131 (51.0%) |
| 95% CI[e] | (34.3%, 63.5%) | (44.4%, 72.3%) | (43.6%, 64.3%) | (28.2%, 44.4%) | (44.5%, 61.6%) | (40.4%, 57.4%) | (44.9%, 57.0%) |
| N | 41 | 44 | 85 | 131 | 128 | 129 | 257 |
| Subjects in clinical response[c] | 23 (56.1%) | 28 (63.6%) | 51 (60.0%) | 58 (44.3%) | 76 (59.4%) | 75 (58.1%) | 151 (58.8%) |
| 95% CI[e] | (41.0%, 70.1%) | (48.9%, 76.2%) | (49.4%, 69.8%) | (36.1%, 52.8%) | (50.7%, 67.5%) | (49.5%, 66.3%) | (52.7%, 64.6%) |
| N | 41 | 44 | 85 | 131 | 128 | 129 | 257 |
| Subjects in corticosteroid-free clinical remission[d] | 19 (46.3%) | 26 (59.1%) | 45 (52.9%) | 38 (29.0%) | 58 (45.3%) | 53 (41.1%) | 111 (43.2%) |
| 95% CI[e] | (32.1%, 61.3%) | (44.4%, 72.3%) | (42.4%, 63.2%) | (21.9%, 37.3%) | (37.0%, 53.9%) | (33.0%, 49.7%) | (37.3%, 49.3%) |
| Subjects in clinical remission at Week I-8/Week 0 | | | | | | | |
| N | 23 | 24 | 47 | 79 | 78 | 78 | 156 |
| Subjects in Clinical Remission at Week M-44/Week 44 among Subjects in Clinical Remission at Week I-8/Week 0[b] | 17 (73.9%) | 15 (62.5%) | 32 (68.1%) | 36 (45.6%) | 52 (66.7%) | 44 (56.4%) | 96 (61.5%) |
| 95% CI[e] | (53.5%, 87.5%) | (42.7%, 78.8%) | (53.8%, 79.6%) | (35.0%, 56.5%) | (55.6%, 76.1%) | (45.4%, 66.9%) | (53.7%, 68.8%) |
| Change from baseline[g] | | | | | | | |
| CRP, mg/L[h] | | | | | | | |
| N | 41 | 43 | 84 | 131 | 128 | 129 | 257 |
| Mean (SD) | -6.00 (14.475) | -7.28 (21.999) | -6.65 (18.609) | -0.88 (15.621) | -3.46 (24.170) | -5.16 (19.556) | -4.31 (21.949) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Range | (-64.4; 9.2) | (-102.5; 11.6) | (-102.5; 11.6) | (-78.0; 92.3) | (-120.6; 187.3) | (-97.6; 58.6) | (-120.6; 187.3) |
| IQ range | (-6.90; 0.00) | (-4.30; 0.00) | (-4.60; 0.00) | (-0.74; 0.26) | (-6.07; 0.00) | (-3.80; 0.00) | (-4.84; 0.00) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fecal calprotectin, mg/kg[h] | | | | | | | |
| N | 37 | 40 | 77 | 128 | 127 | 125 | 252 |
| Mean (SD) | -893.00 (3538.401) | -554.05 (1239.296) | -716.92 (2597.662) | -167.80 (1128.767) | -332.71 (879.609) | -249.07 (693.317) | -291.22 (792.227) |
| Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Range | (-20878.0; 1205.0) | (-6030.0; 858.0) | (-20878.0; 1205.0) | (-7601.9; 1927.6) | (-5295.1; 2083.7) | (-4466.0; 3071.2) | (-5295.1; 3071.2) |
| IQ range | (-536.00; 0.00) | (-833.00; 0.00) | (-632.00; 0.00) | (-27.46; 10.61) | (-378.32; 0.00) | (-296.86; 0.00) | (-356.26; 0.00) |

[a] For CRD3004: full clinical responder analysis set was used; for CRD3003: randomized subjects excluding those enrolled prior to study re-start was used.
[b] For CRD3004, clinical remission is defined as a PCDAI score ≤10 points. For CRD3003, clinical remission is defined as a CDAI score of <150 points.
[c] For CRD3004, 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 points. For CRD3003, clinical response is defined as a reduction from Week 0 of induction study CNTO1275CRD3001 or CNTO1275CRD3002 in the CDAI score of ≥ 100 points at Week 44. Subjects with a CDAI score of ≥ 220 to ≤ 248 points at Week 0 of induction study CNTO1275CRD3001 or CNTO1275CRD3002 are considered to be in clinical response if a CDAI score of < 150 is attained at Week 44.
[d] For CRD3004, corticosteroid-free remission is defined as PCDAI score of ≤10 points and not receiving corticosteroids for at least 90 days prior to Week M-44. For CRD3003, corticosteroid-free remission is defined as clinical remission at Week 44 and not receiving corticosteroids for at least 90 days prior to Week 44.
[e] The confidence intervals are based on the Wilson statistic.
[f] Endoscopic response for CRD3004 is defined as a reduction from baseline in SES-CD score ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3. Endoscopic response for CRD3003 is defined as a reduction from baseline in SES-CD score ≥50%.
[g] For CRD3004, baseline is defined as the last observation prior to or at the time of the first study intervention. For CRD3003, baseline is defined as the last observation prior to or at the time of the first study intervention in the CRD3001/CRD3002.
[h] For CRD3003, subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint had their induction baseline value carried forward. Subjects who had insufficient data at the designated analysis timepoint had their last value carried forward. For CRD3004,subjects that have ICEs 1-5, and 7 prior to a visit are considered to have no change from baseline for that endpoint at that visit and subsequent visit. Subjects with ICE 6 have their data assumed missing after the ICE 6 occurred.
Note: For CRD3004, intercurrent events (ICEs) include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6. ICEs strategies: Subjects that have ICEs 1-5, and 7 prior to Week M-44 are considered to not achieve that endpoint at Week M-44 (ie. composite strategy). Subjects with ICE 6 prior to Week M-44 are considered to have missing data for the endpoint from the time of the event onward (ie. hypothetical strategy). After accounting for the ICEs, subjects who have missing data for the endpoint are considered to not have achieved the endpoint at Week M-44.
Note: For CRD3003, subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to achieve the endpoint, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to achieve the endpoint. Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to the designated analysis timepoint are considered not to achieve the endpoint, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to achieve the endpoint.
Adult studies data were adapted from (Mod5.3.5.1/CNTO1275CRD3003/W44/AttTEFCREM01A, AttTEFCREM05, AttTEFCREM06B, AttTEFCRES01), (Mod5.3.5.3/endoscopy_substudy/AttTEFSES18, AttTEFSES22).

**Endoscopic Response**

At Week M-44, the proportion of paediatric participants who achieved endoscopic response in CNTO1275CRD3004 (27.7%) was numerically higher with overlapping CIs than adult participants on ustekinumab SC 90 mg (17.4%) in CNTO1275CRD3003 (Table 62). Endoscopic response was not captured in the CNTO1275CRD1001 paediatric study after Week 16 and is thus not reported here.

**Table 62: Number of participants in endoscopic response at Week M-44 in paediatric and adult studies; Full Clinical Responder Set (Study CNTO1275CRD3004, CNTO1275CRD3003)**

| | Pediatric | | | Adult | | | |
|---|---|---|---|---|---|---|---|
| | CRD3004 | | | CRD3003 | | | |
| | q8w | q12w | Total | Placebo | q8w, 90 mg | q12w, 90 mg | Combined, 90 mg |
| Analysis Set[a1]: Subjects with a baseline SES-CD score ≥3 | 41 | 44 | 85 | 24 | 29 | 17 | 46 |
| Week M-44 | | | | | | | |
| N[a2] | 40 | 43 | 83 | 24 | 29 | 17 | 46 |
| Subjects in Endoscopic Response[b1,b2,c1,c2] | 10 (25.0%) | 13 (30.2%) | 23 (27.7%) | 1 (4.2%) | 7 (24.1%) | 1 (5.9%) | 8 (17.4%) |
| 95% CI[d] | (14.2%, 40.2%) | (18.6%, 45.1%) | (19.2%, 38.2%) | (0.7%, 20.2%) | (12.2%, 42.1%) | (1.0%, 27.0%) | (9.1%, 30.7%) |

[a1] For study CRD3004, subjects from the full clinical responder analysis set are summarized. For study CRD3003, only subjects who were randomized and with eligible SES-CD score at baseline of induction are summarized.
[a2] For CRD3004, N is the number of subjects with a baseline SES-CD score of ≥3.
[b1] For CRD3004, endoscopic response is defined as a reduction from baseline in SES-CD score ≥50% or SES-CD score ≤2 in subjects with a baseline SES-CD score of ≥3.
[b2] For CRD3003, endoscopic response was defined as a reduction from induction baseline in SES-CD score ≥50%.
[c1] For CRD3004, intercurrent events (ICEs) include: (1) Had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Discontinued study intervention due to COVID-19 related reasons. (5) Discontinued study intervention due to reasons other than ICEs 2 or 4. ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 are considered to not have achieved the endpoint at Week M-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint.
[c2] For CRD3003, Subjects who, prior to the designated analysis timepoint, had a Crohn's disease-related surgery due to lack of efficacy or had an initiation of specified prohibited medication had their baseline score carried forward. Subjects with missing segments at the designated analysis timepoint had their baseline score for the missing segment(s) carried forward.
[d] The 95% CIs are based on the Wilson statistic.

**Alternative Scoring Systems**

**Clinical Remission Based on PCDAI and CDAI Criteria**

Across all studies, treatment groups, endpoints, and definitions (cut-scores), the proportions of participants achieving clinical remission at Week M-44 varied from 45.5% to 59.1%. Nevertheless, clinical remission rates based on the primary definition of clinical remission in CNTO1275CRD3004 and CNTO1275CRD1001 (PCDAI ≤10) and the prespecified alternative definition of clinical remission (PCDAI <10) were similar for both paediatric studies and comparable with clinical remission derived from CDAI scores of <150 in the adult CNTO1275CRD3003 study.

**Supportive Data for Efficacy Based on CDAI Measurements in Paediatrics**

The CDAI scores indicated that ustekinumab induction therapy in paediatric participants induced similar proportions of CDAI clinical remission (30 [29.7%] participants) and CDAI clinical response (42 [41.6%] participants) at Week I-8 compared with corresponding CDAI efficacy endpoints in the adult Phase 3 induction studies at Week 8 (136 [29.7%] and 215 [46.9%] of 458 participants, respectively). However, ustekinumab maintenance therapy given to paediatric participants induced numerically lower proportions of participants who achieved CDAI clinical remission (33 [38.8%] of 85 participants) and CDAI clinical response (40 [47.1%] of 85 participants) at Week M-44 compared with that of the corresponding CDAI endpoints in the adult Phase 3 maintenance study at Week 44 (131 [51.0%] and 151 [58.8%] of 257 participants, respectively).

The lower rates obtained when the CDAI was completed by paediatric patients at Week M-44 may be attributed to many factors, in addition to the obvious differences in the characteristics and measurement properties of the PCDAI and CDAI. First, in paediatric participants, mean (SD) CDAI scores were numerically higher at baseline (mean [SD]: 365.20 [120.588]) compared with the CDAI scores of the adult CNTO1275CRD3003 study participants (316.7 [62.50]). Second, there was a larger amount of missing CDAI data compared to the primary outcome measure PCDAI (42 [49.4%] of 85 participants with 1 to 7 CDAI subscores missing versus 10 [11.8%] of 85 participants with 1 to 4 PCDAI subscores missing) in the paediatric study, which may be attributable to participants and sites deprioritizing CDAI diary entry for this exploratory endpoint. Because the CDAI subjective diary information contributes approximately 39% of the CDAI score, missing CDAI diary data will have had a large impact on the results, in an already small, exploratory study. Third, the CDAI is developed for adult patients and is not validated for use in paediatric patients. Despite these limitations, the CDAI data in the paediatric study showed a consistent trend in efficacy compared with what was seen in the adult studies and provides supportive evidence for the efficacy of ustekinumab in paediatric patients.

**Table 63: Descriptive comparison of clinical remission at Week M-44/Week 48 based on PCDAI and CDAI Criteria; Full Clinical Responder Analysis Set (Study CNTO1275CRD3001, CNTO1275CRD3004 and CNTO1275CRD3003)**

| | Ustekinumab | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | PCDAI < 10 | | | | PCDAI <= 10 | | | | CDAI < 150 | | |
| | CRD1001 | CRD3004 | | | CRD1001 | CRD3004 | | | CRD3003 | | |
| | q8w | q8w | q12w | Combined | q8w | q8w | q12w | Combined | q8w, 90 mg | q12w, 90 mg | Combined, 90 mg |
| Total N[a] | 22 | 41 | 44 | 85 | 22 | 41 | 44 | 85 | 128 | 129 | 257 |
| Week M-44 (Week 44)/Week 48 | | | | | | | | | | | |
| N | 22 | 41 | 44 | 85 | 22 | 41 | 44 | 85 | 128 | 129 | 257 |
| Subjects in clinical remission[b1, b2, b3] | 10 (45.5%) | 19 (46.3%) | 24 (54.5%) | 43 (50.6%) | 13 (59.1%) | 20 (48.8%) | 26 (59.1%) | 46 (54.1%) | 68 (53.1%) | 63 (48.8%) | 131 (51.0%) |
| 95% CI[c] | (26.9%, 65.3%) | (32.1%, 61.3%) | (40.1%, 68.3%) | (40.2%, 61.0%) | (38.7%, 76.7%) | (34.3%, 63.5%) | (44.4%, 72.3%) | (43.6%, 64.3%) | (44.5%, 61.6%) | (40.4%, 57.4%) | (44.9%, 57.0%) |

[a] For CRD1001, subjects who entered LTE and receiving 90 mg maintenance ustekinumab set were summarized. For CRD3004, subjects in full clinical responder analysis set were summarized. For CRD3003, randomized subjects excluding those enrolled prior to study re-start were summarized.
[b1] For CRD3004, intercurrent events (ICEs) include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6. ICEs strategies: Subjects who had ICEs 1-5, and 7 prior to a visit are considered to have no change from baseline for that endpoint at that visit and subsequent visit. Subjects with ICE 6 have their data assumed missing after the ICE 6 occurred. ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 were not considered to have achieved the endpoint at Week I-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endpoint data from the time of the event onward (ie, hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint.
[b2] For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint. Subjects who had insufficient data to calculate the PCDAI score at a visit are considered to not have achieved the endpoint.
[b3] For CRD3003, Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to achieve the endpoint, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to achieve the endpoint.
[c] The confidence intervals are based on the Wilson statistic.
Note: For CRD3004, Week M-44 data was used. For CRD1001, Week 48 data was used. For CRD3003, Week 44 data was used.

**Subpopulation Efficacy (Prior Biologic and Non-biologic Failure Status)**

Ustekinumab demonstrated effectiveness in paediatric participants who had previously failed treatment with biologics as well as those who had never been treated with or failed treatment with biologics (non-biologic failures). The treatment response among paediatric and adult study participants who were non-biologic failures was generally stronger compared with those who were biologic failures.

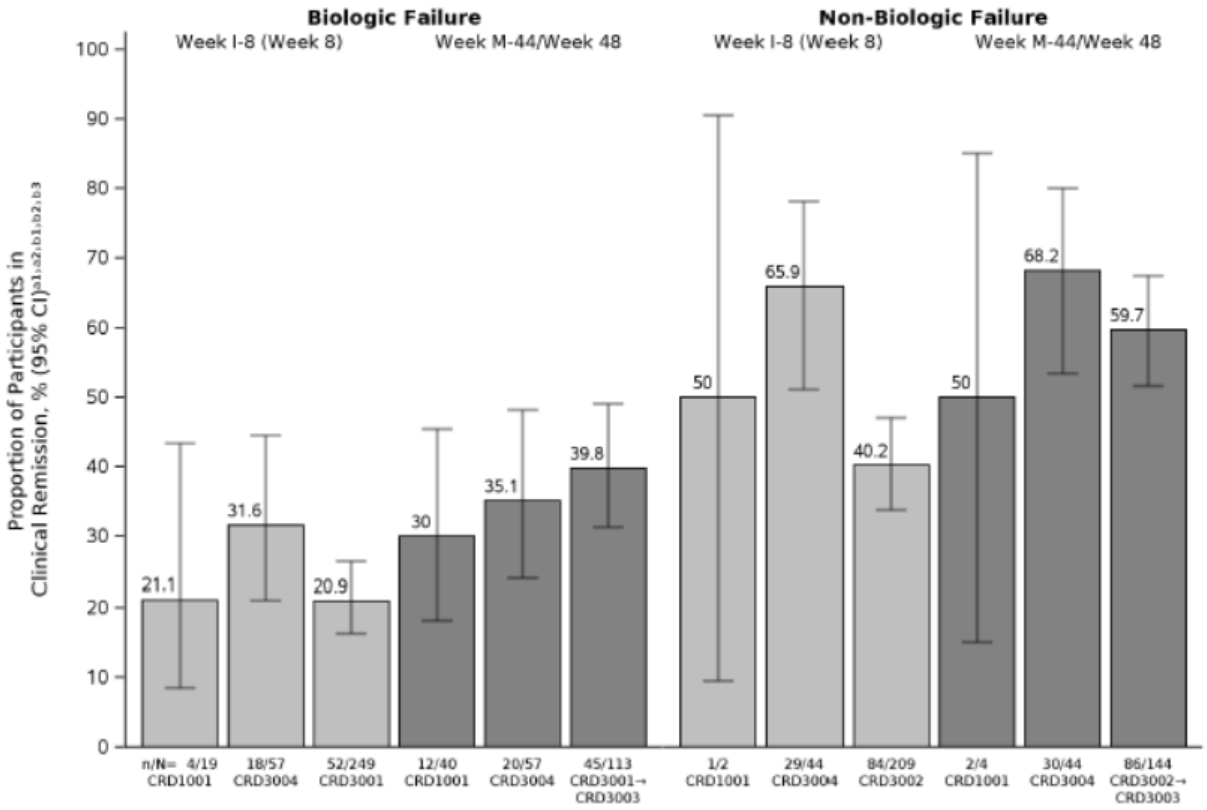
For all comparison between CNTO1275CRD3004 and CNTO1275CRD1001, it should be noted that CNTO1275CRDCRD1001 was predominantly a biologic failure study population, with only 2 participants who were non-biologic failures.

**Clinical Remission**

- In CNTO1275CRD3004 and CNTO1275CRD1001, the proportions of paediatric participants in clinical remission at Week I-8/Week 8 and Week M-44/Week 48 were numerically higher in those paediatric participants without a history of failing treatment with biologic therapy at baseline than in paediatric participants with a history of biologic failure at baseline (Figure 45).

- Similar to the paediatric studies, a greater proportion of participants in the CNTO1275CRD3002 study (non-biologic failures) ustekinumab 6 mg/kg treatment group achieved clinical remission (40.2%) at Week I-8 compared with participants in the CNTO1275CRD3001 study (biologic failures) ustekinumab 6 mg/kg group (20.9%). In addition, a greater proportion of participants from CNTO1275CRD3002 (non-biologic failures) who entered the maintenance study CNTO1275CRD3003 achieved clinical emission (59.7%) compared with participants from CNTO1275CRD3001 who entered the maintenance study (39.8%).
- Similar to the findings in adults, at a given ustekinumab concentration, the proportions of paediatric participants in clinical remission at Week I-8 and Week M-44 were higher in the non-biologic failure population compared with the biologic failure population.

**Figure 45: Comparison of Clinical Remission Across paediatric and adult studies with Biologic and Non-biologic Failure at Study Entry; Full Analysis Set (Study CNTO1275CRD3001, CNTO1275CRD3002, CNTO1275CRD3003 and CNTO1275CRD3004)**



[a1] For CRD1001 and CRD3004, clinical remission is defined as a PCDAI score ≤10 points.
[a2] For CRD3001, CRD3002, and CRD3003, clinical remission is defined as a CDAI score of < 150 points.
[b1] For CRD1001, subjects who had a prohibited Crohn's disease-related surgery, discontinued study intervention due to an AE of worsening Crohn's disease or due to lack of efficacy, or had prohibited concomitant medication changes are considered to not have achieved the endpoint regardless of their PCDAI score. Subjects who had insufficient data to calculate the PCDAI score at that visit are considered as missing. Subjects with both baseline and postbaseline values were included in the analysis.
[b2] For CRD3004 intercurrent events (ICEs) include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) Used rescue medication for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Were eligible for dose adjustment after Week M-8, (6) Discontinued study intervention due to COVID-19 related reasons, (7) Discontinued study intervention due to reasons other than ICEs 2 or 6. ICEs strategies: Subjects who had ICEs 1-5, and 7 prior to the specified timepoint are considered to not have achieved the endpoint at that timepoint (ie. composite strategy). Subjects with ICE 6 prior to the specified timepoint are considered to have missing endpoint data from the time of the event onward (ie. hypothetical strategy). After accounting for the ICEs, subjects who had missing endpoint data are considered to not have achieved the endpoint.
[b3] For CRD3001, CRD3002, and CRD3003, subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to achieve the endpoint, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to achieve the endpoint.
Note: For Week I-8 (Week 8), subjects receiving 9 mg/kg or 390 mg induction ustekinumab IV in CRD1001, subjects receiving 6 mg/kg ustekinumab IV in CRD3001 and CRD3002, and all subjects in CRD3004 are included. For Week M-44 (Week 48), all subjects in CRD1001, CRD3003, and CRD3004 are included.
Note: The confidence intervals are based on the Wilson statistic.

## 2.5.4. Discussion on clinical efficacy

**CNTO1275CRD3004 - Pivotal phase 3 study**

The applicant presents a pivotal phase 3 study of ustekinumab in paediatric Crohn's disease patients. An interim report for this study was previously assessed in procedure EMEA/H/C/000958/II/0108 to support an extension of indication for paediatric patients ≥40kg. This patient group now includes 73 children and thus an additional 25 children have been included in this population since the former application. It is acknowledged that moderately to severely active Crohn's disease in the youngest and lightest children is a rare condition, leading to feasibility issues when conducting clinical trials in this patient population. Thus, the presented study was designed as part of a paediatric extrapolation plan to evaluate efficacy, safety and PK.

The primary endpoint of the trial is clinical remission at week 8 assessed by PCDAI. As per EMA guideline CPMP/EWP/2284/99 Rev. 2 'Guideline on the development of new medicinal products for the treatment of Crohn's Disease', "Endoscopic MH (mucosal healing) and disease activity scores (similar to adults) should be used as co-primary end points in clinical studies. Paediatric patient reported outcomes (pPRO) should be used as co-primary endpoint (instead of activity scores) as soon as a validated tool is available. If adolescents are to be included in adult studies, adult PRO endpoints could be used for adolescents". The MAH has not used a co-primary endpoint, however using PCDAI is in line with using the single activity index primary endpoint of CDAI for the adult studies and is therefore accepted.

The main secondary endpoints include clinical remission at different timepoints, clinical response, endoscopic response, corticosteroid-free clinical remission, CRP concentrations, faecal calprotectin and faecal lactoferrin levels and Quality of Life questionnaires. Endoscopy assessments were evaluated by the gold standard for clinical trials, SES-CD, and also by SEMA-CD.

The inclusion criteria are found to be relevant to identify moderately to severely active Crohn's disease in paediatric patients both in the clinical trial and in a clinical treatment setting.

The paediatric study has no placebo group, but compares two different treatment arms (q8w and q12w).

The statistical analysis for the trial is mainly descriptive in nature. This can be accepted based on the design of the trial as there is no comparator or placebo arm in the trial for formal comparison purposes. However, patients received placebo administrations to maintain the blind given the different frequencies of administration during the maintenance phase. Blinding and randomisation procedures are appropriate.

The doses proposed in the SmPC for paediatric patients <40kg are mg/$m^2$ BSA based and have been selected based on popPK modelling. This is accepted.

The sample size is small however this can be accepted as this is an extension of indication application and a lot of data is to be leveraged from the adult population.

Overall, the trial design is accepted. The clinical trial has been performed broadly in line with that agreed in the PIP.

101 patients are included in the FAS for the primary analysis. 15 (14.9%) patients discontinued treatment throughout the maintenance phase with similar numbers discontinuing treatment in the main treatment arms, q8w and q12w. 26 (25.7%) patients entered the exposure optimisation study (EOS) substudy and received q4w dosing – 23 patients who experienced a loss of response and low exposure levels and 3 patients who met the criteria for early escape criteria.

The protocol deviations with the most common reason being missed study visits and missed assessments (eg, PCDAI and CDAI diary information) are not deemed to have affected the interpretability of results.

The baseline characteristics are generally evenly spread between the two treatments groups with a caveat that there is no formal comparison with a comparator or placebo arm in this clinical trial,. There were only 2 (2%) patients recruited who were 2-5 years old and 18 (17.8%) patients 6-11 years old. The study recruited 29 (28.7%) patients who weighed less than 40kg, including 11 (10.9%) subjects who weighed less than 30kg. Two included patients weighed less that 20kg (12.6kg and 16.2kg). These limitations of the study are now included in the SmPC, section 5.1**.** Compliance was 100%, no subject missed an administration of ustekinumab during the study.

The included number of patients is in accordance with the requirements stated in the latest updated PIP (EMEA-000311-PIP04-13-M06) revised to enrol a total of 60 participants (aged 2 to <18 years) with at least 24 participants <40 kg and at least 5 participants <30 kg.

As per inclusion criteria, patients must have moderately to severely active Crohn's disease as defined by a baseline PCDAI score >30, however a small number of patients were included with PCDAI score of less than 30 in both arms. These patients were included based on screening laboratory values however baseline PCDAI scores were determined using laboratory results collected at the baseline I-0 visit. Following queries raised during assessment of the interim report, the applicant demonstrated that excluding 3 of these patients had a minimal impact on the primary endpoint analysis**.**

Lower BMI z-score in the younger patients (11 years and below) as well as a greater proportion of participants <40 kg being categorised as underweight and had lower BMI z-scores than participants ≥40 kg, is described as not unexpected. However, this finding could also be related to a more severe disease burden in this population.

When comparing patients based on weight, patients <40 kg compared to patients ≥40 kg had higher levels of ileocolonic disease (75.9% versus 50%), more severe per PCDAI scores (51.7% v 40.3%), more severe endoscopic disease severity (41.4% v 26.8%, SES-CD) and higher mean IMPACT III scores 111.6 v 98.9 at baseline overall suggesting more severe disease in the lower weight patients.

This is in line with the clinical finding that children with CD may have more severe disease at presentation than adult patients with CD.

A similar percentage of patients received concomitant CD medications in patients <40 kg compared to patients ≥40 kg (72.4% v 70.8%), with a lower number receiving corticosteroids (17.2% v 27.8%), and a higher percentage receiving immunomodulatory drugs (55.2% v 37.5%).

History of biological failure is higher in the complete paediatric population compared to paediatric cohort >40kg used in the interim analyses (56.7% versus 39.6%). Contributing to this difference could be the proportion of biologic-naïve patients in the same two cohorts (42.3% versus 56.3%), based on the limited available biological treatment options for the paediatric CD population (from 6 years of age: Remicade, Humira and from 40kg: Stelara).

The primary analysis was clinical remission (PCDAI score ≤10 points) at week 8. 46.5% of patients had entered clinical remission. 3% of patients had an intercurrent event and 4% of patients had no PCDAI data and were all considered to be non-responders. 12.9% of patients were missing one (of four) PCDAI sub scores. All missing data was related to missing laboratory values, however PCDAI scores were still calculatable imputing missing Week I-8 laboratory values with LOCF. A higher proportion of males than females experienced a clinical remission at 8 weeks (55% v 34%) and those without a history of failure to treatment with biologics (failed conventional therapy) (66% v 32%) at baseline. The percentage of patients with a clinical response at week 8 was high at 84% (SmPC section 5.1).

The numbers of patients who maintained clinical remission throughout the study remained steady over time and was higher in the q12w arm. Overall, at week M-44, 54% of patients were in clinical remission and 53% were in corticosteroid free remission. The percentage of patients who experienced a clinical response gradually decreased over the maintenance period with 60% of patients in response at week M-44 (falling from 84% after induction), rates were also generally higher in the q12w arm. 28% of patients had endoscopic responses at M-44 (by SES-CD score) (SmPC section 5.1). Overall results were similar across both dosing frequencies. Discontinued patients or patients that experienced an intercurrent event including a reduction in dosing frequency were considered to not have clinical/endoscopic remission/responses after the event. The MAH has provided the secondary (and tertiary) maintenance results based on the 'Full Clinical Responder' data-set. Including only patients who were in clinical response to ustekinumab induction therapy at Week I-8 is in contrast to how the data was presented in the interim report. However, it is aligned with how the adult data is presented in the SmPC as the adult maintenance study (IM-UNITI) only evaluated patients who achieved clinical response in the induction studies UNITI-1 and UNITI-2. Following queries, the MAH has presented results using the Full Randomised Analysis Set (FASR), results are generally consistent between the two analysis sets.

The graphical and tabulated presentation of data comparing individuals with weight above and below 40kg is limited. For subgroup analyses, patients <40kg compared to patients ≥40kg experienced lower but comparable rates of clinical remission (38% v 50%) and response (72% v 89%) at week I-8. Low but comparable rates were also obtained for clinical remission at M-44 (48% v 56%). While similar rates were obtained for clinical response at M-44 (62% v 59%).

A comparison of the key efficacy endpoints by age in the induction period are described as generally consistent between the younger (2 to 11 years of age) and older (12 to 17 years of age) study populations, with a tendency towards more favourable outcomes in the younger subset for clinical remission at Week I-6 and Week I-8. During the maintenance period, generally similar trends were observed between the 2 to 11 years and 12 to 17 years of age subgroups.

The occasional divergent outcomes in the youngest and lightest children are expected to be due to the limited number of patients.

Following tertiary analyses with an alternative definition of PCDAI (<10, as opposed to ≤10 points), CDAI and sPCDAI (I-6) questionnaires, clinical remission results were broadly comparable at I-8 at 40%, 30% and 45.5%. With the alternative definition of PCDAI, CDAI and sPCDAI (M-40) questionnaires, clinical

remission results at M-44 were 51%, 39% and 54%. At the same timepoints clinical response rates of CDAI and sPCDAI were not comparable at I-6/8, 42% and 89%, but were generally comparable at M-40/44, 47% and 63.5%.

An additional analysis used PCDAI diary data instead of a recall period of 1 week which is likely to be a more accurate method of data recording, results demonstrated clinical remission rates of 37 and 47% at I-8 and M-44, and clinical response rates of 68% and 54% at I-8 and M-44 timepoints which are broadly in line with the results from the main endpoints and the other tertiary analyses centred around PCDAI scores.

Corticosteroid-free clinical remission results by CDAI were 29% and 38% at I-8 and M-44.

The MAH presented a summarised table of the similarities and differences between the different scoring systems used across the clinical trial programme. The MAH also provided discussions on the suitability of the different scoring systems and it is agreed that PCDAI is the most suitable scoring system for paediatric patients, while CDAI is the most suitable scoring system for adults with CD. In addition, the use of sPCDAI is a pragmatic and practical tool for use in real world settings. As clinical response rates differed significantly between CDAI and PCDAI/sPCDAI scoring systems, any comparisons between studies using CDAI versus PCDAI/sPCDAI scoring systems is limited.

The mean (SD) change from baseline at maintenance week 44 in C-Reactive protein (CRP) and faecal calprotectin concentrations were -6.65 mg/L (18.609) mg/L and -716.9 mg/kg (2597.66) mg/kg, respectively (SmPC section 5.1). By the end of the study, a modest 17% of patients had returned to normalised CRP levels (<3mg/L). A similar trend was also observed for faecal lactoferrin levels. Similar trends were observed for both q8w and q12w treatment groups. At the end of the study 12.5% and 8% of patients has normalised faecal calprotectin (≤250 mg/kg) and lactoferrin (>7.24 $\mu$g/g) levels.

At M-44, there was a small increase in the average BMI z-scores for both sexes. For PRO QoL questionnaires (IMPACT-III), scores increased from baseline by 19 by the end of the study in subjects ≥10 years of age at Week I-0. The total IMPACT-III scores and all subdomains (bowel symptoms, fatigue-related systemic symptoms, and well-being) demonstrated clinically meaningful improvements after 52 weeks (SmPC section 5.1).

The percentage of patients in endoscopic remission (SES-CD score ≤2 (in participants with a baseline SES-CD score of ≥3) was 18 and 16%, and for endoscopic response (reduction in the SES-CD score of ≥ 50% OR SES-CD score ≤2, in participants with a baseline SES-CD score of ≥3) was 36 and 28% at M-8 and M-44 timepoints. At the same timepoints 57% and 50% of patients who had 1 or more fistulas at baseline achieved complete fistula response however the numbers involved were very limited (n=7 and n=4).

Finally, the applicant presented data from the Exposure Optimisation Substudy (EOS) Analyses, where participants who had a LOR during the maintenance period of the main study and had a trough serum ustekinumab concentration of <1.4 µg/mL during the maintenance period (Week M-8 or Week M-32) were eligible to enrol in the optional EOS cohort and were administered open-label SC ustekinumab q4w dosing regimen. Results demonstrated that 16 weeks after entering the sub study, 19/20 (95%) and 10/20 (50%) of subjects were in clinical response and clinical remission. While these rates are in line with those from the main study population treated q8w or q12w, the patient numbers involved are low, the results are calculated based on a denominator of 20 patients when 26 (26.8%) entered the substudy, and results are based on sPCDAI as opposed to PCDAI. Following further justification submitted by the MAH of shortening the dosage interval supported by additional simulations in LOR paediatric participants receiving q4w maintenance dosing, stratified by body weight <40 kg and >40 kg the CHMP agreed to the recommendation that "Patients receiving treatment every 12 weeks who have a loss of response may increase their frequency to every 8 weeks (see sections 5.1 and 5.2). Patients receiving treatment every

12 or 8 weeks who lose response and have low ustekinumab trough levels (<1.4 µg/mL by a validated ECLIA or ELISA testing method or equivalent assay) may benefit from shortening the dosing interval to every 4 weeks if clinically indicated. A repeat trough level should be drawn at either 12 or 16 weeks after dose adjustment to every 4 weeks administration. If trough levels are >7.2 µg/mL and the patient has achieved response and is maintaining a response, the dosage interval may be changed to every 8 weeks." (see also PK and safety discussions)

Regarding the B/R evaluation the unmet need in the youngest paediatric population is higher compared to older children, adolescents and adults, due to the lack of authorised products on the market for treatment of moderately to severely active Crohn's disease in the youngest paediatric patients.

Overall data from this phase 3 trial demonstrates positive efficacy to support the use of ustekinumab in paediatric patients with moderately to severely active Crohn's disease.

**CNTO1275CRD1001 – Phase 1 study**

The MAH performed a phase 1 study of ustekinumab in paediatric subjects 2 to <18 years old with moderately to severely active Crohn's disease. The main objective of this study was analysis of PK parameters. Further details on the trial design can be found in the PK section of this AR. This study was previously assessed in procedure EMEA/H/C/000958/II/0108, albeit with a focus on paediatric patients ≥40kg.

In the induction dose, patients were randomised to 1 of 2 treatment doses: Group 1: 3 mg/kg for subjects <40 kg or 130 mg for subjects ≥40 kg (low induction dose) and group 2: 9 mg/kg for subjects <40 kg or 390 mg for subjects ≥40 kg (high induction dose). 59% (26 subjects) had a body weight ≥40 kg at the start of the trial. For patients <40 kg and ≥40kg, the induction dosing was not aligned with the proposed dosing in the SmPC or with that from the phase 3 trial. As there was no formal comparison with a comparator or placebo arm in the induction phase of this clinical trial, any baseline differences between the two treatment groups were of low importance. Due to these limitations, the efficacy results from the induction phase are of less relevance than the maintenance phase.

Patients ≥40kg received a 90mg maintenance dose which is aligned to the proposed dosing. Patients <40 kg received a maintenance dose of 2mg/kg which is not aligned to the proposed posology of 60mg/$m^2$ thus limiting the interpretation of results in paediatric patients <40kg. Any patients who received benefit from ustekinumab at week 16 had the opportunity to participate in the open label long term extension (LTE) study receiving the same maintenance dose q8w, up to 224 weeks. 77% (34 of 44) patients entered the LTE study.

Patients weighing less than 10kg were not included in the study.

Deviations related to administration of study drug were not considered to have impacted on efficacy analysis as deviations were related to duration of infusion times or infusion outside of window, and no doses were missed. Other deviations were also considered not to impact the efficacy analyses.

Over the course of the LTE study, the majority (76.5%) of patients discontinued treatment, the main reasons included a lack of efficacy and Crohn's disease-related events (such as surgery and worsening of the disease), but also positively, 4 (of 34) patients withdrew due to switching to commercial Stelara.

Results demonstrated that at week 8 the percentage of patients experiencing clinical remission (PCDAI score ≤10 points), was 20.5% with similar results across both treatment arms. This number reduced to 13.5% when patients not meeting the inclusion criteria for baseline PCDAI score of >30 (mild disease/remission) were excluded in a sensitivity analysis. In the LTE study, the clinical remission rate was 41% while the corticosteroid-free remission rate was 38% at week 48.

At week 8, 48% of patients overall had entered clinical response (PCDAI score ≥15 points), with similar results across both treatment arms. For the LTE study at week 48, the clinical response rate was 59%. Outcomes were not assessed by other scoring systems such as sPCDAI or CDAI.

The increased clinical remission and response rates for the LTE study may in part be explained by the rates being based on the number of patients that entered the LTE study (n=34), as opposed to the numbers of patients who entered at baseline initially (n=44). The applicant provided clinical remission and response rates up to week 224 however as only a small number of patients remained in the study after 1 year, the response estimates for later timepoints beyond 1 year need to be interpreted with caution due to imputation of response at missing visits to failures.

Average PCDAI scores reduced from 43.6 at baseline, to 26.1 at week 8 and to 15.4 at week 48. The reduction in PCDAI was maintained throughout the LTE although patient numbers towards the end of the study were low.

56% and 44% of patients had complete PCDAI scores at week 8 and 48 respectively. The majority of these patients were only missing one subscore. As this was a phase 1 trial and not the pivotal trial and considering only a subset (n=10) of patients were treated with the relevant posology, this issue is not pursued further.

Of the 4 patients who had a fistula at baseline, none had a fistula response at week 8 (≥50% reduction in the number of draining fistulas). Improvements in weight, height and BMI were observed and maintained throughout the LTE.

Average CRP values decreased from 23mg/L at baseline to 16mg/L at week 8 and 12mg/L by week 48. By week 8 and 48, 22% and 59% of patients had normalised CRP levels (<3mg/L). Faecal calprotectin levels decreased from 3915mg/kg at baseline to 2588mg/kg at week 8 and to 1505mg/kg at week 48. Faecal Lactoferrin levels decreased from 252mg/g at baseline to 235mg/g at week 8 and to 180mg/g at week 48. At week 8, 8% and 5% of patients has normalised faecal calprotectin (≤250 mg/kg) and lactoferrin (>7.24 $\mu$g/g) levels. Of note, at week 8, the level of faecal lactoferrin increased in patients ≥40kg but decreased in patients <40kg in weight. This unexpected result was not observed at week 16 where average levels decreased regardless of weight.

For PRO QoL questionnaires (IMPACT-III), scores increased from 108.5 baseline by 10 at week 8 and by 24 at week 48.

The percentage of patients in endoscopic remission (SES-CD score ≤2) was 13.5%, and for endoscopic response (reduction in the SES-CD score of ≥50% from baseline) was 30% at week 16, as per the SES-CD scoring system. At week 16, 38% of patients experienced a clinically meaningful endoscopic improvement (reduction in SES-CD of ≥3 points from baseline).

The impact of ustekinumab treatment on subjects' CD disease-related hospitalisations and surgeries was assessed, 26% and 5% of patients in the low and high-induction dose group were hospitalised, while 9% and 0% required surgery.

Efficacy endpoints analysed by subgroup analyses for potential impact of baseline age, body weight, history of TNF-antagonist exposure, baseline BSA and PCDAI severity showed similar results or the number of patients in the subgroups was too low to allow for interpretation. Specifically, when looking at key efficacy endpoints by baseline body weight subgroups, clinical response rates at week 16 were similar in patients weighing < 40kg compared to those weighing ≥40 kg (55.6% versus 50%). Clinical remission rates at week 16 were also similar in patients weighing < 40kg compared to those weighing ≥40 kg (27.8% versus 23.1%). Subgroup analyses were not performed for the LTE study.

When looking at ustekinumab serum concentrations, a positive exposure-response (E-R) relationship was observed for clinical response and improvement of PCDAI scores at week 8, however no positive

relationship was observed for clinical remission at week 8. The levels of inflammatory markers weren't comparable at baseline between low and high ustekinumab serum groups limiting interpretation at week 8. No clear E-R could be obtained for the LTE at week 48 due to low subject numbers (n=16).

Fistula outcomes, endoscopy assessments, medical resource utilisation data and efficacy results analysed by subgroups were not available from the LTE as they were for the first part of the study.

Further discussion on this phase 1 trial can be found in the section 'Analysis performed across trials'.

**CNTO1275CRD3010 – RWE study**

The MAH has submitted a retrospective study examining the effects of ustekinumab on Crohn's disease in paediatric patients. This study was previously assessed in procedure EMEA/H/C/000958/II/0108, albeit with a focus on paediatric patients ≥40kg. This study utilises the ICN registry database, a large resource of outpatient IBD data, mainly obtained from US patients. As with any registry study, this registry has limitations including limited data capture with potential information missing on induction dose, history of treatment with prior biologic agent, reasons for starting and discontinuing ustekinumab, endoscopic reports for central review, and AEs of special interest. To gather some of this information a manual chart review was undertaken for the study. As is expected of such a database its source data cannot be verified, and data is captured from outpatient appointments only. Nonetheless this database contains a large number of useable patients and is a valuable source of real-word data.

Scientific advice was obtained on the study design and the study has largely been performed in line with these recommendations. Overall, a lot of the same endpoints are used in this study as per the clinical trials, these include clinical remission, clinical response, corticosteroid-free remission, change in growth parameters and endoscopy assessments (SEMA-CD). The time-point analysis for each endpoint was week 52 which corresponds to M-44 of the pivotal clinical trial. Clinical remission was assessed mainly by sPCDAI, but also where available by PCDAI. After further justification, sPCDAI was endorsed as an acceptable endpoint by SAWP as the MAH confirmed that sPCDAI and PCDAI are highly correlated.

The RWE paediatric data was directly compared with young adults (18 to < 26 yrs). Baseline was considered from -12 weeks to +2 weeks of index date (Ustekinumab initiation). A wide window exists around the week 52 timeline used to assess all endpoints (week 52 +/- 16 weeks).

A number of different cohorts were analysed, however for the purposes of the previous EOI case, cohort 1 (paediatric patients ≥40kg, severe/moderate CD) and cohort 7 (young adults, severe/moderate CD) were the most relevant and the focus of the CSR.

Cohort 3 (paediatric patients, all weights, severe/moderate CD) is the main focus for this submission. It had 145 patients, while cohort 7 had 51 patients. A similar number of patients discontinued in both cohorts 3 and 7, 24.1 and 25.5% respectively. Patients on a Q8w posology were more likely to discontinue treatment compared to patients receiving Q4w posology suggesting a possible lack of efficacy for some patients resulting in a need for more frequent dosing.

Apart from age, the demographics of the patients were reasonably well balanced for an observational study, the majority of patients were white. Of note, there was only a small difference in the average weight between the two groups, with an average weight of 52kg in cohort 3 (paediatric patients, severe-moderate CD) and 61.6kg in cohort 7 (young adults) subgroups.

Regarding baseline disease characteristics, cohort 7 patients had a higher median duration of Crohn's disease than cohort 3 (6.2 v 3.7 years) which is not surprising given the age difference between the two cohorts. Cohort 3 and 7 patients had the same median sPCDAI score at baseline (45). In both cohorts, the majority of patients had previously used biologics, 99% (cohort 3) vs 96% (cohort 7).

Overall, the majority of patients received induction and maintenance doses in line with the licenced posology.

The primary analysis demonstrated 23% of paediatric patients 2 to <18 years of age were in clinical remission (sPCDAI) 52 weeks after initiation of ustekinumab treatment.

Comparable results were obtained for young adults in cohort 7 with 22% of patients in clinical remission 52 weeks after initiation of ustekinumab.

Two analyses were performed comparing cohort 3 to external adult placebo rates. The limitations of comparing with adult placebo rates are the different scoring systems used, CDAI v sPCDAI, the different study design across the studies, no formal hypothesis testing possible, and the timing of the placebo endpoints being limited to the induction phase of treatment.

In the first placebo comparison, the percentage of paediatric patients 2 to <18 years of age in clinical remission at week 52 is favourable when compared to the placebo group in the pivotal adult clinical trial CRD3001 (biologic-failure population) where only 8% of patients were in clinical remission. A meta-analysis was also performed to estimate the clinical remission rate of placebo treated adult patients with moderate to severe Crohn's disease from published clinical studies. 12 suitable studies were identified and results demonstrated the pooled proportion of adult patients on placebo, in clinical remission at Week 52, was 14%. The upper limit of the 95% CI for placebo for all meta-analysis studies overlapped with the lower limit of the 95% CI for cohort 3 suggesting no difference when compared to placebo. A sensitivity analysis was also performed excluding 2 of these studies, results demonstrated there was no overlap in 95% CIs when compared to cohort 3 which would support effectiveness of ustekinumab;this sensitivity analysis was not pre-specified in the protocol or SAP. Nevertheless it is not suitable to directly compare the meta-analysis of the adult placebo rate to the paediatric RWE and it is agreed that the heterogeneity and variations in study design in the adult meta-analysis and the difference in populations challenge the validity of this comparison and the generalisability of the results.

Other outcomes demonstrated that at week 52, the percentage of patients in clinical response and PGA clinical remission was higher in paediatric patients 2 to <18 years of age compared to young adults, 51 vs 40% (clinical response) and 34.5 vs 27.5% (PGA remission). A similar percentage of patients were in corticosteroid-free clinical remission (21 vs 20% for paediatrics v young adults).

Of the patients with endoscopy assessments, only a subset of these were evaluable for endoscopy remission at week 52, these results demonstrated 24 and 33% of patients in cohort 3 and cohort 7 were in endoscopic remission.

Of the patients who could be assessed by full PCDAI at Week 52, 23 and 44% of patients in cohort 3 and cohort 7 experienced clinical remission. For cohort 3, the PCDAI results are comparable to the sPCDAI results. For cohort 7, the PCDAI results are higher than the sPCDAI results, this is likely influenced by the small numbers of patients evaluable for PCDAI scores in cohort 7, n=9.

47 patients switched to a q4w dosing frequency and the applicant provides some limited efficacy data, for this group. The rate of clinical remission is 18% in the q4w group compared to 28% in the q8w group. This data is in addition to the 26 patients who switched to q4w in the pivotal phase 3 trial. There are proposed updates to the product information where the MAH recommends dosing every 4 weeks for patients who lose clinical response and have low ustekinumab exposure (see above).

Overall, the results of this observational study should be interpreted with caution due to some limitations mentioned above. However, there are also advantages to this study, the main advantage being that it allows a direct, within study, comparison of the targeted paediatric population compared to adults, a direct comparison that is not available from clinical trials.

Overall, this observational real-world evidence can be considered supportive to the clinical trial data for the paediatric extrapolation of ustekinumab efficacy in adults in CD.

**Comparison of studies CRD3004 and CRD1001**

Results are presented side by side between the phase 1 and the phase 3 trials. Many differences exist in the design of these studies limiting their interpretation. These differences include different inclusion/exclusion criteria, missing data rules and intercurrent or treatment failure rules. Other major differences include the different definitions used for clinical response and endoscopic response between the 2 studies. For the induction phase, data from all patients from the phase 3 trial are presented, however only 21 patients (390mg IV dose) are included for the phase 1 trial. As previously mentioned, this dosing is not in line with the proposed dosing in the SmPC, nor that of the phase 3 trial again limiting comparisons between the trials.

Induction results demonstrated a higher percentage of patients in clinical remission (>20% difference), clinical response (>20% difference) and endoscopic response (M-8) and a larger reduction from baseline in PCDAI scores and faecal calprotectin levels in the phase 3 trial compared to the phase 1 trial at week 8. The applicants comment that these differing results may be partly explained by a much higher percentage of biologic failure participants in CRD1001 (90.5% v 56%) is plausible and is suggestive of these patients representing a harder to treat population. However differing results may also be explained by the differences in trial designs and different induction posology. In addition, for clinical remission and endoscopic response, the 95% CIs overlap suggesting any difference in results may not be significant, however the small number of patients included in the analysis, particularly for CRD1001 (n=21), and absence of formal statistical analyses limits interpretation. CRP levels reduced by a comparable level in both trials at week 8. Following queries the MAH acknowledged a discrepancy in the reported clinical remission rates at Week I-8 in the CRD1001 CSR (19.0%) and the SCE (23.8%). The MAH explains that this difference arises from how 1 participant's missing laboratory data was analysed in each document - the Week 16 CSR analysis used the LOCF meaning the participant was not considered in remission, whereas in the SCE the laboratory value at Week I-3 was not carried forward, and the participant was considered to be in clinical remission. The handling rules and output in the CSR are considered more conservative and more appropriate; however this does not affect the overall conclusion of the comparisons between the two studies.

For the maintenance phase, data from all patients from the full clinical responder analysis set of the phase 3 trial are presented but for comparative purposes the q8w group (n=41) is most relevant. For the phase 1 trial data from patients who entered the long-term extension study and who were clinical responders at week 8 were included regardless of induction dose (n=22). The main time point also differs across the two studies, M-44 (52 weeks in total) v week 48.

Maintenance results demonstrated a lower but comparable percentage of patients in clinical remission, clinical response and corticosteroid-free clinical remission, a smaller change from baseline PCDAI scores, CRP levels and faecal calprotectin levels in the phase 3 trial compared to the phase 1 trial at week 48/M-44.

Overall, while there are a number of differences across the trials limiting interpretation, results from the phase 1 and 3 trials are broadly comparable with ustekinumab demonstrating positive effects in paediatric patients 2 to <18 years of age with moderate to severe Crohn's disease.

**Comparison of studies CRD3004 and adult studies**

Results are presented side by side between the pivotal paediatric trial 3004 and the pivotal adult trials (induction studies (UNITI-1, CRD3001 and UNITI-2, CRD3002) and a maintenance study (IM-UNITI,

CRD3003)). Again, many differences exist across the design of these studies limiting any interpretation of comparisons between the trials. In this case, the most important difference between the paediatric and adult trials is that the scoring system was PCDAI for the paediatric trials, and CDAI for the adult trials and these different scoring systems were used in a number of endpoint analyses.

Overall, disease characteristics were similar though a bit higher for paediatric patients compared to the adult studies, with higher CDAI scores and faecal calprotectin levels in the paediatric patients. A noticeable difference was also duration of disease which was considerably longer in the adult patients, 13 yrs (CRD3001) and 9 yrs (CRD3002)) compared to the paediatric population, 2.7 yrs, as would be expected giving the difference in age between the patients.

For the induction phase at week 8, the rate of clinical remission was higher in the paediatric patients (46.5%) when compared with adult patients (30% (the 2 induction studies combined). For the induction phase at week 8, the rate of clinical response was also higher in the paediatric patients (84%) when compared with adult patients (38% (CRD3001) and 58% (CRD3002). CIs for clinical response did not overlap suggesting there may be a significant difference between the paediatric patients and adults although no formal statistical comparison was performed.

In CRD3004, 56% of patients had a history of biologic failure, compared to 90.0% in CRD3001 and 1% CRD3002. Clinical remission and response rates in paediatric and adult patients who were non-biologic failures was generally stronger compared with those who were biologic failures.

Clinical remission rates were comparable for PCDAI, sPCDAI and CDAI in the pivotal phase 3 paediatric trial. Clinical response rates were also comparable for PCDAI and sPCDAI in the phase 3 trial. However clinical response rates during the induction phase differed significantly between CDAI and PCDAI/sPCDAI scoring systems therefore limiting any comparisons between studies using CDAI versus PCDAI/sPCDAI scoring systems. In turn this also emphasises the importance of the head-to-head within study comparison of the real-world study which uses the same scoring system in paediatric and adult patients.

Similar trends were also observed when looking at reductions from baseline in faecal calprotectin levels with a greater reduction in the paediatric study compared to the corresponding adult studies.

For the maintenance phase the main time point differs across the studies, M-44 (52 weeks in total - paediatrics) vs week 48 (adults). However, the results demonstrated that levels of clinical remission, clinical response, endoscopic response and corticosteroid-free clinical remission were higher or comparable across the paediatric and adult studies. For CRP and faecal calprotectin levels, there were greater reductions in paediatric patients compared to adult studies. As CDAI scores were also measured for the phase 3 trial CRD3001, the MAH compared CDAI results in paediatric patients to adult studies. While results demonstrated comparable CDAI clinical remission and response rates for the induction periods between paediatric and adult studies, CDAI clinical remission and response rates were lower in the maintenance periods in paediatrics (39% and 47%) compared to adults (51% and 59%). The MAH attributes these differences may be due to a number of factors including the CDAI scoring system not being validated for paediatric patients, a higher baseline CDAI scores in paediatrics compared to adults (365 vs 317) and a large amount of missing CDAI data for paediatric patients – 49% had at least 1 subscore missing. This is acknowledged.

Overall, while there are a number of differences across the trials limiting interpretation, results from the phase 3 trial in paediatric patients 2 to < 18 years of age are broadly comparable with ustekinumab in the adult pivotal trials demonstrating positive effects in paediatric patients with moderate to severe Crohn's disease and a maintenance of efficacy for up to 1 year of treatment.

### 2.5.5. Conclusions on the clinical efficacy

The extension of indication variation application to include paediatric patients from the age of 2 years and older, can accommodate an unmet need for the treatment of moderately to severely active Crohn's disease in paediatric patients. The study CRD3004 is designed as part of a paediatric extrapolation plan to evaluate efficacy, safety and PK. For the efficacy endpoints 'clinical remission at Week I-8' and 'clinical remission at week M44' it is found that generally the response rates are similar to the outcomes in the adult population. The occasional divergent outcomes in the youngest and lightest children are expected to be due to the limited number of patients. Despite indicators that disease burden could be higher in the youngest population, the response rates are similar in paediatric patients compared to the outcomes in the adult population.

Overall data demonstrates positive efficacy to support the use of ustekinumab in paediatric patients with moderately to severely active Crohn's disease.

## *2.6. Clinical safety*

## Introduction

With this variation, the MAH seeks to extend further the current indication for the treatment of paediatric patients with moderately to severely active Crohn's disease from the age of 2 years, with no weight qualification. The proposed new posology for children weighing under 40kg is a single IV **induction** dose, based on Body Surface Area.

**And for maintenance**: a subcutaneous dosing regime is proposed, also based on BSA, for children under 40kg, with a 12-weekly interval (after first maintenance dose 8 weeks after induction dose), with a possibility to increase to an 8-weekly, or 4-weekly interval as required.

Of note, the possibility of a q4w frequency is proposed in the STELARA SmPC, for the paediatric population; this frequency is not currently approved in other indications including the adult Crohn's indication.

The clinical development program for ustekinumab in 'Paediatric Crohn's disease' consists of;

Paediatric Crohn's disease clinical studies-

- Phase 3 Study CRD3004 (UNITI Jr.), including its optional CRD3004 Exposure Optimisation Substudy (EOS)- complete
- Phase 1 PK Study CRD1001 (UNISTAR), including its LTE phase- complete
- LTE basket study CNTO1275**ISD3001** (UNITED), (ongoing) which was designed for CD (CRD3004 and CRD1001), UC (CNTO1275**PUC3001** [UNIFI Jr]), and juvenile psoriatic arthritis (CNTO1275JPA3001 [PSUMMIT Jr]) study participants who are deriving clinical benefit to monitor safety and provide uninterrupted pre-approval access to ustekinumab under pharmacovigilance. This study forms part of the RMP as a category 3 additional pharmacovigilance activity to address the missing information of long-term safety in paediatric patients with moderately to severely active Crohn's disease.

**Table 64: Overview of Clinical Studies**

| Study Number/ Description/Status | Study Population and Primary Endpoint | Treatment Period | Number of Participants Enrolled/Treated Participants |
|---|---|---|---|
| **Pediatric CD studies** | | | |
| CNTO1275CRD3004 (UNITI Jr)<br><br>Phase 3, multicenter, open-label induction period with a single IV ustekinumab induction dose followed by a maintenance period with a randomized, double-blind, parallel-group, and 2-arm regimens<br><br>Participants in either dosing arm (q12w or q8w) who were induction nonresponders with 8-week trough low exposure or participants who had LOR with 8-week trough low exposure during the maintenance phase were eligible to enroll in an optional open-label EOS<br><br>Completed | Pediatric participants 2 to <18 years of age with moderately to severely active CD (defined by a PCDAI score of >30)<br><br>Global primary endpoint: clinical remission at Week I-8 as assessed by PCDAI<br><br>US-specific endpoint: clinical remission at Week M-44 evaluated among participants who were in clinical response at Week I-8 | Main study: from Week I-0 to Week 52 (ie, Week M-44) | 101 participants<br><br>q12w (n=49)<br>q8w (n=48)<br>q12w or q8w → q4w optional substudy (n=26)<br>(Attachment TSIDS02 and Attachment TSIDS04) |
| CNTO1275CRD1001 (UniStar)<br><br>Phase 1 (PK), randomized, double-blind, PK study of IV ustekinumab induction followed by SC ustekinumab maintenance<br><br>Completed | Pediatric participants (2 to <18 years of age in the US; 6 to <18 years of age elsewhere) with moderately to severely active CD (defined by a PCDAI score of >30)<br><br>There was no primary efficacy endpoint, and no formal hypothesis testing was performed | Main study: from Week 0 to Week 16<br><br>LTE period: from Week 16 to Week 240 (note: post hoc, this SCS has redefined the maintenance phase of CNTO1275CRD1001 to include Week 16 to Week 48, in order to align with the phases of the Phase 3 CNTO1275CRD3004 study) | 44 participants were treated (of which 34 participated in the LTE period) at Week 16 (Attachment TSIDS02 and Attachment TSIDS04) |
| CNTO1275ISD3001 (UNITED)<br><br>Phase 3, multicenter, open-label, basket LTE study of SC ustekinumab<br><br>Ongoing | Pediatric participants (2 to <18 years of age) who have participated in a pediatric ustekinumab clinical study<br><br>Endpoints: long-term safety data including AEs, SAEs, AEs leading to discontinuation of study intervention, and AESIs (as determined for each indication), laboratory results, injection-site reactions, and addition of concomitant medications due to LOR | Participants from the established unblinded primary study protocol remain on the same SC ustekinumab dose regimen as assigned in the primary study<br><br>Participants from the blinded primary study are assigned to the q8w dose regimen in the LTE, regardless of prior dosing. Following unblinding, investigators may adjust dosing intervals based on the participant's original regimen and clinical judgment | As of 18 November 2024, participants included in the SCS analyses:<br><br>CNTO1275CRD1001: 6<br>CNTO1275CRD3004: 66 |

Additional supportive data is provided from:

- safety and efficacy from the confirmatory Crohn's disease studies in adults.
    - Two adult Phase 3 induction studies CRD3001 (UNITI 1), and CRD3002 (UNITI 2).
    - A single Phase 3 randomised withdrawal maintenance Study CRD3003 (IM-IMUNITI).
- Recently completed CNTO1275**PUC3001**, a Phase 3 study in paediatric participants (aged 2 to <18 years) with moderately to severely active Ulcerative Colitis (defined by a Mayo score of 6 to 12, inclusive, with an endoscopy subscore of ≥2 determined by central review of the video of the endoscopy), and its Exposure Optimisation SubStudy (EOS). Limited, preliminary data is available from the EOS only.
- Paediatric safety data for plaque PsO from two Phase 3 studies - Study PSO3006 (CADMUS) and Study PSO3013 (CADMUS Jr).
- Post- authorisation safety study of ustekinumab in paediatric patients 6 to 17 years of age with moderate-to-severe plaque psoriasis PSO4056 (STELLAR Teens).
- PASS of the long-term safety and clinical status of paediatric patients <17 years of age with IBD (Crohn's disease, UC, or indeterminate colitis) treated with infliximab and collects data on other medical therapies for IBD as part of routine clinical care (C0168Z02 (DEVELOP)).
- Observational Real-world Evidence Effectiveness Study CNTO1275**CRD3010**. Paediatric Cohort 3 consisted of all paediatric patients (<40 kg and ≥40 kg) with moderately to severely active CD (145 patients).

***Please note: Data from the EOS substudy of CRD3004 where a q4w treatment interval was applied to 26 patients are discussed in the Additional Clinical data section.***

## Patient exposure

Overall paediatric exposure (patient numbers) to Ustekinumab across all indications

In the entire ustekinumab clinical development program, a total of 258 paediatric participants have been exposed to ustekinumab in the completed clinical studies across 3 disease indications:

- 145 CD participants in the SAS from CRD3004 (n=101) and CRD1001 (n=44),
- 21 UC participants from PUC3001 EOS, and
- 117 participants with PsO from PSO3006 and PSO3013.

There are 2 additional observational PASSs conducted in paediatric patients exposed to ustekinumab. These include the ongoing DEVELOP IBD study which includes the 165 paediatric patients (<18 years of age) with CD who were enrolled as part of the overall study of 6,069 paediatric patients (but of which only 165 paediatric patients with CD received ustekinumab exposure), and the ongoing CNTO1275PSO4056 study in 125 adolescent participants with PsO.

Crohn's Disease paediatric exposure

The primary evidence of safety of ustekinumab in paediatric patients with Crohn's disease comes from the pivotal Phase 3 CRD3004 study and phase 1 PK Study (CRD1001). Of note the doses in CRD1001 do not match the proposed posology.

The following tables outlines the paediatric Crohn's Disease exposure to Ustekinumab to date.

**Table 65: Number of subjects who received scheduled SC study agent ustekinumab by timepoint from Week M-0 through Week M-44; Safety Randomised Analysis Set (Study CNTO1275CRD3004)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | Randomized at Week M-0 | | |
| | q12w | q8w | Combined |
| Analysis set: Safety Randomized | 49 | 48 | 97 |
| Subjects receiving a scheduled study agent | | | |
| Week M-0 | 49 (100.0%) | 48 (100.0%) | 97 (100.0%) |
| Week M-8 | 0 | 46 (95.8%) | 46 (47.4%) |
| Week M-12 | 41 (83.7%) | 1 (2.1%) | 42 (43.3%) |
| Week M-16 | 0 | 43 (89.6%) | 43 (44.3%) |
| Week M-24 | 37 (75.5%) | 37 (77.1%) | 74 (76.3%) |
| Week M-32 | 1 (2.0%) | 34 (70.8%) | 35 (36.1%) |
| Week M-36 | 33 (67.3%) | 1 (2.1%) | 34 (35.1%) |
| Week M-40 | 2 (4.1%) | 31 (64.6%) | 33 (34.0%) |

Note: Data from the time of substudy onward are not included.

**Table 66: Summary of treatment with ustekinumab through Week M-44/Week 48; Safety Analysis Set (Studies CNTO1275CRD3001, CNTO1275CRD3004)**

| | Ustekinumab | | | | |
|---|---|---|---|---|---|
| | CRD1001 | CRD3004 | | | |
| | q8w | Not Randomized | q12w | q8w | Total |
| Analysis set: Safety Analysis Set | 44 | 4 | 49 | 48 | 101 |
| Total duration of ustekinumab exposure (weeks)[a] | | | | | |
| Intravenous + Subcutaneous | | | | | |
| N | 44 | 4 | 49 | 48 | 101 |
| Mean (SD) | 29.7 (15.38) | 0.1 (0.00) | 36.4 (14.48) | 40.3 (12.88) | 36.8 (15.44) |
| Median | 39.3 | 0.1 | 44.1 | 48.1 | 44.3 |
| Range | (0; 43) | (0; 0) | (8; 54) | (8; 50) | (0; 54) |
| IQ range | (15.7; 40.1) | (0.1; 0.1) | (32.1; 45.1) | (31.9; 49.1) | (24.1; 48.1) |
| Total number of ustekinumab infusions received | | | | | |
| N | 44 | 4 | 49 | 48 | 101 |
| Mean (SD) | 1.0 (0.00) | 1.0 (0.00) | 1.0 (0.00) | 1.0 (0.00) | 1.0 (0.00) |
| Median | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Range | (1; 1) | (1; 1) | (1; 1) | (1; 1) | (1; 1) |
| IQ range | (1.0; 1.0) | (1.0; 1.0) | (1.0; 1.0) | (1.0; 1.0) | (1.0; 1.0) |
| Total number of ustekinumab injections received | | | | | |
| N | 40 | 0 | 49 | 48 | 97 |
| Mean (SD) | 4.1 (1.59) | - | 4.0 (1.93) | 5.9 (2.62) | 4.9 (2.47) |
| Median | 5.0 | - | 4.0 | 6.0 | 4.0 |
| Range | (1; 5) | - | (1; 8) | (1; 12) | (1; 12) |
| IQ range | (3.0; 5.0) | - | (4.0; 4.0) | (4.0; 6.0) | (4.0; 6.0) |

A total of 101 participants in **CRD3004** were treated at Week I-0 with a single IV dose of ustekinumab. At Week M-0, a total of 97 participants were randomised to either receive the q12w (49 participants) or q8w (48 participants) SC regimen of ustekinumab. A total of 44 participants were treated with an induction dose of ustekinumab in **CRD1001**.

The median total duration of exposure (weeks) through the end of the maintenance period (Week M-44/Week 48):

- In CRD3004, the q12w and q8w treatment groups were 44.1 and 48.1 weeks, respectively.
- In CRD1001 was 39.3 weeks.

The median total number of SC ustekinumab injections received in the q12w and q8w treatment groups in CRD3004 were 4.0 and 6.0, respectively, and was 5.0 in CRD1001.

The median total doses of ustekinumab (mg) (IV induction and SC maintenance) received in the q12w and q8w treatment groups in CRD3004 were 620.0 mg and 800.0 mg, respectively.

In CRD1001, the median total dose of ustekinumab (mg) (IV induction and SC maintenance) received was 493.5 mg.

**Exposure in CRD3004's Exposure Optimisation substudy**

**Table 67: Overall Summary of treatment-emergent Adverse Events Through the End of Substudy Period; Substudy Analysis Set (Study CNTO1275CRD3004)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | q12w->q4w | q8w->q4w | Combined |
| Analysis set: Substudy | 11 | 15 | 26 |
| Avg duration of follow-up (weeks) | 22.4 | 20.4 | 21.3 |
| Avg exposure (number of administrations) | 7.3 | 5.4 | 6.2 |

**Exposure in CD studies Long-term Extension: CRD1001's Longterm extension phase and the LTE UNITED Basket study ISD3001 (which took subjects from both CRD1001 and CRD3004)**

CRD1001's Longterm extension phase

At Week 48, a total of 26 participants were treated with ustekinumab in CRD1001 in its LTE period. From Week 48 onwards, the median total duration of exposure was 66.2 weeks, and the median total number of SC injections was 10.0. The median total dose (mg) of ustekinumab SC received was 900.0 mg.

LTE Basket study ISD3001 (UNITED, which took subjects from both CRD1001 and CRD3004)

A total of 66 participants from **CRD3004** were treated with ustekinumab in **ISD3001 UNITED**; 48 participants in the q8w treatment group and 18 participants in the q4w treatment group (after at least 52 weeks in **CRD3004)**. The median total duration of exposure in **ISD3001** (UNITED) was 48.8 weeks (48.8 and 41.1 weeks in the q8w and q4w treatment groups, respectively). The median total number of SC injections in the q8w treatment group was 8.0, and in the q4w treatment group was 9.0. The median total dose of ustekinumab SC received by these participants was 630.0 mg (630.0 mg and 810.0 mg in the q8w and q4w treatment groups, respectively).

Six participants from **CRD1001** were treated with ustekinumab in **ISD3001 UNITED**, with a median total duration of exposure of 94.5 weeks, median total number of SC injections of 13.0, and a median total dose of 1,170.0 mg of ustekinumab SC.

**Table 68: Summary of treatment with ustekinumab during the long-term extension period; Safety Analysis Set (Studies CNTO1275CR1001 and CNTO1275ISD3001)**

| | Ustekinumab | | | | |
|---|---|---|---|---|---|
| | | ISD3001 | | | |
| | CRD1001 | CRD1001 | CRD3004 | | |
| | q8w | q8w | q8w | q4w | Total |
| Analysis set: Safety Analysis Set | 26 | 6 | 48 | 18 | 66 |
| Total duration of ustekinumab exposure (weeks)[a] | | | | | |
| Subcutaneous | | | | | |
| N | 26 | 6 | 48 | 18 | 66 |
| Mean (SD) | 92.0 (69.35) | 93.6 (50.90) | 54.4 (32.41) | 39.9 (28.84) | 50.4 (31.93) |
| Median | 66.2 | 94.5 | 48.8 | 41.1 | 48.8 |
| Range | (0; 193) | (41; 146) | (0; 121) | (5; 91) | (0; 121) |
| IQ range | (32.0; 168.0) | (41.0; 145.1) | (32.8; 79.6) | (12.1; 60.0) | (24.1; 72.3) |
| Total number of ustekinumab injections received[b] | | | | | |
| N | 26 | 6 | 48 | 18 | 66 |
| Mean (SD) | 12.5 (8.50) | 12.7 (6.35) | 8.1 (4.20) | 9.9 (6.58) | 8.6 (4.97) |
| Median | 10.0 | 13.0 | 8.0 | 9.0 | 8.0 |
| Range | (1; 25) | (6; 19) | (1; 16) | (2; 23) | (1; 23) |
| IQ range | (5.0; 22.0) | (6.0; 19.0) | (5.0; 12.0) | (4.0; 14.0) | (5.0; 13.0) |
| Total dose of ustekinumab administrations received (mg)[b] | | | | | |
| Subcutaneous | | | | | |
| N | 26 | 6 | 48 | 18 | 66 |
| Mean (SD) | 1052.7 (735.97) | 1138.2 (568.92) | 652.9 (346.14) | 892.5 (591.03) | 718.2 (435.38) |
| Median | 900.0 | 1170.0 | 630.0 | 810.0 | 630.0 |
| Range | (72; 2250) | (540; 1710) | (90; 1440) | (180; 2070) | (90; 2070) |
| IQ range | (450.0; 1872.0) | (540.0; 1699.0) | (411.8; 900.0) | (360.0; 1260.0) | (360.0; 990.0) |

**Table 69: Demographic characteristics at baseline; Safety Analysis Set (Studies CNTO1275CR1001, CNTO1275CRD3004 and CNTO1275ISD3001)**

| | Ustekinumab | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ISD3001 | | | |
| | CRD1001 | CRD3004 | | | | CRD1001 | CRD3004 | | |
| | q8w | Not Randomized | q12w | q8w | Total | q8w | q8w | q4w | Total |
| Analysis set: Safety Analysis Set | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Age, years | | | | | | | | | |
| N | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Mean (SD) | 13.4 (2.74) | 13.3 (1.50) | 13.5 (2.92) | 13.4 (2.65) | 13.5 (2.73) | 14.7 (2.25) | 13.8 (3.11) | 14.8 (1.99) | 14.1 (2.87) |
| Median | 13.0 | 14.0 | 14.0 | 14.0 | 14.0 | 14.5 | 15.0 | 14.5 | 15.0 |
| Range | (6; 17) | (11; 14) | (5; 17) | (2; 17) | (2; 17) | (11; 17) | (3; 17) | (10; 17) | (3; 17) |
| IQ range | (12.0; 16.0) | (12.5; 14.0) | (12.0; 16.0) | (12.0; 15.0) | (12.0; 15.0) | (14.0; 17.0) | (12.0; 16.0) | (13.0; 17.0) | (13.0; 16.0) |
| ≥2-<12 years | 10 (22.7%) | 1 (25.0%) | 12 (24.5%) | 7 (14.6%) | 20 (19.8%) | 1 (16.7%) | 11 (22.9%) | 1 (5.6%) | 12 (18.2%) |
| ≥2-<6 years | 0 | 0 | 1 (2.0%) | 1 (2.1%) | 2 (2.0%) | 0 | 1 (2.1%) | 0 | 1 (1.5%) |
| ≥6-<12 years | 10 (22.7%) | 1 (25.0%) | 11 (22.4%) | 6 (12.5%) | 18 (17.8%) | 1 (16.7%) | 10 (20.8%) | 1 (5.6%) | 11 (16.7%) |
| ≥12-<18 years | 34 (77.3%) | 3 (75.0%) | 37 (75.5%) | 41 (85.4%) | 81 (80.2%) | 5 (83.3%) | 37 (77.1%) | 17 (94.4%) | 54 (81.8%) |
| Sex | | | | | | | | | |
| N | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Female | 26 (59.1%) | 2 (50.0%) | 21 (42.9%) | 18 (37.5%) | 41 (40.6%) | 4 (66.7%) | 18 (37.5%) | 7 (38.9%) | 25 (37.9%) |
| Male | 18 (40.9%) | 2 (50.0%) | 28 (57.1%) | 30 (62.5%) | 60 (59.4%) | 2 (33.3%) | 30 (62.5%) | 11 (61.1%) | 41 (62.1%) |
| Body mass index, kg/m$^2$ | | | | | | | | | |
| N | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Mean (SD) | 17.9 (3.30) | 17.4 (2.09) | 18.4 (3.79) | 18.7 (3.50) | 18.5 (3.58) | 21.1 (3.18) | 19.6 (3.35) | 19.7 (3.99) | 19.6 (3.51) |
| Median | 17.4 | 17.4 | 17.4 | 18.0 | 17.5 | 21.5 | 19.0 | 18.8 | 18.9 |
| Range | (13; 28) | (15; 20) | (13; 29) | (14; 30) | (13; 30) | (17; 25) | (14; 29) | (14; 31) | (14; 31) |
| IQ range | (15.4; 20.1) | (15.7; 19.1) | (15.5; 21.7) | (16.0; 21.1) | (15.8; 21.1) | (17.8; 23.0) | (16.9; 21.7) | (17.3; 21.7) | (16.9; 21.7) |
| Underweight <18.5 | 29 (65.9%) | 2 (50.0%) | 30 (61.2%) | 25 (52.1%) | 57 (56.4%) | 2 (33.3%) | 19 (39.6%) | 8 (44.4%) | 27 (40.9%) |
| Normal 18.5-<25 | 13 (29.5%) | 2 (50.0%) | 17 (34.7%) | 21 (43.8%) | 40 (39.6%) | 3 (50.0%) | 26 (54.2%) | 8 (44.4%) | 34 (51.5%) |
| Overweight 25-<30 | 2 (4.5%) | 0 | 2 (4.1%) | 1 (2.1%) | 3 (3.0%) | 1 (16.7%) | 3 (6.3%) | 1 (5.6%) | 4 (6.1%) |
| Obese ≥30 | 0 | 0 | 0 | 1 (2.1%) | 1 (1.0%) | 0 | 0 | 1 (5.6%) | 1 (1.5%) |

Key: IQ = interquartile
[a] Age and sex-specific.
Note: N's for each parameter reflect non-missing values.

**Table 70: Baseline Crohn's disease characteristics; Safety Analysis Set (Studies CNTO1275CR1001, CNTO1275CRD3004 and CNTO1275ISD3001)**

| | Ustekinumab | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ISD3001 | | | |
| | CRD1001 | CRD3004 | | | | CRD1001 | CRD3004 | | |
| | q8w | Not Randomized | q12w | q8w | Total | q8w | q8w | q4w | Total |
| Analysis set: Safety Analysis Set | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Age at diagnosis, years | | | | | | | | | |
| N | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Mean (SD) | 9.0 (3.99) | 12.2 (2.30) | 10.7 (3.58) | 10.9 (2.99) | 10.9 (3.25) | 7.3 (3.45) | 10.2 (3.49) | 10.9 (2.40) | 10.4 (3.23) |
| Median | 9.0 | 13.1 | 10.8 | 11.5 | 11.3 | 8.1 | 10.5 | 10.9 | 10.7 |
| Range | (1; 17) | (9; 14) | (1; 17) | (1; 17) | (1; 17) | (1; 11) | (1; 15) | (6; 16) | (1; 16) |
| IQ range | (6.4; 11.3) | (10.8; 13.6) | (8.3; 13.5) | (9.1; 12.9) | (8.8; 13.1) | (6.1; 9.2) | (8.3; 12.9) | (10.5; 11.7) | (8.4; 12.7) |
| CD disease duration, years | | | | | | | | | |
| N | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Mean (SD) | 4.4 (3.06) | 1.2 (0.90) | 2.8 (2.51) | 2.6 (1.98) | 2.6 (2.24) | 3.6 (1.96) | 2.6 (2.26) | 2.8 (1.77) | 2.7 (2.13) |
| Median | 3.6 | 0.9 | 2.2 | 2.0 | 2.0 | 3.8 | 2.0 | 2.6 | 2.1 |
| Range | (0; 12) | (0; 2) | (0; 13) | (0; 8) | (0; 13) | (1; 6) | (0; 13) | (0; 6) | (0; 13) |
| IQ range | (2.0; 6.4) | (0.5; 1.9) | (1.0; 4.4) | (1.0; 3.9) | (1.0; 4.1) | (1.9; 5.4) | (1.0; 3.6) | (1.2; 4.1) | (1.0; 3.6) |
| ≤1 yr | 4 (9.1%) | 2 (50.0%) | 14 (28.6%) | 12 (25.0%) | 28 (27.7%) | 1 (16.7%) | 12 (25.0%) | 3 (16.7%) | 15 (22.7%) |
| >1-<5 yrs | 23 (52.3%) | 2 (50.0%) | 27 (55.1%) | 28 (58.3%) | 57 (56.4%) | 3 (50.0%) | 30 (62.5%) | 11 (61.1%) | 41 (62.1%) |
| ≥5 yrs | 17 (38.6%) | 0 | 8 (16.3%) | 8 (16.7%) | 16 (15.8%) | 2 (33.3%) | 6 (12.5%) | 4 (22.2%) | 10 (15.2%) |
| PCDAI Score | | | | | | | | | |
| N | 41 | 4 | 49 | 48 | 101 | 5 | 48 | 18 | 66 |
| Mean (SD) | 42.93 (10.824) | 39.38 (4.270) | 41.48 (7.822) | 40.99 (7.714) | 41.16 (7.620) | 39.00 (16.919) | 40.00 (7.402) | 41.94 (5.724) | 40.53 (6.996) |
| Median | 42.50 | 38.75 | 40.00 | 40.00 | 40.00 | 37.50 | 37.50 | 41.25 | 40.00 |
| Range | (12.5; 65.0) | (35.0; 45.0) | (25.0; 62.5) | (20.0; 60.0) | (20.0; 62.5) | (12.5; 55.0) | (30.0; 62.5) | (27.5; 52.5) | (27.5; 62.5) |
| IQ range | (37.50; 50.00) | (36.25; 42.50) | (35.00; 47.50) | (35.00; 45.00) | (35.00; 45.00) | (37.50; 52.50) | (35.00; 45.00) | (37.50; 47.50) | (35.00; 45.00) |
| Remission or mild ≤30 | 5 (12.2%) | 0 | 3 (6.1%) | 2 (4.2%) | 5 (5.0%) | 1 (20.0%) | 1 (2.1%) | 1 (5.6%) | 2 (3.0%) |
| Moderate >30-≤40 | 10 (24.4%) | 3 (75.0%) | 25 (51.0%) | 24 (50.0%) | 52 (51.5%) | 2 (40.0%) | 30 (62.5%) | 8 (44.4%) | 38 (57.6%) |
| Severe >40 | 26 (63.4%) | 1 (25.0%) | 21 (42.9%) | 22 (45.8%) | 44 (43.6%) | 2 (40.0%) | 17 (35.4%) | 9 (50.0%) | 26 (39.4%) |
| SES-CD Score | | | | | | | | | |
| N | 44 | 4 | 48 | 48 | 100 | 6 | 47 | 18 | 65 |
| Mean (SD) | 14.4 (10.43) | 13.3 (9.81) | 12.4 (6.20) | 12.6 (7.92) | 12.6 (7.14) | 16.2 (10.13) | 12.7 (6.87) | 11.6 (9.40) | 12.4 (7.59) |
| Median | 14.0 | 12.0 | 12.0 | 12.0 | 12.0 | 16.5 | 13.0 | 7.0 | 12.0 |
| Range | (0; 37) | (3; 26) | (3; 26) | (0; 34) | (0; 34) | (4; 28) | (3; 27) | (0; 34) | (0; 34) |
| IQ range | (5.0; 21.5) | (6.0; 20.5) | (7.0; 18.0) | (6.0; 19.0) | (6.5; 18.5) | (6.0; 26.0) | (6.0; 19.0) | (6.0; 17.0) | (6.0; 19.0) |

## Adverse events

### Induction Period; AE Overview, Safety Analysis Set (CRD1001 and CRD3004)

**Table 71: Overall Summary of Treatment-emergent Adverse Events From Week I-0 (Week 0) Through Week I-8 (Week 8); Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Safety Analysis Set | 44 | 101 |
| Average duration of follow-up (weeks) | 8.0 | 8.1 |
| Average exposure (number of administrations) | 1.0 | 1.0 |
| Subjects with 1 or more: | | |
| AEs | 28 (63.6%) | 63 (62.4%) |
| Serious AEs | 4 (9.1%) | 3 (3.0%) |
| AEs leading to death | 0 | 0 |
| AEs leading to discontinuation of study intervention | 3 (6.8%) | 3 (3.0%) |
| AEs reasonably related to study intervention[a] | 11 (25.0%) | 8 (7.9%) |
| AEs of severe intensity | 2 (4.5%) | 3 (3.0%) |
| Infections | 10 (22.7%) | 30 (29.7%) |
| Serious infections | 0 | 1 (1.0%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 3 (6.8%) | 7 (6.9%) |
| Malignancy | 0 | 0 |
| Active tuberculous infections | 0 | 0 |

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Opportunistic infections | 0 | 0 |
| AEs temporally associated with the infusion of study intervention at Week I-0 (Week 0)[b] | 1 (2.3%) | 4 (4.0%) |

**Induction Phase: AE breakdown, Safety Analysis Set (CRD1001 and CRD3004)**

**Table 72: Number of subjects with Treatment-emergent Adverse Events From Week I-0 (Week 0) Through Week I-8 (Week 8) by SOC and PT; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Safety Analysis Set | 44 | 101 |
| Average duration of follow-up (weeks) | 8.0 | 8.1 |
| Average exposure (number of administrations) | 1.0 | 1.0 |
| Subjects with 1 or more AEs | 28 (63.6%) | 63 (62.4%) |
| System organ class<br>Preferred term | | |
| Infections and infestations | 11 (25.0%) | 30 (29.7%) |
| Upper respiratory tract infection | 2 (4.5%) | 13 (12.9%) |
| Gastroenteritis | 1 (2.3%) | 4 (4.0%) |
| Nasopharyngitis | 1 (2.3%) | 4 (4.0%) |
| COVID-19 | 0 | 3 (3.0%) |
| Oral herpes | 0 | 2 (2.0%) |
| Otitis externa | 0 | 2 (2.0%) |
| Viral infection | 1 (2.3%) | 2 (2.0%) |
| Acarodermatitis | 0 | 1 (1.0%) |
| Anal abscess | 1 (2.3%) | 1 (1.0%) |
| Clostridium difficile colitis | 0 | 1 (1.0%) |
| Onychomycosis | 0 | 1 (1.0%) |
| Otitis externa bacterial | 0 | 1 (1.0%) |
| Otitis media | 0 | 1 (1.0%) |
| Pharyngitis streptococcal | 0 | 1 (1.0%) |
| Respiratory tract infection | 0 | 1 (1.0%) |
| Rhinitis | 0 | 1 (1.0%) |
| Clostridium difficile infection | 1 (2.3%) | 0 |
| Eczema infected | 1 (2.3%) | 0 |
| Gastroenteritis viral | 1 (2.3%) | 0 |
| Localised infection | 1 (2.3%) | 0 |
| Pharyngitis | 1 (2.3%) | 0 |
| Viral upper respiratory tract infection | 1 (2.3%) | 0 |
| Gastrointestinal disorders | 14 (31.8%) | 19 (18.8%) |
| Nausea | 0 | 6 (5.9%) |
| Crohn's disease | 4 (9.1%) | 4 (4.0%) |
| Vomiting | 2 (4.5%) | 4 (4.0%) |
| Anal fistula | 4 (9.1%) | 2 (2.0%) |
| Abdominal pain upper | 0 | 1 (1.0%) |
| Abdominal tenderness | 0 | 1 (1.0%) |
| Anal fissure | 1 (2.3%) | 1 (1.0%) |
| Diarrhoea | 0 | 1 (1.0%) |
| Dyspepsia | 0 | 1 (1.0%) |
| Gastrointestinal pain | 0 | 1 (1.0%) |
| Gastrooesophageal reflux disease | 1 (2.3%) | 1 (1.0%) |
| Constipation | 1 (2.3%) | 0 |
| Food poisoning | 1 (2.3%) | 0 |
| Haematochezia | 1 (2.3%) | 0 |
| Intestinal obstruction | 1 (2.3%) | 0 |

Overall, 30 (29.7%) of 101 participants in CRD3004 and 11 (25.0%) of 44 participants in CRD1001 reported AEs within the Infections and infestations SOC.

Infections and Infestations and gastrointestinal disorders were the most commonly represented SOC during the induction phases of both CRD3004 and CRD1001.

Overall, 19 (18.8%) participants in CRD3004 and 14 (31.8%) participants in CRD1001 reported AEs within the Gastrointestinal disorders SOC.

In CRD3004, nausea was the most frequently reported PT in 6 (5.9%) participants, followed by Crohn's disease and vomiting, each in 4 (4.0%) participants.

In CRD1001, the most frequently reported PTs were Crohn's disease and anal fistula, each in 4 (9.1%) participants, followed by vomiting in 2 (4.5%) participants.

In CRD3004, other PTs reported in ≥5% of participants were anemia (9 [8.9%] participants; SOC Blood and lymphatic system disorders) and headache (7 [6.9%] participants).

In CRD1001, other PTs reported in ≥5% of participants were headache (8 [18.2%] participants; SOC Nervous system disorders), anemia (6 [13.6%] participants), pyrexia (3 [6.8%] participants), and fatigue (3 [6.8%] participants

Headache was the most frequent reasonably related PT in CRD1001 (3 [6.8%] participants), whereas in CRD3004, headache and vomiting were equally the most frequent PTs (2 [2.0%] participants each). In both studies no other PT considered reasonably related occurred with a frequency of > 1.

Maintenance Period; AE Overview, Safety Analysis Set (CRD1001 and CRD3004)

**Table 73: Overall summary of Treatment-emergent Adverse Events From Week M-0 (Week 8) Through Week M-44/Week 48; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q12w | q8w | Total |
| Analysis set: Safety Analysis Set | 43 | 49 | 48 | 97 |
| Average duration of follow-up (weeks) | 32.3 | 36.2 | 36.5 | 36.4 |
| Average exposure (number of administrations) | 4.1 | 7.7 | 7.6 | 7.6 |
| Subjects with 1 or more: | | | | |
| AEs | 34 (79.1%) | 44 (89.8%) | 40 (83.3%) | 84 (86.6%) |
| Serious AEs | 10 (23.3%) | 6 (12.2%) | 7 (14.6%) | 13 (13.4%) |
| AEs leading to death | 0 | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 5 (11.6%) | 3 (6.1%) | 2 (4.2%) | 5 (5.2%) |
| AEs reasonably related to study intervention[a] | 9 (20.9%) | 2 (4.1%) | 1 (2.1%) | 3 (3.1%) |
| AEs of severe intensity | 8 (18.6%) | 5 (10.2%) | 1 (2.1%) | 6 (6.2%) |
| Infections | 21 (48.8%) | 32 (65.3%) | 29 (60.4%) | 61 (62.9%) |
| Serious infections | 1 (2.3%) | 2 (4.1%) | 2 (4.2%) | 4 (4.1%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 10 (23.3%) | 11 (22.4%) | 11 (22.9%) | 22 (22.7%) |
| Malignancy | 0 | 0 | 0 | 0 |
| Active tuberculous infections | 0 | 0 | 0 | 0 |
| Opportunistic infections | 0 | 0 | 0 | 0 |
| Injection site-reaction[b] | 0 | 0 | 0 | 0 |

Key: AE = adverse event
[a] An adverse event that is assessed by the investigator as related to study agent or if the relationship to study agent is missing.
[b] Injection-site reaction is any reaction at an SC study intervention injection site that was recorded as an injection-site reaction by the investigator on the eCRF.
Note: Subjects are counted only once for any given event type, regardless of the number of times they actually experienced the event.
Note: Subjects who were randomized into the maintenance period of the study and received at least 1 administration of study intervention during maintenance are included. Data from the time of substudy onward in study CRD3004 are not included and are summarized separately.

Maintenance Period; AE Breakdown, Safety Analysis Set (CRD1001 and CRD3004)

As for the induction period, overall Infections and Infestations and gastrointestinal disorders were the most commonly represented SOC in the maintenance periods of both CRD3004 and CRD1001.

Overall, 60 (61.9%) of 97 participants in CRD3004 (similarly reported in the q12w and q8w treatment groups) and 20 (46.5%) of 43 participants in CRD1001 reported AEs within the Gastrointestinal disorders SOC.

The most frequently reported PT in both CRD3004 and CRD1001 was Crohn's disease (36 [37.1%] participants and 11 [25.6%] participants, respectively).

Abdominal pain, diarrhoea, nausea, and vomiting were the next most frequently reported PTs in the Gastrointestinal disorders SOC for both the CRD3004 and CRD1001 studies, occurring in <8% of participants in each study.

Overall, 57 (58.8%) participants in CRD3004 (similarly reported in the q12w and q8w treatment groups) and 21 (48.8%) participants in CRD1001 reported AEs within the Infections and infestations SOC.

Upper respiratory tract infection was the most frequently reported PT in both CRD3004 (23 [23.7%] participants) and CRD1001(10 [23.3%] participants).

COVID-19 was reported in 15 (15.5%) participants in CRD3004, but was not reported in any CRD1001 participant, consistent with the relative timing of the global COVID-19 pandemic and timing of the CRD1001 study.

Following upper respiratory tract infection (and excluding COVID-19), nasopharyngitis was the next most frequently reported PT in 12 (12.4%) participants and 4 (9.3%) participants of CRD3004 and CRD1001, respectively.

No participant in either the CRD3004 or CRD1001 studies experienced an injection-site reaction.

In CRD3004, all reasonably related AEs were singular events with none occurring in more than 1 participant, whereas Crohn's disease was the most common reasonably related PT among CRD1001 participants (3 [7.0%] participants).

Long term extension period: i.e. LTE period of CRD1001 and in ISD3001(UNITED)

**Table 74: Overall summary of Treatment-Emergent Adverse Events during long-term extension; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275ISD3001)**

| | Ustekinumab | | |
|---|---|---|---|
| | | ISD3001 | |
| | CRD1001 | CRD1001 | CRD3004 |
| Analysis set: Safety Analysis Set | 26 | 6 | 48 |
| Average duration of follow-up (weeks) | 97.3 | 109.9 | 61.9 |
| Average exposure (number of administrations) | 12.4 | 12.7 | 8.1 |
| Subjects with 1 or more: | | | |
| AEs | 24 (92.3%) | 4 (66.7%) | 35 (72.9%) |
| Serious AEs | 6 (23.1%) | 1 (16.7%) | 5 (10.4%) |
| AEs leading to death | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 3 (11.5%) | 0 | 1 (2.1%) |
| AEs reasonably related to study intervention[a] | 10 (38.5%) | 1 (16.7%) | 3 (6.3%) |

| | Ustekinumab | | |
|---|---|---|---|
| | | ISD3001 | |
| | CRD1001 | CRD1001 | CRD3004 |
| AEs of severe intensity | 2 (7.7%) | 1 (16.7%) | 1 (2.1%) |
| Infections | 16 (61.5%) | 4 (66.7%) | 25 (52.1%) |
| Serious infections | 0 | 1 (16.7%) | 1 (2.1%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 9 (34.6%) | 3 (50.0%) | 13 (27.1%) |
| Malignancy | 0 | 0 | 0 |
| Active tuberculous infections | 0 | 0 | 0 |
| Opportunistic infections | 0 | 0 | 0 |
| Injection site-reaction[b] | 0 | 0 | 1 (2.1%) |

As for the induction and maintenance periods, overall, Infections and Infestations and gastrointestinal disorders were the most commonly represented SOCs in the LTE period, i.e. CRD1001's LTE phase and ISD3001(UNITED).

Overall, 18 (69.2%) of 26 participants in CRD1001 and, in ISD3001(UNITED), 26 (54.2%) of 48 participants from CRD3004 and 4 (66.7%) of 6 participants from CRD1001 reported AEs in the Infections and infestations SOC (data not shown).

Overall, 15 (57.7%) CRD1001 participants, and, in ISD3001(UNITED), 11 (22.9%) participants from CRD3004 and 2 (33.3%) participants from CRD1001 reported AEs in the Gastrointestinal disorders SOC (data not shown).

Only 1 (2.1%) participant from CRD3004 experienced an injection-site reaction AE during the ISD3001 (UNITED) study.

**Table 75: Overall summary of Treatment-Emergent Adverse Events during long-term extension through 18 Nov 2024; Safety Analysis Set (Study CNTO1275ISD3001)**

| | Ustekinumab SC | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q8w | q4w | Combined |
| Analysis set: Safety | 6 | 48 | 18 | 66 |
| Avg duration of follow-up (weeks) | 109.9 | 61.9 | 52.1 | 59.2 |
| Avg exposure (number of administrations) | 12.7 | 8.1 | 9.9 | 8.6 |
| Subjects with 1 or more: | | | | |
| AEs | 4 (66.7%) | 35 (72.9%) | 15 (83.3%) | 50 (75.8%) |
| Serious AEs | 1 (16.7%) | 5 (10.4%) | 5 (27.8%) | 10 (15.2%) |
| AEs leading to death | 0 | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 0 | 1 (2.1%) | 5 (27.8%) | 6 (9.1%) |
| AEs related to study intervention | 0 | 3 (6.3%) | 4 (22.2%) | 7 (10.6%) |
| AEs of severe intensity | 1 (16.7%) | 1 (2.1%) | 3 (16.7%) | 4 (6.1%) |
| Infections | 4 (66.7%) | 25 (52.1%) | 11 (61.1%) | 36 (54.5%) |
| Serious infections | 1 (16.7%) | 1 (2.1%) | 2 (11.1%) | 3 (4.5%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 3 (50.0%) | 13 (27.1%) | 4 (22.2%) | 17 (25.8%) |
| Malignancy | 0 | 0 | 0 | 0 |
| Active Tuberculous infections | 0 | 0 | 0 | 0 |
| Opportunistic infections | 0 | 0 | 0 | 0 |
| Possible anaphylactic or serum-sickness like reactions | 0 | 0 | 0 | 0 |
| Injection site reactions | 0 | 1 (2.1%) | 1 (5.6%) | 2 (3.0%) |

## Serious adverse event/deaths/other significant events

Induction period SAEs: Safety Analysis Set (CRD1001 and CRD3004)

**Table 76: Number of Subjects with Treatment-emergent Serious Adverse Events From Week I-0 (Week 0) Through Week I-8 (Week 8) by SOC and PT; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Safety Analysis Set | 44 | 101 |
| Average duration of follow-up (weeks) | 8.0 | 8.1 |
| Average exposure (number of administrations) | 1.0 | 1.0 |
| Subjects with 1 or more SAEs | 4 (9.1%) | 3 (3.0%) |
| System organ class<br>Preferred term | | |
| Immune system disorders | 0 | 1 (1.0%) |
| Infusion related hypersensitivity reaction | 0 | 1 (1.0%) |
| Infections and infestations | 0 | 1 (1.0%) |
| Viral infection | 0 | 1 (1.0%) |
| Renal and urinary disorders | 0 | 1 (1.0%) |
| Nephrolithiasis | 0 | 1 (1.0%) |
| Eye disorders | 1 (2.3%) | 0 |
| Vision blurred | 1 (2.3%) | 0 |
| Gastrointestinal disorders | 2 (4.5%) | 0 |
| Constipation | 1 (2.3%) | 0 |
| Intestinal obstruction | 1 (2.3%) | 0 |
| Musculoskeletal and connective tissue disorders | 1 (2.3%) | 0 |
| Myalgia | 1 (2.3%) | 0 |

Key: SAE = serious adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 27.1.

Maintenance period SAEs: Safety Analysis Set (CRD1001 and CRD3004)

**Table 77: Overall summary of Treatment-emergent Adverse Events From Week M-0 (Week 8) Through Week M-44/Week 48 by SOC and PT; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q12w | q8w | Total |
| Analysis set: Safety Analysis Set | 43 | 49 | 48 | 97 |
| Average duration of follow-up (weeks) | 32.3 | 36.2 | 36.5 | 36.4 |
| Average exposure (number of administrations) | 4.1 | 7.7 | 7.6 | 7.6 |
| Subjects with 1 or more SAEs | 10 (23.3%) | 6 (12.2%) | 7 (14.6%) | 13 (13.4%) |
| System organ class<br>Preferred term | | | | |
| Gastrointestinal disorders | 10 (23.3%) | 4 (8.2%) | 2 (4.2%) | 6 (6.2%) |
| Crohn's disease | 6 (14.0%) | 4 (8.2%) | 1 (2.1%) | 5 (5.2%) |
| Anal fistula | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| Anal ulcer | 1 (2.3%) | 0 | 0 | 0 |
| Large intestinal stenosis | 2 (4.7%) | 0 | 0 | 0 |
| Pancreatitis | 1 (2.3%) | 0 | 0 | 0 |
| Small intestinal obstruction | 1 (2.3%) | 0 | 0 | 0 |
| Infections and infestations | 1 (2.3%) | 2 (4.1%) | 1 (2.1%) | 3 (3.1%) |
| Aeromonas infection | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| COVID-19 | 0 | 1 (2.0%) | 0 | 1 (1.0%) |
| Respiratory tract infection viral | 0 | 1 (2.0%) | 0 | 1 (1.0%) |
| Abscess intestinal | 1 (2.3%) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | 0 | 1 (2.0%) | 1 (2.1%) | 2 (2.1%) |
| Clavicle fracture | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| Stoma site discharge | 0 | 1 (2.0%) | 0 | 1 (1.0%) |
| Blood and lymphatic system disorders | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| Anaemia | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| Investigations | 1 (2.3%) | 0 | 1 (2.1%) | 1 (1.0%) |
| Hepatic enzyme increased | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| Weight decreased | 1 (2.3%) | 0 | 0 | 0 |
| Nervous system disorders | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| Syncope | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| Psychiatric disorders | 0 | 1 (2.0%) | 0 | 1 (1.0%) |
| Suicide attempt | 0 | 1 (2.0%) | 0 | 1 (1.0%) |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| Oropharyngeal pain | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| General disorders and administration site conditions | 3 (7.0%) | 0 | 0 | 0 |
| Fatigue | 1 (2.3%) | 0 | 0 | 0 |
| General physical health deterioration | 1 (2.3%) | 0 | 0 | 0 |
| Pyrexia | 2 (4.7%) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | 2 (4.7%) | 0 | 0 | 0 |
| Malnutrition | 2 (4.7%) | 0 | 0 | 0 |

Long term extension period SAEs: i.e. LTE period of CRD1001 and in ISD3001(UNITED)

During the LTE periods in CRD1001 and ISD3001(UNITED) 6 (23.1%) of 26 participants in CRD1001, and in ISD3001(UNITED), 5 (10.4%) of 48 participants from CRD3004 and 1 (16.7%) of 6 participants from CRD1001 had 1 or more SAEs (data not shown).

The SOC with the highest proportion of participant SAEs was Gastrointestinal disorders (5 [19.2%] participants in CRD1001 and 3 [6.3%] participants in ISD3001 (UNITED), each from CRD3004). All PTs in the Gastrointestinal disorders SOC were either Crohn's disease or other CD-related events.

All SAEs in ISD3001(UNITED) were singular events.

**Table 78: Incidence of TE Serious Adverse Events Per 100 Person-years by SOC and PT; Safety Analysis Set (Studies CNTO1275CRD1001, CNTO1275CRD3004 and CNTO1275ISD3001)**

| | Ustekinumab | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | From Week I-0 (Week 0) Through Week M-44/Week 48 | | | | | Long-term Extension ISD3001 | | | |
| | CRD1001 | CRD3004 | | | | CRD1001 | CRD3004 | | |
| | q8w | Not Randomized | q12w | q8w | Total | q8w | q8w | q4w | Total |
| Analysis set: Safety Analysis Set | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Average duration of follow-up (weeks) | 38.8 | 7.9 | 44.4 | 44.6 | 43.0 | 109.9 | 61.9 | 52.1 | 59.2 |
| Average exposure (number of administrations) | 4.7 | 1.0 | 8.7 | 8.6 | 8.3 | 12.7 | 8.1 | 9.9 | 8.6 |
| Total person-year of FU | 32.73 | 0.60 | 41.68 | 41.00 | 83.28 | 12.64 | 56.96 | 17.97 | 74.93 |
| Number of subjects with 1 or more SAEs | 11 | 2 | 8 | 7 | 17 | 1 | 5 | 5 | 10 |
| Any SAEs (n/incidence rate (95% CI)) | 24/73.33 (46.98, 109.11) | 3/498.07 (102.71, 1455.57) | 12/28.79 (14.88, 50.29) | 8/19.51 (8.42, 38.45) | 23/27.62 (17.51, 41.44) | 1/7.91 (0.20, 44.08) | 5/8.78 (2.85, 20.48) | 8/44.53 (19.22, 87.74) | 13/17.35 (9.24, 29.67) |

In CRD3004, the incidence rates of SAEs were 19.51 per 100 person-years in the q8w treatment group and 28.79 per 100 person-years in the q12w treatment group. Among the 4 participants not randomised, the incidence rate of SAEs was 498.07 per 100 person-years of follow-up. Across the q12w, q8w, and not randomised groups combined, the incidence rate of SAEs was 27.62 per 100 person-years.

From Week I-0 through Week M-44/Week 48, among CRD1001 participants, the incidence rate of SAEs was 73.33 per 100 person-years.

During the LTE phase, among participants in ISD3001 study from CRD3004, the incidence rate of SAEs was 17.35 per 100 person-years. Among participants from the CRD1001 study, the incidence rate of SAEs was 7.91 per 100 person-years.

The PT with the highest rate of SAEs per 100 person-years was Crohn's disease (8.41 per 100 person-years in, 21.39 per 100 person-years in CRD1001, and 5.34 per 100 person-years in ISD3001).

### Serious infection AEs

The incidence of serious infection TEAEs in both CRD1001 and CRD3004 are presented in Tables TSFAE11a (induction) and TSFAE11b (maintenance) below.

**Table 79: Number of Subjects with Treatment-emergent Serious Infections From Week I-0 (Week 0) Through Week I-8 (Week 8) by SOC and PT; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Safety Analysis Set | 44 | 101 |
| Average duration of follow-up (weeks) | 8.0 | 8.1 |
| Average exposure (number of administrations) | 1.0 | 1.0 |
| Subjects with 1 or more serious infections | 0 | 1 (1.0%) |
| System organ class<br>Preferred term | | |
| Infections and infestations | 0 | 1 (1.0%) |
| Viral infection | 0 | 1 (1.0%) |

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 27.1.

**Table 80: Number of subjects with Treatment-emergent Serious Infections From Week M-0 (Week 8) Through Week M-44/Week 48 by SOC and PT; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q12w | q8w | Total |
| Analysis set: Safety Analysis Set | 43 | 49 | 48 | 97 |
| Average duration of follow-up (weeks) | 32.3 | 36.2 | 36.5 | 36.4 |
| Average exposure (number of administrations) | 4.1 | 7.7 | 7.6 | 7.6 |
| Subjects with 1 or more serious infections | 1 (2.3%) | 2 (4.1%) | 2 (4.2%) | 4 (4.1%) |
| System organ class<br>Preferred term | | | | |
| Infections and infestations | 1 (2.3%) | 2 (4.1%) | 1 (2.1%) | 3 (3.1%) |
| Aeromonas infection | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| COVID-19 | 0 | 1 (2.0%) | 0 | 1 (1.0%) |
| Respiratory tract infection viral | 0 | 1 (2.0%) | 0 | 1 (1.0%) |
| Abscess intestinal | 1 (2.3%) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 1 (2.1%) | 1 (1.0%) |
| Oropharyngeal pain | 0 | 0 | 1 (2.1%) | 1 (1.0%) |

## Laboratory findings

Haematology

In general, the proportions of participants experiencing markedly abnormal values in haematology laboratory test results were low, in the CRD3004, CRD1001 and LTE ISD3001(UNITED) studies, and there were no consistent trends observed that suggested an association of ustekinumab treatment with changes in routine laboratory parameters.

A large proportion of all participants had ≥1 grade anaemia. For example, 68.4% in CRD3004 and 67.5% in CRD1001 had ≥1 grade anaemia in the maintenance phase. Although over 50% of all participants had Grade 1 or Grade 2 values, this is not uncommon for the therapeutic setting, paediatric Crohn's disease. Such anaemia was seen at a similar rate in both the q4w and q8w doses.

Only one serious TEAE of anaemia was reported studies during CRD3004 and CRD1001, and this event was considered to be unrelated.

Haematology - induction period: Safety Analysis Set (CRD1001 and CRD3004)

**Table 81: Summary of Worst Postbaseline NCI-CTCAE Toxicity Grades for Haematology Parameters from Week I-0 (Week 0) Through Week I-8 (Week 8); Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Safety Analysis Set | 44 | 101 |
| Anemia | | |
| N | 43 | 89 |
| Any grade ≥1 | 26 (60.5%) | 44 (49.4%) |
| Grade 1 | 20 (46.5%) | 37 (41.6%) |
| Grade 2 | 6 (14.0%) | 7 (7.9%) |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |
| Hemoglobin Increased | | |
| N | 43 | 89 |
| Any grade ≥1 | 0 | 0 |
| Grade 1 | 0 | 0 |
| Grade 2 | 0 | 0 |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |
| Leukocytosis | | |
| N | 43 | 89 |
| Any grade ≥1 | 0 | 0 |
| Grade 1 | 0 | 0 |
| Grade 2 | 0 | 0 |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |
| Lymphocyte Count Decreased | | |
| N | 43 | 89 |
| Any grade ≥1 | 10 (23.3%) | 11 (12.4%) |
| Grade 1 | 2 (4.7%) | 6 (6.7%) |
| Grade 2 | 7 (16.3%) | 4 (4.5%) |
| Grade 3 | 1 (2.3%) | 1 (1.1%) |
| Grade 4 | 0 | 0 |
| Lymphocyte Count Increased | | |
| N | 43 | 89 |
| Any grade ≥1 | 0 | 0 |
| Grade 1 | 0 | 0 |
| Grade 2 | 0 | 0 |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |
| Neutrophil Count Decreased | | |
| N | 43 | 89 |
| Any grade ≥1 | 1 (2.3%) | 0 |
| Grade 1 | 1 (2.3%) | 0 |
| Grade 2 | 0 | 0 |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |
| Platelet Count Decreased | | |
| N | 42 | 88 |
| Any grade ≥1 | 0 | 0 |
| Grade 1 | 0 | 0 |

Haematology - maintenance period: Safety Analysis Set (CRD1001 and CRD3004)

**Table 82: Summary of Worst Postbaseline NCI-CTCAE Toxicity Grades for Haematology Parameters from Week M-0 (Week 8) Through Week M-44 /Week 48; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q12w | q8w | Total |
| Analysis set: Safety Analysis Set | 43 | 49 | 48 | 97 |
| Anemia | | | | |
| N | 40 | 48 | 47 | 95 |
| Any grade ≥1 | 27 (67.5%) | 33 (68.8%) | 32 (68.1%) | 65 (68.4%) |
| Grade 1 | 19 (47.5%) | 24 (50.0%) | 27 (57.4%) | 51 (53.7%) |
| Grade 2 | 8 (20.0%) | 9 (18.8%) | 5 (10.6%) | 14 (14.7%) |
| Grade 3 | 0 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Hemoglobin Increased | | | | |
| N | 40 | 48 | 47 | 95 |
| Any grade ≥1 | 1 (2.5%) | 0 | 0 | 0 |
| Grade 1 | 1 (2.5%) | 0 | 0 | 0 |
| Grade 2 | 0 | 0 | 0 | 0 |
| Grade 3 | 0 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Leukocytosis | | | | |
| N | 40 | 48 | 47 | 95 |
| Any grade ≥1 | 0 | 0 | 0 | 0 |
| Grade 1 | 0 | 0 | 0 | 0 |
| Grade 2 | 0 | 0 | 0 | 0 |
| Grade 3 | 0 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Lymphocyte Count Decreased | | | | |
| N | 40 | 48 | 46 | 94 |
| Any grade ≥1 | 14 (35.0%) | 15 (31.3%) | 12 (26.1%) | 27 (28.7%) |
| Grade 1 | 6 (15.0%) | 8 (16.7%) | 4 (8.7%) | 12 (12.8%) |
| Grade 2 | 5 (12.5%) | 7 (14.6%) | 6 (13.0%) | 13 (13.8%) |
| Grade 3 | 3 (7.5%) | 0 | 2 (4.3%) | 2 (2.1%) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Lymphocyte Count Increased | | | | |
| N | 40 | 48 | 46 | 94 |
| Any grade ≥1 | 0 | 0 | 0 | 0 |
| Grade 1 | 0 | 0 | 0 | 0 |
| Grade 2 | 0 | 0 | 0 | 0 |
| Grade 3 | 0 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Neutrophil Count Decreased | | | | |
| N | 40 | 48 | 46 | 94 |
| Any grade ≥1 | 1 (2.5%) | 5 (10.4%) | 0 | 5 (5.3%) |
| Grade 1 | 0 | 1 (2.1%) | 0 | 1 (1.1%) |
| Grade 2 | 1 (2.5%) | 4 (8.3%) | 0 | 4 (4.3%) |
| Grade 3 | 0 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Platelet Count Decreased | | | | |
| N | 39 | 48 | 47 | 95 |
| Any grade ≥1 | 1 (2.6%) | 0 | 0 | 0 |

Chemistry

In general, the proportions of participants experiencing markedly abnormal values in chemistry laboratory test results were low, in the CRD3004, CRD1001 and LTE ISD3001(UNITED) studies, and there were no consistent trends observed that suggested an association of ustekinumab treatment with changes in routine laboratory parameters.

No Grade 4 clinical chemistry parameter abnormalities were observed during CRD3004, CRD1001, or ISD3001(UNITED). Small numbers of clinical chemistry parameter related AEs were reported, typically only one case of each, and only one was considered serious only 1 was considered serious by the

investigator. This SAE was reported as hepatic enzyme increased, reported as a Grade 3 abnormality of AST increased (max AST was 252U/L, reference range 10-40U/L), in a female participant. ALT was also raised. The investigator considered that the SAE was not related to ustekinumab. The elevation resolved within 14 days.

One case of DILI (maintenance phase) in a male participant was reported as mild, not related, and resolved in 4 weeks. The subject was hospitalised for an SAE no hospital lab results were transmitted to the Sponsor.

No participants met the criteria of possible Hy's law during CRD3004, CRD1001, or ISD3001(UNITED).

Liver chemistry –transaminases: maintenance period: Safety Analysis Set (CRD1001 and CRD3004)

**Table 83: Summary of Maximum Postbaseline ALT measurements from Week M-0 (Week 8) Through Week M-44/Week 48; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q12w | q8w | Total |
| Analysis set: Safety Analysis Set | 43 | 49 | 48 | 97 |
| Average duration of follow-up (weeks) | 32.3 | 36.2 | 36.5 | 36.4 |
| Subjects with ALT ≤ ULN at Baseline[a,b] | 40 | 48 | 46 | 94 |
| Subjects within normal range (≤1 x ULN ALT) | 40 (100.0%) | 45 (93.8%) | 42 (91.3%) | 87 (92.6%) |
| Subjects with abnormalities (> 1 x ULN ALT) | 0 | 3 (6.3%) | 4 (8.7%) | 7 (7.4%) |
| > 1 and ≤ 3 x ULN ALT | 0 | 3 (6.3%) | 4 (8.7%) | 7 (7.4%) |
| > 3 and ≤ 5 x ULN ALT | 0 | 0 | 0 | 0 |
| > 5 and ≤ 20 x ULN ALT | 0 | 0 | 0 | 0 |
| > 20 x ULN ALT | 0 | 0 | 0 | 0 |
| Subjects with ALT > ULN at Baseline[a,b] | 0 | 0 | 1 | 1 |
| Subjects within normal range (≤1 x ULN ALT) | 0 | 0 | 0 | 0 |
| Subjects with abnormalities (> 1 x ULN ALT) | 0 | 0 | 1 (100.0%) | 1 (100.0%) |
| > 1 and ≤ 3 x ULN ALT | 0 | 0 | 0 | 0 |
| > 3 and ≤ 5 x ULN ALT | 0 | 0 | 0 | 0 |
| > 5 and ≤ 20 x ULN ALT | 0 | 0 | 1 (100.0%) | 1 (100.0%) |
| > 20 x ULN ALT | 0 | 0 | 0 | 0 |

**Table 84: Summary of Maximum Postbaseline AST measurements from Week M-0 (Week 8) Through Week M-44/Week 48; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

TSFLAB09b: Summary of Maximum Postbaseline AST Measurements From Week M-0 (Week 8) Through Week M-44/Week 48; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)

| | Ustekinumab | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q12w | q8w | Total |
| Analysis set: Safety Analysis Set | 43 | 49 | 48 | 97 |
| Average duration of follow-up (weeks) | 32.3 | 36.2 | 36.5 | 36.4 |
| Subjects with AST ≤ ULN at Baseline[a,b] | 40 | 48 | 47 | 95 |
| Subjects within normal range (≤1 x ULN AST) | 39 (97.5%) | 47 (97.9%) | 40 (85.1%) | 87 (91.6%) |
| Subjects with abnormalities (> 1 x ULN AST) | 1 (2.5%) | 1 (2.1%) | 7 (14.9%) | 8 (8.4%) |
| > 1 and ≤ 3 x ULN AST | 1 (2.5%) | 1 (2.1%) | 6 (12.8%) | 7 (7.4%) |
| > 3 and ≤ 5 x ULN AST | 0 | 0 | 0 | 0 |
| > 5 and ≤ 20 x ULN AST | 0 | 0 | 1 (2.1%) | 1 (1.1%) |
| > 20 x ULN AST | 0 | 0 | 0 | 0 |
| Subjects with AST > ULN at Baseline[a,b] | 0 | 0 | 0 | 0 |
| Subjects within normal range (≤1 x ULN AST) | 0 | 0 | 0 | 0 |
| Subjects with abnormalities (> 1 x ULN AST) | 0 | 0 | 0 | 0 |
| > 1 and ≤ 3 x ULN AST | 0 | 0 | 0 | 0 |
| > 3 and ≤ 5 x ULN AST | 0 | 0 | 0 | 0 |
| > 5 and ≤ 20 x ULN AST | 0 | 0 | 0 | 0 |
| > 20 x ULN AST | 0 | 0 | 0 | 0 |

Key: AST = aspartate aminotransferase, ULN = upper limit of normal
[a] Includes only subjects with both baseline and at least one postbaseline AST measurement.
[b] Baseline is defined as the last observation prior to or at the time of the first study intervention.
Note: Subjects who were randomized into the maintenance period of the study and received at least 1 administration of study intervention during maintenance are included. Data from the time of substudy onward in study CRD3004 are not included and are summarized separately.

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### Physical Findings and Growth

See Efficacy section for more discussion on growth parameters. No meaningful trends related to physical findings and growth were observed in CRD3004 and CRD1001, and the changes were consistent with a normal pattern of growth. In the CRD1001 study, a few isolated AEs of weight decreased (4 [9.3%] participants) and malnutrition (2 [4.7%] participants) were reported which were associated with worsening of CD and not related to study intervention.

## Safety in special populations

*Biologic failure status*

The potential for any effect of prior biologic failure is most usefully examined by looking at CRD3004 where there was a fairly even representation of biologic failure subjects (n=57, induction phase) and non-biologic failure patients (n=44, induction phase). By contrast, in study CRD1001 almost all subjects were prior biologic failures.

<u>CRD3004 participants: induction period, Safety Analysis Set(CRD3004)</u>

At least 1 AE was reported in 70.2% of biologic failure participants and 52.3% of non-biologic failure participants.

At least 1 SAE was reported in 1.8% of biologic failure participants and 4.5% of non-biologic failure participants.

At least 1 AE treatment discontinuation reported in 1.8% of biologic failure participants and 4.5% of non-biologic failure participants.

At least 1 infection was reported in 33.3% of biologic failure participants and 25.0% of non-biologic failure participants.

At least 1 infection requiring oral and/or parenteral antimicrobial treatment reported in 8.8% of biologic failure participants and 4.5% of non-biologic failure participants.

At least 1 AE reasonably related to study intervention was reported in 8.8% of biologic failure participants and 6.8% of non-biologic failure participants.

CRD3004 participants: maintenance period, Safety Analysis Set(CRD3004) - See Table 85 below.

Both q8w and q12w frequencies are combined in the following comparisons.

At least 1 AE were reported in 87.3% of biologic failure participants and 85.7% of non-biologic failure participants.

At least 1 SAE were reported in 12.7% of biologic failure participants and 14.3% of non-biologic failure participants.

At least 1 AE treatment discontinuation reported in 7.3% of biologic failure participants and 2.4% of non-biologic failure participants.

At least 1 infection were reported in 70.9% of biologic failure participants and 52.4% of non-biologic failure participants.

At least 1 infection requiring oral and/or parenteral antimicrobial treatment were reported in 30.9% of biologic failure participants and 11.9% of non-biologic failure participants.

At least 1 AE reasonably related to study intervention were reported in 5.5% of biologic and none of the non-biologic failure participants.

**Table 85: Overall Summary of Treatment-emergent Adverse Events From Week M-0 (Week 8) Through Week M-44/Week 48 by Prior Biologic Failure Status; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q12w | q8w | Total |
| Analysis set: Safety Analysis Set | 43 | 49 | 48 | 97 |
| Prior biologic failure status | | | | |
| Biologic failure | 39 | 25 | 30 | 55 |
| Average duration of follow-up (weeks) | 32.4 | 31.1 | 34.6 | 33.0 |
| Average exposure (number of administrations) | 4.0 | 6.9 | 6.9 | 6.9 |
| Subjects with 1 or more: | | | | |
| AEs | 32 (82.1%) | 22 (88.0%) | 26 (86.7%) | 48 (87.3%) |
| Serious AEs | 10 (25.6%) | 4 (16.0%) | 3 (10.0%) | 7 (12.7%) |
| AEs leading to death | 0 | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 5 (12.8%) | 3 (12.0%) | 1 (3.3%) | 4 (7.3%) |
| AEs reasonably related to study intervention[a] | 9 (23.1%) | 2 (8.0%) | 1 (3.3%) | 3 (5.5%) |
| AEs of severe intensity | 8 (20.5%) | 4 (16.0%) | 0 | 4 (7.3%) |
| Infections | 19 (48.7%) | 18 (72.0%) | 21 (70.0%) | 39 (70.9%) |
| Serious infections | 1 (2.6%) | 1 (4.0%) | 1 (3.3%) | 2 (3.6%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 10 (25.6%) | 9 (36.0%) | 8 (26.7%) | 17 (30.9%) |
| Malignancy | 0 | 0 | 0 | 0 |

| | Ustekinumab | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q12w | q8w | Total |
| Active tuberculous infections | 0 | 0 | 0 | 0 |
| Opportunistic infections | 0 | 0 | 0 | 0 |
| Injection site-reaction[b] | 0 | 0 | 0 | 0 |
| Non-biologic failure | 4 | 24 | 18 | 42 |
| Average duration of follow-up (weeks) | 30.7 | 41.6 | 39.7 | 40.8 |
| Average exposure (number of administrations) | 5.0 | 8.5 | 8.8 | 8.6 |
| Subjects with 1 or more: | | | | |
| AEs | 2 (50.0%) | 22 (91.7%) | 14 (77.8%) | 36 (85.7%) |
| Serious AEs | 0 | 2 (8.3%) | 4 (22.2%) | 6 (14.3%) |
| AEs leading to death | 0 | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 0 | 0 | 1 (5.6%) | 1 (2.4%) |
| AEs reasonably related to study intervention[a] | 0 | 0 | 0 | 0 |
| AEs of severe intensity | 0 | 1 (4.2%) | 1 (5.6%) | 2 (4.8%) |
| Infections | 2 (50.0%) | 14 (58.3%) | 8 (44.4%) | 22 (52.4%) |
| Serious infections | 0 | 1 (4.2%) | 1 (5.6%) | 2 (4.8%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 0 | 2 (8.3%) | 3 (16.7%) | 5 (11.9%) |
| Malignancy | 0 | 0 | 0 | 0 |
| Active tuberculous infections | 0 | 0 | 0 | 0 |
| Opportunistic infections | 0 | 0 | 0 | 0 |
| Injection site-reaction[b] | 0 | 0 | 0 | 0 |

Key: AE = adverse event
[a] An adverse event that is assessed by the investigator as related to study agent or if the relationship to study agent is missing.
[b] Injection-site reaction is any reaction at an SC study intervention injection site that was recorded as an injection-site reaction by the investigator on the eCRF.
Note: Subjects are counted only once for any given event type, regardless of the number of times they actually experienced the event.
Note: Subjects who were randomized into the maintenance period of the study and received at least 1 administration of study intervention during maintenance are included. Data from the time of substudy onward in study CRD3004 are not included and are summarized separately.

Prior biologic failure status had no impact on AEs in LTE participants from CRD3004 in the ISD3001 (UNITED) study.

*Age*

The age range of the enrolled participants was 2 to 17 years. 30 participants ≥2 to <12 years of age and 115 subjects ≥12 to <18 years of age were recruited into the Crohn's paediatric studies. It should be noted that there is most limited evidence relating to the much younger ages, i.e. 2-6 years. No patient aged 2-6 years was recruited in CRD1001, and only 2 subjects in this age bracket were recruited in CRD3004, one each treated at q4w and q8w.

**Table 86: Summary of Demographics at Baseline; Safety Analysis Set (Studies CNTO1275CRD1001, CNTO1275CRD3004 and CNTO1275ISD3001)**

| | Ustekinumab | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | CRD1001 | CRD3004 | | | | ISD3001 CRD1001 | ISD3001 CRD3004 | | |
| | q8w | Not Randomized | q12w | q8w | Total | q8w | q8w | q4w | Total |
| Analysis set: Safety Analysis Set | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Age, years | | | | | | | | | |
| N | 44 | 4 | 49 | 48 | 101 | 6 | 48 | 18 | 66 |
| Mean (SD) | 13.4 (2.74) | 13.3 (1.50) | 13.5 (2.92) | 13.4 (2.65) | 13.5 (2.73) | 14.7 (2.25) | 13.8 (3.11) | 14.8 (1.99) | 14.1 (2.87) |
| Median | 13.0 | 14.0 | 14.0 | 14.0 | 14.0 | 14.5 | 15.0 | 14.5 | 15.0 |
| Range | (6; 17) | (11; 14) | (5; 17) | (2; 17) | (2; 17) | (11; 17) | (3; 17) | (10; 17) | (3; 17) |
| IQ range | (12.0; 16.0) | (12.5; 14.0) | (12.0; 16.0) | (12.0; 15.0) | (12.0; 15.0) | (14.0; 17.0) | (12.0; 16.0) | (13.0; 17.0) | (13.0; 16.0) |
| ≥2-<12 years | 10 (22.7%) | 1 (25.0%) | 12 (24.5%) | 7 (14.6%) | 20 (19.8%) | 1 (16.7%) | 11 (22.9%) | 1 (5.6%) | 12 (18.2%) |
| ≥2-<6 years | 0 | 0 | 1 (2.0%) | 1 (2.1%) | 2 (2.0%) | 0 | 1 (2.1%) | 0 | 1 (1.5%) |
| ≥6-<12 years | 10 (22.7%) | 1 (25.0%) | 11 (22.4%) | 6 (12.5%) | 18 (17.8%) | 1 (16.7%) | 10 (20.8%) | 1 (5.6%) | 11 (16.7%) |
| ≥12-<18 years | 34 (77.3%) | 3 (75.0%) | 37 (75.5%) | 41 (85.4%) | 81 (80.2%) | 5 (83.3%) | 37 (77.1%) | 17 (94.4%) | 54 (81.8%) |

*Sex*

When evaluated according to the participant's sex in the induction periods of both studies, there were no notable safety differences between the subgroups. When evaluated according to the participant's sex in the maintenance periods, the proportion of participants with SAEs and infections were slightly higher in females as compared with males in CCRD1001 (SAEs: 32.0% of females versus 11.1% of males; infections: 56.0% of females versus 38.9% of males); this difference was not apparent in the CRD3004 trial. Overall, the data do not suggest any trends to a different safety based on sex.

*Pregnancy and lactation*

There were no pregnancies reported in the paediatric Crohn's population.

## Safety related to drug-drug interactions and other interactions

Due to the low incidence of antibodies to ustekinumab, the impact on safety could not be assessed.

For study CRD3004, 3 (3.0%) of 100 participants was positive for antibodies to ustekinumab through Week M-44.

For study CRD1001, just 1 subject was positive for antibodies to ustekinumab through Week 48.

All participants from CRD3004 and CRD1001 were included in the immunogenicity analysis regardless of the induction doses received. The incidence of antibodies to ustekinumab in paediatric participants (3.0%; 4 of 135 participants) was similar to the incidence in adult participants (3.1%; 9 of 287 participants) with CD.

**Table 87: Summary of Antibody to Ustekinumab Status in Studies in Adult (CNTO1275CRD3003) and Paediatric Participants (CNTO1275CRD3004 and CNTO1275CRD1001); Immunogenicity Analysis Set (CNTO1275CRD1001, CNTO1275CRD3004, and CNTO1275CRD3003)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | Pediatric Study CNTO1275CRD3004 (through Week M-44) | Pediatric Study CNTO1275CRD1001 (through Week 48) | Pediatric Total | Reference, Adults (CNTO1275CRD3003) |
| Analysis set: Immunogenicity Analysis Set | 101 | 34 | 135 | 287 |
| Participants with appropriate samples | 101 (100.0%) | 34 (100.0%) | 135 (100.0%) | 287 (100.0%) |
| Participants positive for treatment-emergent antibodies to ustekinumab[a] | 3 (3.0%) | 1 (2.9%) | 4 (3.0%) | 9 (3.1%) |
| Peak titers | | | | |
| 1:100 | 1 | 1 | 2 | 5 |
| 1:200 | 1 | 0 | 1 | 0 |
| 1:400 | 0 | 0 | 0 | 1 |
| 1:800 | 1 | 0 | 1 | 1 |
| 1:1600 | 0 | 0 | 0 | 2 |
| Peak titer group | | | | |
| <10 | 0 | 0 | 0 | 0 |
| 10-<100 | 0 | 0 | 0 | 0 |
| 100-<1000 | 3 | 1 | 4 | 7 |
| ≥1000 | 0 | 0 | 0 | 2 |
| Participants negative for treatment-emergent antibodies to ustekinumab[b] | 98 (97.0%) | 33 (97.1%) | 131 (97.0%) | 278 (96.9%) |

Abbreviations: Week M-X=Maintenance Week X.
[a] Participants positive for treatment-emergent antibodies to ustekinumab includes all participants who were positive (treatment-boosted or treatment-induced) at any time after their first ustekinumab administration. Participants with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.
[b] Excludes participants who were treatment-emergent positive.
Note: All participants were included in CNTO1275CRD1001 and CNTO1275CRD3004 regardless of the induction doses.
Note: For CNTO1275CRD1001, participants treated in the study extension were summarized.
Adapted from (Mod5.3.5.1/CNTO1275CRD1001/CSR/AttTPKIR01), (Mod5.3.5.1/CNTO1275CRD3004/CSR/AttTPKIR05).

## Discontinuation due to adverse events

Induction period: Safety Analysis Set(CRD1001 and CRD3004)

During the induction periods in CRD3004 and CRD1001 three (3.0%) of 101 participants in CRD3004 and 3 (6.8%) of 44 participants in CRD1001 had AEs leading to discontinuation of study intervention.

Among CRD1001 participants, 2 (4.5%) SAEs of Crohn's disease and one SAE of intestinal obstruction led to discontinuation of study intervention.

One (1.0%) participant from CRD3004 discontinued due to an AE of Crohn's disease, which was moderate in intensity and not related to study intervention.

Other AEs that led to discontinuation of study intervention among CRD3004 participants included singular events of angina pectoris, tachycardia, dyspnea, tachypnea, pallor, and hypertension all reported in 1 participant aged 14 years of age. The participant recovered after a duration of 1 day. The IV infusion was prematurely discontinued, and the participant did not receive a full dose.

Additionally, another participant in CRD3004 had an AE of infusion related hypersensitivity reaction that was considered serious, related to study intervention, and moderate in intensity.

**Table 88: Number of subjects with treatment-emergent AEs leading to discontinuation of study intervention from Week I-0 (Week 0) through Week I-8 (Week 8) by SOC and PT; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | |
|---|---|---|
| | CRD1001 | CRD3004 |
| Analysis set: Safety Analysis Set | 44 | 101 |
| Average duration of follow-up (weeks) | 8.0 | 8.1 |
| Average exposure (number of administrations) | 1.0 | 1.0 |
| Subjects with 1 or more AEs leading to discontinuation of study intervention | 3 (6.8%) | 3 (3.0%) |
| System organ class<br>Preferred term | | |
| Cardiac disorders | 0 | 1 (1.0%) |
| Angina pectoris | 0 | 1 (1.0%) |
| Tachycardia | 0 | 1 (1.0%) |
| Gastrointestinal disorders | 3 (6.8%) | 1 (1.0%) |
| Crohn's disease | 2 (4.5%) | 1 (1.0%) |
| Intestinal obstruction | 1 (2.3%) | 0 |
| Immune system disorders | 0 | 1 (1.0%) |
| Infusion related hypersensitivity reaction | 0 | 1 (1.0%) |
| Respiratory, thoracic and mediastinal disorders | 0 | 1 (1.0%) |
| Dyspnoea | 0 | 1 (1.0%) |
| Tachypnoea | 0 | 1 (1.0%) |
| Vascular disorders | 0 | 1 (1.0%) |
| Hypertension | 0 | 1 (1.0%) |
| Pallor | 0 | 1 (1.0%) |

Maintenance period: Safety Analysis Set(CRD1001 and CRD3004)

During the maintenance period 5 (5.2%) of 97 participants in CRD3004 (3 [6.1%] of 49 participants in the q12w treatment group and 2 [4.2%] of 48 participants in the q8w treatment group) had AEs leading to discontinuation of study intervention.

5 (11.6%) of 43 participants in CRD1001 had AEs leading to discontinuation of study intervention.

All AEs leading to discontinuation of study intervention were coded to the SOC Gastrointestinal disorders. The most frequent AE by PT was Crohn's disease, with all 5 (5.2%) participants in CRD3004 reporting an event. These AEs were not related to study intervention, and 3 were SAEs. Similarly, in CRD1001, the most frequent AE by PT was Crohn's disease, occurring in 3 (7.0%) participants. Of these events, 2 were considered related to study intervention and 2 were SAEs.

Other AEs were CD-related and included singular events of large intestinal stenosis and small intestinal obstruction in CRD1001.

**Table 89: Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Intervention From Week M-0 (Week 8) Through Week M-44/Week 48 by System Organ Class and Preferred Term; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q12w | q8w | Total |
| Analysis set: Safety Analysis Set | 43 | 49 | 48 | 97 |
| Average duration of follow-up (weeks) | 32.3 | 36.2 | 36.5 | 36.4 |
| Average exposure (number of administrations) | 4.1 | 7.7 | 7.6 | 7.6 |
| Subjects with 1 or more AEs leading to discontinuation of study intervention | 5 (11.6%) | 3 (6.1%) | 2 (4.2%) | 5 (5.2%) |
| System organ class<br>Preferred term | | | | |
| Gastrointestinal disorders | 5 (11.6%) | 3 (6.1%) | 2 (4.2%) | 5 (5.2%) |
| Crohn's disease | 3 (7.0%) | 3 (6.1%) | 2 (4.2%) | 5 (5.2%) |
| Large intestinal stenosis | 1 (2.3%) | 0 | 0 | 0 |
| Small intestinal obstruction | 1 (2.3%) | 0 | 0 | 0 |

Long term extension period: i.e. LTE period of CRD1001 and in ISD3001(UNITED)

In CRD1001, 3 (11.5%) of 26 participants had at least 1 AE that led to discontinuation of study intervention.

In ISD3001(UNITED), 1 (2.1%) of 48 participants enrolled from the CRD3004 study had an AE leading to discontinuation of study intervention.

All AEs leading to discontinuation of study intervention were coded to the SOC Gastrointestinal disorders. All 3 participants in CRD1001 had an AE of Crohn's disease, each reported as serious and not related to study intervention. An AE of enterovesical fistula was reported in 1 participant from the ISD3001(UNITED) study.

## Additional clinical data

Study CRD3004 Exposure Optimisation Substudy (EOS)

**Exposure in CRD3004's Exposure Optimisation substudy**

A total of 26 (26.8%) of 97 participants from the maintenance period of CNTO1275CRD3004 were enrolled in the EOS.

**Adverse events in CRD3004's Exposure Optimisation Substudy (EOS)**

AEs that occurred during the EOS are summarised in Table 90 below.

**Table 90: Overall summary of treatment-emergent AEs through the end of the substudy period; Substudy Analysis Set (CNTO1275CRD3004)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | q12w->q4w | q8w->q4w | Combined |
| Analysis set: Substudy | 11 | 15 | 26 |
| Avg duration of follow-up (weeks) | 22.4 | 20.4 | 21.3 |
| Avg exposure (number of administrations) | 7.3 | 5.4 | 6.2 |
| Subjects with 1 or more: | | | |
| AEs | 7 (63.6%) | 12 (80.0%) | 19 (73.1%) |
| Serious AEs | 2 (18.2%) | 1 (6.7%) | 3 (11.5%) |
| AEs leading to death | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 1 (9.1%) | 1 (6.7%) | 2 (7.7%) |
| AEs reasonably related to study intervention | 0 | 2 (13.3%) | 2 (7.7%) |
| AEs of severe intensity | 2 (18.2%) | 1 (6.7%) | 3 (11.5%) |
| Infections | 5 (45.5%) | 7 (46.7%) | 12 (46.2%) |
| Serious infections | 2 (18.2%) | 1 (6.7%) | 3 (11.5%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 3 (27.3%) | 2 (13.3%) | 5 (19.2%) |
| Malignancy | 0 | 0 | 0 |
| Active tuberculous infections | 0 | 0 | 0 |
| Opportunistic infections | 1 (9.1%) | 0 | 1 (3.8%) |
| Injection site-reactions[a] | 0 | 0 | 0 |

During the EOS (q4w)

- 73.1% of participants were reported with 1 or more AEs.
- 11.5% (3 participants) reported an SAE.
- 11.5% (3 participants) reported an AE of severe intensity.
- 46.2% of participants experienced an infection.
- 3 (11.5%) participants reported a serious infection
- 7.7% (2 participants) discontinued due to an AE.
- 3.8% (1 participant) had an opportunistic infection
- There were no malignancies, no cases of TB, no deaths, and no injection-site reactions.

The most frequent AEs reported in the EOS participants were in the Gastrointestinal disorders SOC (10 [38.5%] of 26 participants) and the Infections and infestations SOC (9 [34.6%] participants).

Crohn's disease and upper respiratory tract infection were the most frequently reported PTs in these SOCs (4 [15.4%] and (3 [11.5%] participants, respectively).

3 (11.5%) participants reported a serious infection - 5 events: these serious infections were associated and/or related to CD and were considered not related. 2 serious infection events of terminal ileitis, 1 pyrexia post ileocolonoscopy. Also, 1 participant reported serious infection events of gastroenteritis (aeromonas species) and cytomegalovirus colitis (reported term of "CMV colitis"). Both of these were considered unrelated, and both resolved. The event of cytomegalovirus colitis was also considered an opportunistic infection.

AEs that occurred during the LTE study ISD3001(UNITED) are summarised in Table 91 below, which includes those EOS patients that entered LTE.

**Table 91: Overall summary of treatment-emergent AEs in the LTE through 18 Nov 2024; Safety Analysis Set (CNTO1275ISD3001)**

| | Ustekinumab SC | | | |
|---|---|---|---|---|
| | CRD1001 | CRD3004 | | |
| | q8w | q8w | q4w | Combined |
| Analysis set: Safety | 6 | 48 | 18 | 66 |
| Avg duration of follow-up (weeks) | 109.9 | 61.9 | 52.1 | 59.2 |
| Avg exposure (number of administrations) | 12.7 | 8.1 | 9.9 | 8.6 |
| Subjects with 1 or more: | | | | |
| AEs | 4 (66.7%) | 35 (72.9%) | 15 (83.3%) | 50 (75.8%) |
| Serious AEs | 1 (16.7%) | 5 (10.4%) | 5 (27.8%) | 10 (15.2%) |
| AEs leading to death | 0 | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 0 | 1 (2.1%) | 5 (27.8%) | 6 (9.1%) |
| AEs related to study intervention | 0 | 3 (6.3%) | 4 (22.2%) | 7 (10.6%) |
| AEs of severe intensity | 1 (16.7%) | 1 (2.1%) | 3 (16.7%) | 4 (6.1%) |
| Infections | 4 (66.7%) | 25 (52.1%) | 11 (61.1%) | 36 (54.5%) |
| Serious infections | 1 (16.7%) | 1 (2.1%) | 2 (11.1%) | 3 (4.5%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 3 (50.0%) | 13 (27.1%) | 4 (22.2%) | 17 (25.8%) |
| Malignancy | 0 | 0 | 0 | 0 |
| Active Tuberculous infections | 0 | 0 | 0 | 0 |
| Opportunistic infections | 0 | 0 | 0 | 0 |
| Possible anaphylactic or serum-sickness like reactions | 0 | 0 | 0 | 0 |
| Injection site reactions | 0 | 1 (2.1%) | 1 (5.6%) | 2 (3.0%) |

Key: AE = adverse event, Avg = average

**Discontinuation**

There were 3 (3.0%) of 101 participants in the Safety Analysis Set who discontinued study intervention during the induction period through Week I-8, 1 participant due to an AE of worsening of Crohn's disease, and 2 participants due to an AE other than worsening of Crohn's disease. 14.9% of participants discontinued through Week M-44. The proportions of participants who discontinued study intervention were similar between the q12w and q8w treatment groups. The most common reasons for study intervention discontinuation were due to an AE of worsening of Crohn's disease, followed by withdrawal by parent or guardian, and lack of efficacy. Other reasons for study intervention discontinuation occurred in 1 participant each.

**Paediatric Ulcerative Colitis Study - PUC3001 - UNIFI JR**

The CNTO1275**PUC3001** study is a recently completed Phase 3 study in paediatric participants (aged 2 to <18 years) with moderately to severely active UC. In the induction period (Week I-0 through Week I-8), all participants received a single open-label IV administration of ustekinumab at Week I-0. For participants ≥40 kg, dosing was based on a weight-tiered induction dose which was the same as the approved adult dose regimen. For participants <40 kg, dosing was BSA-adjusted. In the maintenance period (Week M-0 through Week M-44), all participants who completed the Week I-8 visit were to be randomised at Week M-0 in a blinded fashion in a 1:1 ratio stratified by response status at Week I-8

(induction responders and induction non-responders) and weight (<40 kg and ≥40 kg) to receive 1 of 2 SC dose regimens (q8w or q12w).

Participants who lost response during PUC3001 and had an 8-week postdose serum ustekinumab concentration of <1.4 µg/mL during the maintenance period (at the Week M-8 or Week M-32 visit) were eligible to enroll in the optional, **open-label Exposure Optimisation Substudy (EOS)**, of minimum 16 weeks duration, with dose adjustment to q4w. This EOS was identical to the EOS for the paediatric Crohn's study CRD3004.

Regarding **PUC3001,** data(preliminary) is currently only available for the **open-label Exposure Optimisation Substudy (EOS),** and is summarised below.

A total of 21 of 109 participants from PUC3001 who did not achieve response by Week M-8 and were documented to have low exposure, or had LOR and low exposure, entered the optional EOS and received an adjustment to an open-label SC ustekinumab q4w dose regimen.

2/21 were aged 2-6 years, 7/21 were 6 to 12 years, and 12/21 were 12-18 years.

17 (81.0%) of 21 participants reported 1 or more AEs.

Upper respiratory tract infection was the most frequently reported PTs (6 [28.6%] participants), followed by anaemia, and colitis ulcerative, occurring in 4 (19.0%) participants each.

2 (9.5%) participants reported SAEs. 1 participant had 2 SAEs of iron deficiency anaemia and colitis ulcerative (exacerbation) and another participant reported an SAE of acute kidney injury (prerenal acute renal failure due to CMV infection).

One participant reported concurrent nonserious opportunistic infection of CMV infection and the SAE prerenal acute renal failure. The CMV infection was judged by the investigator as moderate in intensity, not related to Ustekinumab. The SAE prerenal acute renal failure was also considered unrelated.

There were no deaths, malignancies, active TB infections, or injection site reactions.

57.1% of participants experienced an infection, and no participant had a serious infection.

**Table 92: Overall summary of treatment-emergent AEs; Substudy Analysis Set (Study CNTO1275PUC3001)**

| | Ustekinumab SC | | |
|---|---|---|---|
| | q12w→q4w | q8w→q4w | Combined |
| Analysis set: Substudy | 12 | 9 | 21 |
| Avg duration of follow-up (weeks) | 19.8 | 27.6 | 23.2 |
| Avg exposure (number of administrations) | 6.2 | 7.0 | 6.5 |
| Subjects with 1 or more: | | | |
| AEs | 8 (66.7%) | 9 (100.0%) | 17 (81.0%) |
| Serious AEs | 1 (8.3%) | 1 (11.1%) | 2 (9.5%) |
| AEs leading to death | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 1 (8.3%) | 0 | 1 (4.8%) |
| AEs reasonably related to study intervention | 0 | 0 | 0 |
| AEs of severe intensity | 1 (8.3%) | 1 (11.1%) | 2 (9.5%) |
| Infections | 5 (41.7%) | 7 (77.8%) | 12 (57.1%) |

| | Ustekinumab SC | | |
|---|---|---|---|
| | q12w→q4w | q8w→q4w | Combined |
| Serious infections | 0 | 0 | 0 |
| Infection requiring oral and/or parenteral antimicrobial treatment | 2 (16.7%) | 0 | 2 (9.5%) |
| Malignancy | 0 | 0 | 0 |
| Active tuberculous infections | 0 | 0 | 0 |
| Opportunistic infections | 1 (8.3%) | 0 | 1 (4.8%) |
| Injection site-reactions[a] | 0 | 0 | 0 |

## Post marketing experience

Pharmacovigilance Data

Study C0168Z02 (DEVELOP) is a multicentre, prospective, observational, non-interventional post authorisation safety study (for REMICADE) of the long-term safety and clinical status of paediatric patients <17 years of age with IBD (Crohn's disease, UC, or indeterminate colitis) treated with infliximab and collects data on other medical therapies (including ustekinumab) for IBD as part of routine clinical care. The DEVELOP Registry was created to fulfill postmarketing commitments to health authorities.

An update on from this study as relevant for the paediatric indication was presented at the time variation EMEA/H/C/000958/II/0108 to extend the indication for Crohn's Disease to include children weighing ≥40kg.

The applicant provides an update from the DEVELOP study (report dated March 2025) with this variation, with a data cut off of June 2024.

165 paediatric patients (<18 years of age) treated with ustekinumab have been included in this safety analysis. During the Registry, the 165 patients had 521.0 PY of ustekinumab exposure. Their mean overall exposure to ustekinumab was 164.8 weeks. The ustekinumab-treated Crohn's Disease population in DEVELOP were children with refractory disease. Most patients (161 [97.6%]) received an IBD-targeted biologic prior to ustekinumab treatment in the Registry, with 71 (43.0%) patients receiving at least 2 prior biologics and 41 (24.8%) patients receiving at least 3 prior biologics. Median age at initial ustekinumab exposure was 16 years.

These patients experienced AEs at a rate of 137.43 AEs/100 PY of exposure. By SOC, the most reported AEs were Gastrointestinal Disorders (213 events) and Infections and Infestations (155 events). The most common AEs were Crohn's disease(40 events), abdominal pain (21 events), diarrhoea (21 events), *Clostridium difficile* infection(14 events), and nausea (14 events).

No patients died during the registry follow-up or transition periods.

During ustekinumab exposure, the rate of patients with at least one SAE per 100 patient-years of exposure was 13.93 (40 patients with events among 287.1 patient-years of exposure). The rate of SAEs per 100 patient-years of exposure was 25.42 (73 events). By SOC, the most commonly reported SAEs were Gastrointestinal disorders (13.93 SAEs per 100 patient-years [40 SAEs]) and Infections and infestations (5.92 [17]). There were 31 reported SAEs of Crohns disease, 4 events each for abdominal pain and anal fistula, and 2 events each of abdominal abscess, anal abscess, UC, GI fistula, intestinal obstruction, malnutrition, perirectal abscess, stoma site abscess, UTI. All other SAEs were reported just once.

The rate of patients experiencing at least one serious infection was 3.84 per 100 patient-years of exposure (20 patients). The rate of serious infections was 4.61 per 100 patient-years of exposure (24 events). Most of the serious infections were reported only once, except for abdominal abscess and anal abscess, perirectal abscess, and stoma site abscess, each reported twice.

One case of septic shock was reported in a female patient with a central line previously treated with vedolizumab and adalimumab. This patient may also have been treated with Ustekinumab- but this was not possible to confirm.

There were no reported cases of TB or colonic dysplasia.

There were 3 cases classified by the treating physician as new autoimmune diseases: 1 case of cholangitis sclerosing, 1 case of chronic recurrent multifocal osteomyelitis, and 1 case of psoriasis.

There were 3 cases of opportunistic infections reported: 1 AE of CMV infection, 1 AE of herpes zoster, and 1 additional AE of candida infection (oral thrush), none of which were serious.

There was one malignancy; malignant carcinoid tumour tip of appendix, which was considered unlikely related; this patient had received multiple biologics in the years prior to the event.

Two patients had infusion reactions, both considered unrelated, and both of which were reported with PTs not suggestive of an infusion reaction - one with the PT of Crohn's disease, the other with the PT of fistula.

Of the 119 patients exposed to ustekinumab, 19 patients discontinued due to an AE. 18 of these 19 events that resulted in discontinuation appear to relate to Crohn's Disease and its complications, with the exception of one event of chronic recurrent multifocal osteomyelitis.

## Real World Evidence

A study report for the REALITI study was submitted at the time of EMEA/H/C/000958/II/0108, Version 1.0, dated Jun 2024.

Real-world evidence is presented in results from the observational, noninterventional paediatric RWE study CRD3010, for the effectiveness and safety of ustekinumab treatment in paediatric patients (aged 2 to <18 years) and young adults (ages 18 to <26 years) with moderately to severely active Crohn's disease using the ICN registry.

The ICN registry does not collect data on the severity of AE/SAE or the relationship of AE/SAE to treatment with ustekinumab, hence limited safety data were collected.

The REALITI study is broken into various cohorts by age, weight disease severity, baseline treatment.

With regard to the proposed paediatric extension to the indication, the Primary Cohort and Cohort 2 are probably the most of interest.

- 114 paediatric patients who weighed ≥40 kg were included in the paediatric Cohort (Primary Cohort).
- 31 paediatric patients who weighed ≤ 40 kg were included in Cohort 2.

Within the paediatric patient cohort the median age was 16 years (range 11:17). The majority (96.5%) were aged 12 to <18 years. Median (IQR) weight was 54.55 kg (45.60; 64.30).

In the paediatric patients (Primary Cohort) there were 43 (37.7%) of 114 patients reported with a safety event of interest. There were 41 (36%) of 114 patients with 1 or more IBD-related hospitalisation, 16 (14%) of 114 patients with 1 or more IBD-related surgeries and 12 (10.5%) of 114 patients with 1 or more AESI. The most common AESI was serious infection in 11 (9.6%) of 114 patients. The rates of opportunistic infections were low, at 1.8%; one case of Staphylococcus epidermidis bacteraemia and one case of Cryptosporidium. There were no cases of tuberculosis, malignancies, or anaphylaxis requiring treatment discontinuation. There were no deaths in this cohort.

**Safety Data for Other Approved Paediatric Indications for Stelara**

Plaque psoriasis in children

Ustekinumab is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. The recommended dose is based on body weight administered at Weeks 0 and 4, then every 12 weeks thereafter.

**Table 93: Dosing in paediatric plaque psoriasis**

| Body weight at the time of dosing | Recommended Dose |
|---|---|
| < 60 kg | 0.75 mg/kg |
| ≥ 60-≤ 100 kg | 45 mg |
| > 100 kg | 90 mg |

Safety data from the paediatric Crohn's disease studies have been compared with data from paediatric patients with moderate to severe plaque PsO from two Phase 3 studies (Study PSO3006 (CADMUS) and Study PSO3013 (CADMUS Jr.)). It should be emphasised that a different dose (lower) and maximum treatment frequency (q12w) is approved for plaque psoriasis in children, so there are limitations in this type of cross study/disease comparison.

**Table 94: Paediatric studies in plaque psoriasis with/without psoriatic arthritis**

| Study Number/ Description/Status | Study Population and Primary Endpoint | Treatment Period | Number of Participants Enrolled/Treated Participants |
|---|---|---|---|
| **Pediatric PsO Studies** | | | |
| PSO3006 (CADMUS)<br><br>Phase 3, multicenter, randomized, double-blind, placebo-controlled study<br><br>Completed | Adolescent participants ≥12 to <18 years with plaque-type PsO for at least 6 months and moderate to severe disease defined by a PASI ≥12, a PGA ≥3, and BSA involvement ≥10%<br><br>Primary endpoint: proportion of participants who achieved a PGA score of cleared or minimal at Week 12 | Participants received study intervention through Week 40 and were followed for efficacy through Week 52 and for safety through Week 60 | 110 participants<br><br>placebo: n=37<br>half-standard dose: n=37<br>standard dose*: n=36<br><br>*standard dose:<br>≤60 kg: 0.75 mg/kg<br>>60 to 100 kg: 45 mg<br>>100 kg: 90 mg<br><br><60 kg: 51<br>≥60 kg: 59<br><br>Safety data set: 110 total participants<br><br>73 ustekinumab-treated participants were included in the SCS safety analyses |
| PSO3013 (CADMUS Jr)<br><br>Phase 3, open-label study of SC administered ustekinumab<br><br>Completed | Pediatric participants ≥6 to <12 years of age with moderate to severe plaque-type PsO with or without PsA as defined by PASI ≥12, PGA ≥3, and BSA involvement ≥10%<br><br>Primary endpoint: proportion of participants with a PGA of cleared (0) or minimal (1) at Week 12 | Participants received study intervention through Week 40 and were followed for efficacy through Week 52 and for safety through Week 56<br><br>LTE study: Week 56 through Week 264 | Main study: 44 participants (28 participants in the LTE study)<br><br><60 kg: 40<br>≥60 kg: 4<br><br>Safety data set: 44 participants (28 participants in the LTE study)<br><br>All 44 participants were included in the SCS safety analyses |

In the comparison analysis set, a slightly higher percentage of participants in studies CRD3004 (93.1%) & CRD1001 (86.4%) experienced AEs compared to PSO3006 (84.9%) or PS03013 (77.3%), see Table 95 below. Additionally, the proportions of participants who had at least 1 reported SAE were different and numerically higher in the paediatric Crohn's disease studies than the paediatric PsO studies. This difference in SAE rates reflects the disease under study as most of the SAEs in the paediatric Crohn's disease studies were related to Crohn's disease. AEs rates relating to infections are broadly similar in the Crohn's studies compared to the psoriasis studies. Related AE rates are quite similar across the studies, and in fact are higher in the psoriasis pivotal studies than in CRD3004.

**Table 95: Overall summary of treatment-emergent AEs through approximately 1 year; (Studies CNTO1275CRD1001, CNTO1275CRD3004, CNTO1275PSO3006 and CNTO1275PSO3013)**

| | Ustekinumab | | | | |
|---|---|---|---|---|---|
| | Pediatric CD (<18 Years) | | | Pediatric PSO (<18 Years) | |
| | CRD1001 | CRD3004 | Total | PSO3006 | PSO3013 |
| Total N[a] | 44 | 101 | 145 | 73 | 44 |
| Average duration of follow-up (weeks) | 38.8 | 43.0 | 41.7 | 56.6 | 53.1 |
| Average exposure (number of administrations) | 4.7 | 8.3 | 7.2 | 5.8 | 4.8 |
| Subjects with 1 or more: | | | | | |
| AEs | 38 (86.4%) | 94 (93.1%) | 132 (91.0%) | 62 (84.9%) | 34 (77.3%) |
| Serious AEs | 11 (25.0%) | 17 (16.8%) | 28 (19.3%) | 6 (8.2%) | 3 (6.8%) |
| AEs leading to death | 0 | 0 | 0 | 1 (1.4%) | 0 |
| AEs leading to discontinuation of study intervention | 8 (18.2%) | 8 (7.9%) | 16 (11.0%) | 2 (2.7%) | 0 |
| AEs reasonably related to study intervention[b] | 17 (38.6%) | 11 (10.9%) | 28 (19.3%) | 18 (24.7%) | 19 (43.2%) |
| AEs of severe intensity | 9 (20.5%) | 10 (9.9%) | 19 (13.1%) | 4 (5.5%) | 0 |
| Infections | 25 (56.8%) | 66 (65.3%) | 91 (62.8%) | 50 (68.5%) | 29 (65.9%) |
| Serious infections | 1 (2.3%) | 6 (5.9%) | 7 (4.8%) | 2 (2.7%) | 1 (2.3%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 12 (27.3%) | 26 (25.7%) | 38 (26.2%) | 0 | 12 (27.3%) |
| Malignancy | 0 | 0 | 0 | 0 | 0 |
| Active tuberculous infections | 0 | 0 | 0 | 0 | 0 |
| Opportunistic infections | 0 | 0 | 0 | 0 | 0 |
| Injection site-reaction[c] | 0 | 0 | 0 | 1 (1.4%) | 6 (13.6%) |
| AEs temporally associated with the infusion of study intervention at Week I-0 (Week 0)[d] | 1 (2.3%) | 4 (4.0%) | 5 (3.4%) | 0 | 0 |

STELLAR Teens

STELLAR Teens is a prospective, observational, multi-centre PASS study of ustekinumab in paediatric patients 6 to 17 years of age with moderate-to-severe plaque psoriasis. The aim of the PASS to monitor long term safety and any potential effect on growth and development in paediatric patients.

At data cut off (16 January 2024),) for 6th Interval Safety Registry Report, 125 paediatric patients with PsO have been included in this safety analysis. A total of 76 (60.8%) patients initiated treatment with a 45 mg dose of ustekinumab while 49 (39.2%) patients received a weight-adjusted first dose (neither 45 mg nor 90 mg). The median duration of exposure to ustekinumab was 93.7 weeks (656 days).

The median age of patients included in the FAS at baseline was 12 years (IQ range: 11.0 to 14.0). A total of 39 (31.2%) patients were aged ≥6 years to <12 years at enrolment, all of whom were included in the FAS. Overall, 77 (61.6%) of 125 patients were female.

Overall mean exposure is 722.4 days (SD 468.88).

At the data cutoff, 79 patients experienced any AE (63.2%); a total of 474 events.

A total of 4 (3.2%) patients reported at least 1 AE leading to discontinuation of ustekinumab.

No deaths were reported during the study.

43 patients (34.4%) had any AE related to ustekinumab.

The most frequently reported related AEs included PTs within SOCs Infections and infestations (26 patients [20.8%]) followed by General disorders and administration site conditions (17 patients [13.6%]) and Respiratory, thoracic and mediastinal disorders (13 patients [10.4%]). Nasopharyngitis was the most frequently reported related AE (15 patients [12%]), followed by pyrexia and headache.

11 (8.8%) patients reported a total of 15 SAEs. Of the 15 reported SAEs, 1 serious infection of appendicitis was considered possibly related, and 1 serious event of acute urticaria was considered very likely related to ustekinumab.

Predefined safety outcomes (malignancies, serious infections, or autoimmunity-related AEs) were reported. There were no reports of malignancy. One (0.8%) patient reported a serious infection (PT appendicitis), and 4 (3.2%) patients reported autoimmunity-related AEs (3 [2.4%] reports of PT psoriasis and 1 [0.8%] report of PT cholangitis sclerosing).

**Safety Data for CD Indication for Stelara in adults compared to paediatric studies**

Safety data from the two adult Phase 3 induction studies CRD3001 (UNITI 1), and CRD3002 (UNITI 2) and single Phase 3 randomised withdrawal maintenance Study CRD3003 (IM-IMUNITI) were presented to demonstrate the established safety profile of ustekinumab. Safety findings in paediatric Crohn's disease studies (CRD3004 and CRD1001) are compared descriptively with those in the Phase 3 adult Crohn's disease studies (CRD3001, CRD3002, and CRD3003) in Table 96 (induction) and Table 97 (maintenance) below.

Induction period

**Table 96: Overall summary of treatment-emergent AEs during induction period; (CNTO1275CRD1001, CNTO1275CRD3004, CNTO1275PSO3001 and CNTO1275CRD3002)**

| | Ustekinumab | | | | |
|---|---|---|---|---|---|
| | Pediatric CD (<18 Years) | | | Adult CD (≥18 Years) | |
| | CRD1001 | CRD3004 | Total | CRD3001 | CRD3002 |
| Total N[a] | 44 | 101 | 145 | 495 | 419 |
| Average duration of follow-up (weeks) | 8.0 | 8.1 | 8.1 | 7.8 | 7.9 |
| Average exposure (number of administrations) | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Subjects with 1 or more: | | | | | |
| AEs | 28 (63.6%) | 63 (62.4%) | 91 (62.8%) | 323 (65.3%) | 221 (52.7%) |
| Serious AEs | 4 (9.1%) | 3 (3.0%) | 7 (4.8%) | 30 (6.1%) | 16 (3.8%) |
| AEs leading to death | 0 | 0 | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 3 (6.8%) | 3 (3.0%) | 6 (4.1%) | 10 (2.0%) | 5 (1.2%) |
| AEs reasonably related to study intervention[b] | 11 (25.0%) | 8 (7.9%) | 19 (13.1%) | 134 (27.1%) | 53 (12.6%) |
| AEs of severe intensity | 2 (4.5%) | 3 (3.0%) | 5 (3.4%) | 44 (8.9%) | 23 (5.5%) |
| Infections | 10 (22.7%) | 30 (29.7%) | 40 (27.6%) | 121 (24.4%) | 76 (18.1%) |
| Serious infections | 0 | 1 (1.0%) | 1 (0.7%) | 10 (2.0%) | 4 (1.0%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 3 (6.8%) | 7 (6.9%) | 10 (6.9%) | 55 (11.1%) | 36 (8.6%) |
| Malignancy | 0 | 0 | 0 | 0 | 0 |
| Active tuberculous infections | 0 | 0 | 0 | 0 | 0 |
| Opportunistic infections | 0 | 0 | 0 | 1 (0.2%) | 1 (0.2%) |
| AEs temporally associated with the infusion of study intervention at Week I-0 (Week 0)[c] | 1 (2.3%) | 4 (4.0%) | 5 (3.4%) | 20 (4.0%) | 8 (1.9%) |

The SOCs with the highest proportions of AEs through the induction period in both the paediatric (CRD3004 and CRD1001) and adult studies (CRD3001 and CRD3002) were Infections and infestations and Gastrointestinal disorders, with broadly similar rates in adults and children.

A numerically higher proportion of paediatric participants in CRD3004 (9 [8.9%] participants) and CRD1001 (6 [13.6%] participants) reported an AE of anaemia (SOC Blood and lymphatic system disorders), than in adults; (5 [1.0%] in CRD3001 participants and 6 [1.4%] in CRD3002 participants, respectively.

Maintenance period

**Table 97: Overall summary of treatment-emergent AEs during maintenance period; (CNTO1275CRD1001, CNTO1275CRD3004, CNTO1275PSO3001 and CNTO1275CRD3002)**

| | Ustekinumab | | | |
|---|---|---|---|---|
| | Pediatric CD (<18 Years) | | | Adult CD (≥18 Years) |
| | CRD1001 | CRD3004 | Total | CRD3003 |
| Total N[a] | 43 | 97 | 140 | 263 |
| Average duration of follow-up (weeks) | 32.3 | 36.4 | 35.1 | 35.9 |
| Average exposure (number of administrations) | 4.1 | 7.6 | 6.6 | 7.5 |
| Subjects with 1 or more: | | | | |
| AEs | 34 (79.1%) | 84 (86.6%) | 118 (84.3%) | 213 (81.0%) |
| Serious AEs | 10 (23.3%) | 13 (13.4%) | 23 (16.4%) | 29 (11.0%) |
| AEs leading to death | 0 | 0 | 0 | 0 |
| AEs leading to discontinuation of study intervention | 5 (11.6%) | 5 (5.2%) | 10 (7.1%) | 14 (5.3%) |
| AEs reasonably related to study intervention[b] | 9 (20.9%) | 3 (3.1%) | 12 (8.6%) | 74 (28.1%) |
| AEs of severe intensity | 8 (18.6%) | 6 (6.2%) | 14 (10.0%) | 36 (13.7%) |
| Infections | 21 (48.8%) | 61 (62.9%) | 82 (58.6%) | 125 (47.5%) |
| Serious infections | 1 (2.3%) | 4 (4.1%) | 5 (3.6%) | 10 (3.8%) |
| Infection requiring oral and/or parenteral antimicrobial treatment | 10 (23.3%) | 22 (22.7%) | 32 (22.9%) | 73 (27.8%) |
| Malignancy | 0 | 0 | 0 | 0 |
| Active tuberculous infections | 0 | 0 | 0 | 0 |
| Opportunistic infections | 0 | 0 | 0 | 0 |
| Injection site-reaction[c] | 0 | 0 | 0 | 14 (5.3%) |

The SOCs with the highest proportions of AEs through the maintenance periods in the paediatric studies (CRD3004 and CRD1001), and the adult maintenance study were Gastrointestinal disorders and Infections and infestations.

The proportions of AEs reported within different SOCs among participants from CRD3004 and CRD1001 were similar (or lower) to those reported for the adult maintenance study CRD3003, with the below exceptions:

- Crohn's disease: 36 (37.1%) participants in CRD3004 and 11 (25.6%) participants in CRD1001, compared with 32 (12.2%) participants in the adult study CRD3003.
- Upper respiratory tract infection reported more frequently in paediatric studies (23 [23.7%] participants in CRD3004 and 10 [23.2%] participants in CRD1001) than the adult study CRD3003 (22 [8.4%] participants).
- Anaemia: a numerically higher proportion of paediatric participants in CRD3004 (12 [12.4%] participants) had this event compared with adult participants in CRD3003 (8 [3.0%] participants), which was more similar to that observed in CRD1001 (1 [2.3%] participant).
- Pyrexia: a numerically higher proportion of paediatric participants in CRD1001 (6 [14.0%] participants) had this event compared with paediatric participants in CRD3004 (5 [5.2%] participants) and adult participants in CRD3003 (20 [7.6%] participants).
- Weight decreased: a numerically higher proportion of paediatric participants in CRD1001 (4 [9.3%] participants) had this event than the adult population in CRD3003 (3 [1.1%] participants).

### 2.6.1. Discussion on clinical safety

*Introduction, scope of variation and outline of safety package*

The scope of this variation is to extend further the Crohn's Disease indication and posology to include children from age 2 years of age, without a weight restriction. The MAH provides clinical data from this population, and also extrapolates from the established safety profile for the adult CD population.

A variation (EMEA/H/C/000958/II/0108) to extend the Crohn's disease population to include children weighing at least 40kg has already been approved. For paediatric subjects weighing ≥ 40kg, the same posology as adults was approved. During that procedure the MAH proposed an optional q4w dosing interval for the paediatric age group, however this dosing frequency was not approved based on insufficient data.

The same studies are presented in this variation, CRD3004, CRD1001, and ISD1001(UNITED); however, the datasets are now somewhat larger taking into account the entire enrolled population including patients < 40kg.

The Phase 3 CRD3004 trial is the pivotal study and the primary study supporting the safety of ustekinumab in the paediatric (from age 2 years) population. Neither CRD3004 nor CRD1001 was placebo controlled or active controlled, which limits in-study safety comparisons. CRD3004 while not placebo controlled, did use placebo injections during the maintenance phase to preserve the blind as both arms were dosed at different frequencies. CRD1001 had a randomisation at induction to low or high dose induction IV infusion, followed by one 8-weekly open label subcutaneous maintenance dose.

In addition, the MAH extrapolates efficacy and safety data for ustekinumab in the treatment of adults with CD to the treatment of children with CD based on similarity of disease pathophysiology in adults and children. From a safety perspective it is agreed that the safety data from adults can be extrapolated to further support the paediatric CD studies listed above. Infections and serious infections were examined in detail in both the paediatric and adults CD studies which is important given that ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. With respect to younger children this is important in case of any negative effect on the less mature immune system through IL12/23 inhibition.

In this procedure the MAH proposes an optional increased dosing frequency of q4w for paediatric patients that lose clinical response and who have low ustekinumab exposure. The clinical data relating to a q4w dosing in paediatric CD subjects comes from the optional open label Exposure Optimisation Substudy (EOS) of CRD3004. There are also some limited provisional data from children with Ulcerative Colitis treated at a q4w interval from a similar substudy. A q4w dosing interval has not been approved for any age group.

*Proposed posology and doses used in the studies*

The proposed new posology for children weighing < 40kg is:

- a single IV **induction** dose, based on Body Surface Area.
- and for **maintenance**: a subcutaneous dose (based on BSA), with a 12-weekly interval (after first maintenance dose 8 weeks after induction dose), that can be increased to an 8-weekly, or 4-weekly interval if required.

This posology is the same as was used in CRD3004. A different type of regime which was weight based rather than BSA based was used in CRD1001. Additionally, half of the subjects in CRD1001 had only a low dose induction dose (3 mg/kg for subjects <40 kg or 130 mg for subjects ≥40 kg), which equates

with approximately half of the proposed induction dose. Hence, the main supporting data for this paediatric extension of indication variation is from CRD3004, with supportive data from CRD1001.

Of note, subjects that moved to the ISD1001(UNITED) LTE study from CRD3004 on a 12-weekly maintenance dose changed to an 8-weekly maintenance dose. Hence most of the data from the UNITED LTE study is based on 8-weekly dosing, not 12-weekly dosing which is the first line dosing frequency recommended for patients starting the maintenance phase.

CRD3004 had a set, open label IV induction dose 250mg/$m^2$, based on BSA, followed by a randomisation to one of 2 maintenance regimes - 60mg/$m^2$ or 90mg/$m^2$ q8w or 60mg/$m^2$ or 90mg/$m^2$ q12w (60mg/$m^2$ for those < 40kg and 90mg/$m^2$ for those > 40kg).

The safety data for CRD3004 and CRD1001 are presented separately, side by side. This approach is appropriate considering that the 2 studies had quite different designs, including, dose regimens, and dose regimen strategies (body weight versus BSA-based). There were also some differences in terms of the population: most notably CRD1001 requiring participants to have previous failure or intolerance to anti-TNF therapy.

Initially, the MAH proposed not to include a BSA table for the induction dose in section 4.2 of the SmPC on the basis that HCPs are familiar with calculating the BSA and that such a table would impact the overall readability of the SmPC. While it is agreed that HCPs are familiar with calculating BSA further detail is required to clearly outline the approach to dose calculation. BSA-based dosing is used for IV induction and maintenance phase in children <40 kg whereas weight-based dosing is used for children > 40kg and for adults. The EMA Good Practice Guide on Medication Error Prevention recommends simplifying dose selection as a risk mitigation strategy promoting inclusion of charts with pre-calculated dose from strength and body weight in the SmPC. Use of standardised tables reduces the need for complex calculations and minimises human-factor error sources, avoid calculation errors.

Following the CHMP request the MAH therefore proposed a simple BSA-tiered dosage table, which minimises wastage, and facilitates more efficient use of existing presentations and therefore is considered acceptable.

*Exposure*

145 paediatric participants were recruited to CRD3004 and CRD1001. Of these, only 30 were aged >2 to 12 years, and only 2 were aged >2 to 6 years; so about 80% of the subjects were adolescents.

101 participants in CRD3004 were treated with a single induction IV dose of ustekinumab. At Week M-0, 97 participants were randomised to either receive the q12w (49 participants) or q8w (48 participants) SC regimen of ustekinumab. The median total duration of exposure through the end of the maintenance period (Week M-44/Week 48) in CRD3004, for the q12w and q8w treatment groups were 44.1 and 48.1 weeks, respectively. 66 participants from CRD3004 were treated with ustekinumab in ISD3001(UNITED); 48 participants in the q8w group and 18 participants in the q4w group (after at least 52 weeks in CRD3004). The median total duration of exposure in ISD3001(UNITED) was 48.8 weeks (48.8 and 41.1 weeks in the q8w and q4w groups, respectively). The median total number of SC injections in the q8wgroup was 8.0, and in the q4w group was 9.0.

A total of 26 patients in CRD3004 met the criteria for the Exposure Optimisation Substudy. These patients had an average follow up in the EOS of 21.3 weeks, and on average received 6.2 doses (q4w).

There was a high completion rate in study CRD3004 for the induction period; 98/101(97%) completed the induction period. For the maintenance period, of 85 subjects randomised at week M-O, only 10 (11.8%) discontinued up to week M44, and of these only one appears to discontinue due to a AE other than worsening of Crohn's.

44 participants were treated with ustekinumab in CRD1001. The median total duration of exposure through the end of the maintenance period (Week M-44/Week 48) in CRD1001 was 39.3 weeks. Only 6 subjects from CRD1001 entered the ISD3001(UNITED) LTE trial. Six participants from CRD1001 were treated with ustekinumab in ISD3001(UNITED), with a median total duration of exposure of 94.5 weeks, median total number of SC injections of 13.0, and a median total dose of 1,170.0 mg of ustekinumab SC.

Overall, there is considered to have been a sufficient number of children exposed for more than a year at the intended doses across CRD3004, CRD1001 and ISD1001(UNITED), albeit that the exposure in children under the age of 12 years is quite limited, and very limited in the age 2-6 years bracket. Long term safety data in paediatric patients 2 to <18 years of age will be collected in the study CNTO1275ISD3001 (UNITED) LTE, category 3 commitment in the RMP.

*Adverse events*

CRD1001 and CRD3004

Overall, there were high rate of AEs in both studies for the induction period (approx. 63% in each study's induction) and higher again for maintenance periods (79.1% for CRD1001 and 86.6% for CRD3004). SAEs rates are also reasonably high- for example, 13.4 % of patients during the maintenance phase of CRD3004 had at least one SAE in CRD3004, and 23% in CRD1001.

There were no deaths across any of the paediatric Crohn's studies.

In both studies, and both phases, the AEs are driven by gastrointestinal AEs and Infections/Infestations AEs. Gastrointestinal AEs appear to be driven by Crohn's Disease, abdominal pain, diarrhoea, nausea and vomiting, nausea and vomiting. Infections/infestations are largely driven by URTI, gastroenteritis, nasopharyngitis, rhinitis. Anaemia, headache, and arthralgia also have occurred commonly.

Comparing the q8w arm and q12w of CRD3004's maintenance phase there is no signal of increased toxicity at the more frequent q8w frequency.

Generally, both the overview of AEs and breakdown of AEs is in keeping with the adult CD data for ustekinumab. There are no apparent new safety signals not already identified in the SmPC; hence no new additions are proposed to the SmPC Section 4.8.

Long term extension data - LTE period of CRD1001 and LTE study ISD3001

Nearly all (92.3%) participants in CRD1001 reported 1 or more AEs in the LTE phase. Among participants in ISD3001, rates were somewhat lower; 72.9% of participants from CRD3004 and 66.7% of participants from CRD1001 reported 1 or more AEs.

As for the induction and maintenance periods, overall, Infections/Infestations and gastrointestinal disorders were the most commonly represented SOCs in the LTE period, i.e. CRD1001 and ISD3001(UNITED).

There were no AEs leading to death, malignancies, active TB infections, or opportunistic infections, and only 1 participant reported an injection-site reaction.

Discrepancies between overall AE profile of CRD1001 and CRD3004/ISD3001

It is noted, that for both the induction and maintenance phase there is a significantly higher rate of related TEAEs in the CRD1001 study versus the CRD3004 study. In the induction phase, AEs considered reasonably related by the investigator occurred in 8 (7.9%) CRD3004 participants versus 11 (25.0%) CRD1001 participants. In the maintenance phase, AEs considered reasonably related by the investigator occurred in 3 (3.1%) CRD3004 participants versus 9 (20.9%) CRD1001 participants. Similar trends are seen in the long-term extension data (both the LTE period of CRD1001 and in the UNITED ISD3001

basket study); 38.5% (10 subjects) in the LTE of CRD1001 had an AE than was considered related versus just 6.3% (3 subjects) in the CRD3004 subjects.

The MAH explains that there was a difference in the guidance to assess relatedness in both studies. The relatedness assessment of ustekinumab to an AE in the CRD3004 included only the options of "related" or "not related." For CRD1001 additional options included "not related," "doubtful," "possible," "probable," and "very likely"; the latter 3 categories were combined and are presented in this SCS as "related" in analyses of CRD1001 data. The MAH offers this a reason as to why there is a difference in related TEAEs. While this may have contributed to some degree, it is noted however, that this trend was not apparent in the data at the time of Variation EMEA/H/C/000958/II/0108 to add children weighing > 40kg. In fact, there were no related TEAEs at that time of assessment in Study CRD1001 study, for either the induction or the maintenance phase, and just 3 in the induction phase (only) of the CRD3004 study. The MAH has identified that a programming error in the SCS resulted in the incorrect (blank) variable being used to identify TEAEs coded as "reasonably related" in Study CRD1001 resulting in underreporting of related AEs. The programming error has been corrected, and the affected tables have been rerun. Four additional AEs were identified in the induction period and 8 in the maintenance period for patients who weighed ≥40 kg. No new safety concerns have been identified. No new ADRs have been included in the SmPC section 4.8. Which was considered acceptable by the CHMP.

Additionally, it is also noted that SAEs, and AEs resulting in discontinuation were also much more frequent in CRD1001 than in CRD3004, both in the induction and maintenance phases, and also in the long-term extension phases; in general rates were 2-fold higher in CRD1001 patients than in CRD3004 patients. In the LTE phases, it is also noted that there was a much higher rate of AEs overall in CRD1001 (92.3%) than in the CRD3004 patients than in ISD 3001(UNITED) (72.9%). The explanation about different criteria for relatedness assessment in studies CRD1001 and CRD3004 would not seem to apply to these differences. The MAH has clarified that the differences in frequencies of SAEs and AEs resulting in discontinuation across these two studies are likely due to differences in study populations and study design. This is accepted.

*Serious Adverse Events, AESIs (serious infection, malignancy, active TB, opportunistic infection)*

In the induction phase overall 7 participants experienced at least 1 SAEs; 4 in CRD1001(9.1%) and 3(3%) in CRD3004.

It should be noted that there were 2 subjects in CRD3004 that had to stop their induction infusion due to infusion related reactions. One was listed as infusion related hypersensitivity reaction, and one was listed as 'cardiac chest pain/dyspnoea, hypertension/pale skin/tachycardia/tachypnoea'. Both were temporally related to the infusion (started soon after starting the infusion), and both required stopping the infusion and adrenaline. Both events were in teenagers - both aged 14 years of age. Only one of these was recorded as an SAE (the infusion related hypersensitivity reaction), although arguably could be considered SAEs. Serious hypersensitivity reaction is a known side effect to monoclonal antibody treatment and is in the Stelara SmPC classified as rare (≥ 1/10,000 to < 1/1,000). The numbers in this data set is too low to conclude on the finding of 2 participants. It is noted that the children affected did not belong to the youngest or lightest subset.

In the maintenance phases of both studies SAE rates were higher than the induction phases. 23 participants had at least 1 SAE; 13 (13.4%) participants in CRD3004 and 10 (23.3%) participants in CRD1001. The proportion of participants who had at least 1 SAE were similar in the CRD3004 q8w (14.6%) and q12w treatment groups (12.2%), but slightly higher in the CRD1001 study q8w (23.3%).

In CRD1001, one participant experienced an SAE of (and severe) serious infection due to an intestinal (ileocaecal) abscess during the maintenance phase, on D186, which was considered 'probably related' to study intervention, and the event resolved but with sequelae. On review of this case (female participant)

it is noted that this event occurred more than 2 months after stopping treatment due to a worsening of Crohn's AE, also considered probably related. Considering the time onset with respect to the stop therapy date, it is possible that this SAE is unrelated to ustekinumab.

There were no AEs leading to death.

No AESIs of malignancy, active TB or opportunistic infection occurred in any of the paediatric CD studies.

There was a small number of participants with serious infections AESIs across the 3 studies; all bar one, were considered unrelated, see also above. There are no new trends or signals arising from the analysis of the SAEs or AESIs. Most of the SAEs are consistent with the expected Crohn's disease activity or established safety profile of ustekinumab, and most were considered unrelated. The AESIs reported are also consistent with the expected Crohn's disease activity or established safety profile of ustekinumab.

*Laboratory parameters*

Across the 3 studies, the proportions of participants experiencing markedly abnormal values in laboratory test results were low, and there were no consistent trends observed that suggested an association of ustekinumab treatment with changes in routine laboratory. There were no cases of Hy's Law in any of the studies.

Anaemia is common, which is expected based on the disease.

Tables summarising the worst postbaseline NCI-CTCAE toxicity grades of laboratory haematology and chemistry values for the EOS(q4w) patients in CRD3004, and also for those EOS subjects that continued on q4w in LTE ISD3001(UNITED), have been provided. No overt differences in the laboratory findings between EOS participants from Study CRD3004 and EOS participants from Study CRD3004 that continued in Study ISD3001 on q4w and those participants that received ustekinumab q8w dosing.

GGT was measured in Study CRD3004 but was not measured in Study 5CRD1001. A single Grade 2 GGT abnormality was observed in Study CNTO1275CRD3004. No participant in the substudy had a post-baseline CTCAE GGT abnormality of Grade 2 or greater (data not presented). No meaningful trends related to physical findings and growth were observed in CRD3004 and CRD1001.

*Special populations*

No distinct trends were observed in the safety profile for ustekinumab across subgroups based on age, and sex. However, it must be acknowledged that safety data in the youngest patients is very limited. Due to the low number of participants ≥2 to <12 years of age (n=30) compared with participants ≥12 to <18 years of age (n=115), limited comparisons can be made between the 2 age groups.

In CRD3004 there was an even representation of biologic failure subjects (n=57, induction phase) and non-biologic failure patients (n=44, induction phase) recruited; however, the relatively small numbers limit drawing conclusions. It is noted that during the maintenance phase infections (70.9% in biologic failure group versus 52.4% in non failure group), and infections requiring treatment with antimicrobials (30.9% in biologic failure group versus 11.9% in non failure group) were more common in the biologic failure subjects, but serious infections were not more common in the biologic failure patients. There was a slightly higher rate of AE leading to discontinuation in the biologic failure group (7.3%) versus the non-biologic failure group (2.4%) again in the maintenance phase. Overall, the limited available data do not particularly indicate any significant impact of prior biologic failure on safety, despite the fact that prior biologic failure may indicate a more severe disease profile.

Weight:

The pattern of AEs was similar in the paediatric population <40kg and ≥40kg and similar to the adult population, except a numerically higher proportion of participants in the <40 kg group reported 1 or more

infections requiring oral and/or parenteral antimicrobial treatment than in participants who weighed ≥40 kg (37.0 vs 17.1%) (overlap with the youngest participants). A higher frequency of infections in the youngest (and lightest) patients, as well as an increased use of antibiotics is not unexpected.

Age:

The pattern of AEs was similar in the paediatric population <12 years and ≥12years and similar to the adult population, except a numerically higher proportion of participants in the 2 to 11 years of age combined group reported 1 or more infections requiring oral and/or parenteral antimicrobial treatment than in participants 12 to 17 years of age (36.8% vs 19.2%) (overlap participants with the lowest weight). A higher frequency of infections in the youngest (and lightest) patients, as well as an increased use of antibiotics is not unexpected.

*Safety related to drug-drug interactions and other interactions*

In keeping with adult ustekinumab studies in Crohn's disease and also in ulcerative colitis, immunogenicity was low in the paediatric Crohn's population. Three of 101 patients (3.0%) were positive for antibodies to ustekinumab through Week M-44. All 3 participants positive for antibodies were positive for NAbs. This is comparable to the adult population (9 of 287; 3.1%).

*Discontinuation due to adverse events*

Rate of discontinuation due to TEAE were reasonably low in both CRD3001 and CRD1004, and lower in CRD3004. In both the induction and maintenance phases TEAEs resulting is discontinuation mainly related to gastrointestinal disorders/Crohn's disease and likely complications of Crohn's Disease. In the induction phase there were 2 subjects with infusion related reactions, which is a known adverse reaction, and clearly identified in the SmPC.

*The proposed (optional) q4w dose interval*

The extent of the data relating to the q4w interval is quite limited both in terms of numbers and duration of treatment. Additionally, data on a q4w interval are open label. Just 26 subjects moved to the EOS, where they were followed for approximately 20 weeks (6 doses). 23/26 were induction responders with LOR. 18 subjects then moved into the LTE study and continued to receive the Q4W if their 4-week ustekinumab trough concentration at the end of EOS (after at least 3 doses) was <7.2 µg/mL. The average duration of treatment at q4w for those 18 subjects was 10 doses (approx. 40 weeks).

The EOS patients were generally demographically similar to those in the main study. They also were a moderate to severe population, but a slightly higher proportion had severe disease based on a PCDAI > 40 than in the main study, and a higher proportion had a history of biologic failure. Twenty-one (80.8%) participants in the EOS compared with 54 (56.4%) participants in the main study (CRD 3004), had a history of biologic failure. Existing PCDAI/sPCDAI cut-off values remain appropriate and valid for assessing clinical response and LOR in paediatric Crohn's disease, regardless of prior biologic treatment history. Data from the small, heterogeneous EOS paediatric cohort could not support development of alternative prognostic thresholds. Furthermore, available evidence (i.e. clinical guidelines ECCO-ESPGHAN 2021, Stride II 2021), does not support altering these thresholds based on previous biologic exposure. Exposure–response analyses show broad overlap in trough concentrations between participants with prior biologic failure and those without such history. Therefore, a single trough concentration threshold can be applied to define low exposure across both subgroups. Comparing the overall AE profile in the 16-week EOS versus the maintenance phase of CRD3004, no significant differences are evident. Overall, there were less AEs in the EOS than in CRD3004, as well as less SAEs and less infections. Related AEs were however more common in the EOS than in the main CRD3004 study as were serious infections. Regarding continued use, it is useful to compare the overall AE profile in the LTE study of the CRD3004 q8w patients and CRD3004 q4w patients (i.e. the previous EOS patients). It does appear that the q4w may have more

slightly more AEs overall, but a significantly higher rate of SAEs (27.8% for q4w versus 10.4% for q8w) and severe AEs (16.7% for q4w versus 2.1% for q8w). There was also a considerably higher rate of AEs resulting in discontinuation (27.8% for q4w versus 2.1% for q8w), related AEs (22.2% for q4w versus 6.3% for q8w), as well as serious infections (11.1% for q4w versus 2.1% for q8w). This could suggest a dose effect with regard to safety, but also could reflect a more severe population, or the small numbers involved.

The overall breakdown of the AEs in terms of SOC/PT generally mirrors the trends seen in the main part of CRD3004, most AEs coming from Gastrointestinal and Infections/infestations, with most of the AEs appearing to be associated with CD.

Overall, the very limited data relating to q4w dosing makes it difficult to compare the safety of this interval vs q8w and q12 weekly intervals. While it could be reasoned that the EOS/q4w subjects may reflect a slightly more severe group, and hence a greater tendency to have CD associated AEs it is noticed that related AEs were also higher in the q4w subjects in the LTE study.

From a review of the PK data it seems that the exposures with q4w in children with CD largely overlaps with exposures seen in adults with CD dosed at q8w.

The proposal to increase to a 4 weekly dosing interval in case of loss of response and low exposure has been further justified. The proposal to measure trough levels and consider dose escalation if the steady state threshold is <1.4mcg/ml is based on E-R analysis in adults. Low exposure is defined as an 8-week, steady-state ustekinumab trough concentration <1.4 µg/mL. The proposed therapeutic ustekinumab target serum drug concentration (>7.2mcg/ml) is based on the average of the 95th percentile of the lowest drug levels measured just before dosing, after 8 weeks of treatment, in adults who participated in the CD clinical studies. In both Study CRD3003 and CRD3004, ustekinumab trough concentrations in the highest quartile were not associated with greater incidence of either serious adverse events or serious infections. The justification for the selection of >7.2 µg/mL threshold as a pharmacokinetic target to ensure that patients who have their dose adjusted to q8w or a q4w regimen maintain sufficient drug levels to achieve optimal therapeutic effect is accepted.

The MAH has further outlined the methodology for assessing ustekinumab levels, the timing of testing and the need for follow up levels (and timing of this), in patients with LOR and who have their dosing interval reduced. Ustkinumab levels are checked when there is loss of clinical response after 2 doses of maintenance treatment. The timing of a repeat trough level has been set at either 12 or 16 weeks after dose adjustment to 4 weekly treatment. The proposal to reassess levels at 12 or 16 weeks after dose adjustment is in line with the ustekinumab testing the Exposure Optimisation Substudy after dose reduction (SmPC section 4.2).

The MAH has proposed revised wording for section 4.2 so that healthcare professionals understand when to consider increasing dosing frequency and what criteria to use (exposure levels, timing, etc.) This includes a recommendation to shorten the dosing interval from 12- to 8-weekly intervals. This recommendation aligns with the approach taken in Study CRD3004 and with the recommendation for dose optimisation in the adult population.

A move from 12-weekly to 8-weekly treatment is a logical step in intensification with a lower-risk escalation; however some children with LOR particularly those <40 kg or with high inflammatory burden, may not achieve therapeutic levels even at q8w. By delaying appropriate dosing, this could result in slower time to improvement in children with high disease burden. The possibility of switching from q12w to q4w in cases of LOR with low ustekinumab trough levels (<1.4 µg/mL) should be considered if clinically indicated i.e. if higher exposure is needed for rapid clinical response. Careful clinical and drug level monitoring is required if dose is adjusted from q8w or q12w to q4w. The posology (SmPC Section 4.2) has been updated to include guidance for HCPs to first increase the frequency to q8w before increasing

the frequency to q4w but also giving clinicians the option to increase the frequency of injection to q4W from q12w, if required.

In paediatric clinical practice, serum ustekinumab levels are measured through trough-level blood samples analysed using ELISA-based assays, often alongside anti-drug antibodies. ELISA is currently the standard and most widely validated method for measuring ustekinumab serum concentrations. While there is no widely used ECLIA-based ustekinumab assay reported in clinical practice today, ECLIA is a newer, highly sensitive platform and is likely to become more widely available. Reference in the SmPC to use of both methodologies has been accepted.

Of the 26 substudy participants, 7 participants had at least one 4-week trough ustekinumab concentration exceeding the 7.2 µg/mL threshold at some point during the EOS. The timings of these elevations varied across EOS timepoints, the earliest at Week 8 with additional elevations seen around Week 12 and Week 16. This occurred regardless of the dosing schedule used (i.e, q12w and q8w). No new safety concerns were identified in participants with ustekinumab elevations >7.2 µg/mL threshold. One participant discontinued treatment due to elevated ustekinumab levels. Safety data indicate that most of the participants enrolled in the substudy who received q4w dosing were able to continue q4w dosing without additional safety signals.

While there is no Q4W dose interval approved for adults, it is noted that there was an MAH sponsored adult CD study where some adults were dosed at a 4-weekly interval. CRD3005 was an open-label, multicentre, phase 3b study in adults with Crohn's disease evaluating whether a treat-to-target (T2T) strategy could improve outcomes compared with standard clinician-directed care. Patients were randomised to either structured dose-adjustment guided by predefined endoscopic and clinical targets or to routine management. Overall safety outcomes were similar across the study arms. Related AEs, SAEs and AEs resulting in discontinuation were slightly higher in the routine arm compared to the T2T arm. Of note two participants died during the maintenance phase of the main treatment period, both from the T2T arm. One participant died of a cardiac event (unrelated to ustekinumab) and the second participant died due to an unknown cause (relationship to study intervention not reported). One participant from the (routine care) RC arm died during the extension period. This participant died of a cervix neoplasm considered to be unrelated to study intervention according to the investigators. However, no new safety signals were identified. The safety profile in the T2T was broadly similar to the safety profile for ustekinumab in the routine care arm.

Some preliminary open label data from the Exposure Optimisation Sub study (EOS) of the recently completed Phase 3 study of ustekinumab in paediatric subjects with ulcerative colitis (PUC3001) is available and has been summarised. The numbers concerned are very small, just 21 children in total and the follow up (at present) is short - approximately 6 months. No new safety signals are evident. These data can be considered supportive only, as CD and UC are two different disease entities. The dosing used in Study PUC3001 and its EOS study was identical to the dosing in the CRD3004 study.

*Post marketing experience*

The applicant has summarised pharmacovigilance data from DEVELOP, an observational PASS of the long-term safety and clinical status of paediatric patients <17 years of age with IBD, focussing on the 165 children treated with ustekinumab. Although the limitations with these data must be acknowledged, the applicant puts forward that in the children followed in this trial treated with Ustekinumab there were similar types of events and rates of events to those seen in the adult Crohn's population, including serious infections. This is agreed.

The applicant has summarised Real World safety data from the REALITI study - an observational non interventional paediatric RWE study, collected within the ICN registry. The ICN registry does not collect data on the severity of AE/SAE or the relationship of AE/SAE to treatment with ustekinumab, hence

limited safety data were collected. Although the limitations with these data must be acknowledged, the applicant puts forward that for those who weighed ≥40 kg there were no deaths, malignancies, TB cases or anaphylaxis requiring treatment discontinuation reported. Cohort 2 included participants aged ≥2 to <18 years, with moderate-to-severe Crohn's disease, who weighed less than 40 kg at baseline. 31 (6.5%) of 479 participants with moderately to severely active CD and who weighed <40 kg were included in this cohort. The safety data through Week 52 show that paediatric participants <40 kg (Cohort 2) had a numerically higher proportion of IBD-related hospitalisation (13 (41.9%) of 31 participants) compared with the ≥40 kg Primary Cohort (41 (36.0%) of 114 participants) and Young Adults (Cohort 7, 11 (21.6%) of 51 participants). The MAH explanation for the higher hospitalisation rates (including surgeries) seen in children <40 kg, i.e. more severe phenotype of paediatric Crohn's disease, generally a more vulnerable, more nutritionally compromised population, pharmacokinetic differences due to their small body and overall lower thresholds for admission, making hospitalisation more common than in ≥40 kg children or young adults, is plausible. Rates of opportunistic infections (OIs) and serious infections were low. Overall, no new safety concerns have been identified. The applicant has summarised data on paediatric use of ustekinumab for paediatric plaque psoriasis. This includes safety data from two Phase 3 studies and an observational PASS study (STELLAR Teens). This is supplementary safety information as study designs, dosing regimens, study population, and disease indications are different. The applicant states that to date no apparent effect on growth and development has been detected. No significant safety concerns have been raised.

The applicant has summarised data on adult use of ustekinumab in CD**.** This includes safety data from two Phase 3 induction studies and one phase 3 maintenance study. Dosing is proportionally similar in the adult studies and pivotal paediatric study CRD3004, and the same dose intervals are used; certainly, the regimen is the same for children weighing more than 40 kg as is used in adults. The overall profile of AEs in terms of SOC is broadly similar between the adult and paediatric studies, for both induction and maintenance phases, with Gastrointestinal and Infections and infestations being the most commonly represented SOCs. Crohn's disease AEs were reported more frequently in the paediatric studies during the maintenance phases. Anaemia, which is probably reflective of disease activity rather than a treatment consequence was also generally reported at a higher rate in the paediatric studies than in the adult studies.

*SmPC Section 4.8*

No new ADRs are proposed for Section 4.8 arising from the paediatric CD data.

### 2.6.2. Conclusions on clinical safety

Overall, the safety of ustekinumab in the paediatric CD population from age 2 years upwards has been sufficiently characterised and no new safety concerns arise compared to adults.

## 2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.7. Risk management plan*

The MAH submitted an updated RMP version 32.1 with this application. The main proposed RMP changes were the following:

Product(s) Overview

- Removed "weighing at least 40 kg" from the paediatric CD indication and added "from the age of 2 years and older."

Safety Specification

- Renamed missing information "Long-term safety in paediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease" as "Long-term safety in paediatric patients 2 years and older with moderately to severely active Crohn's disease."

The CHMP received the following PRAC Advice on the submitted Risk Management Plan: The PRAC considered that the risk management plan version 32.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 32.1 with the following content:

**Safety concerns**

**Table 98: Summary of the Safety Concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • None |
| Important potential risks | • Serious infections (including mycobacterial and salmonella infections)<br>• Malignancy<br>• Cardiovascular events<br>• Serious depression including suicidality<br>• Venous thromboembolism |
| Missing information | • Long-term safety in paediatric psoriasis patients 6 years and older<br>• Long-term impact on growth and development in paediatric psoriasis patients 6 years and older<br>• Long-term safety in adult patients with moderately to severely active Crohn's disease<br>• Long-term safety in adult patients with moderately to severely active ulcerative colitis<br>• Long-term safety in paediatric patients ~~weighing at least 40 kg~~ 2 years and older with moderately to severely active Crohn's disease |

**Pharmacovigilance plan**

**Table 99: On-going and planned additional pharmacovigilance activities**

| **Study and Status** | **Summary of Objectives** | **Safety Concern(s) Addressed** | **Milestones** | **Due Dates** |
|---|---|---|---|---|
| **Category 1:** Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| Not applicable | | | | |

| Study and Status | Summary of Objectives | Safety Concern(s) Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 2:** Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| Not applicable | | | | |
| **Category 3:** Required additional pharmacovigilance activities | | | | |
| CNTO1275PSO4056 (Paediatric Psoriasis Registry): An observational postauthorization safety study of ustekinumab in the treatment of paediatric patients aged 6 years and older with moderate to severe plaque psoriasis<br><br>Ongoing | To confirm the long-term safety profile of STELARA use in paediatric patients 6 years and older and to explore any potential effect on growth and development in paediatric patients 6 years and older in-line with the consideration in the STELARA PIP. | Long-term safety in paediatric psoriasis patients 6 years and older<br>Long-term impact on growth and development in paediatric psoriasis patients 6 years and older | Protocol submission | 21 December 2015 |
| | | | Start of data collection | 25 October 2017 |
| | | | End of data collection | 31 August 2032 |
| | | | Final report | 31 March 2033 |
| An observational postauthorization safety study to describe the safety of ustekinumab and other biologic treatments in a cohort of patients with ulcerative colitis or Crohn's disease using compulsory Swedish Nationwide Healthcare Registers and the independent Swedish National Quality Register for Inflammatory Bowel Disease (SWIBREG; PCSIMM002807)<br><br>Ongoing | To monitor the long-term safety profile of ustekinumab in adult patients with moderately to severely active UC or CD. | Venous thromboembolism<br>Malignancy<br>Cardiovascular events (MACE only)<br>Serious infections (including mycobacterial and salmonella infections)<br>Long-term safety in adult patients with moderately to severely active ulcerative colitis<br>Long-term safety in adult patients with moderately to severely active Crohn's disease | Protocol submission | 23 June 2020 |
| | | | Start of data collection | 30 November 2022 |
| | | | End of data collection | 30 November 2027 |
| | | | Final report | 31 December 2028 |

| Study and Status | Summary of Objectives | Safety Concern(s) Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| An observational postauthorization safety study to describe the safety of ustekinumab and other treatments of ulcerative colitis in a cohort of patients with ulcerative colitis using the independent French Nationwide Claims Database (SNDS; PCSIMM002659)<br><br>Ongoing | To monitor the long-term safety profile of ustekinumab in adult patients with moderately to severely active UC. | Venous thromboembolism<br>Malignancy<br>Cardiovascular events (MACE only)<br>Serious infections (including mycobacterial and salmonella infections)<br>Long-term safety in adult patients with moderately to severely active ulcerative colitis | Protocol submission | 23 June 2020 |
| | | | Start of data collection | 31 December 2022 |
| | | | End of data collection | 31 December 2026 |
| | | | Final report | 31 December 2027 |
| CNTO1275ISD3001 (UNITED) LTE: A Phase 3, multicenter, open-label, basket, long-term extension study of ustekinumab in paediatric clinical study participants (2 to <18 years of age)<br><br>Ongoing | To collect long-term safety data in paediatric patients 2 to <18 years of age who receive ~~SC~~ ustekinumab for at least 1 year after participating in a primary paediatric ustekinumab trial (CNTO1275CRD1001, CNTO1275PUC3001, CNTO1275CRD3004, ~~and~~**or** CNTO1275JPA3001). | Long-term safety in paediatric patients ~~weighing at least 40 kg~~**2 years and older** with moderately to severely active Crohn's disease | Protocol submission | July 2024 |
| | | | Start of data collection | 18 October 2021 |
| | | | End of data collection | 31 July 2029 |
| | | | Final report | 31 January 2030 |

*Category 1 studies are imposed activities considered key to the benefit risk of the product.
Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

**Risk minimisation measures**

**Table 100: Summary Table of Risk Minimisation Activities and Pharmacovigilance Activities by Safety Concern**

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Serious infections (including mycobacterial and salmonella infections) | **Routine risk minimisation measures:**<br>SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects)<br>PL sections 2 and 4<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>TOI TFUQ for Serious Infections and Opportunistic Infections<br>TOI TFUQ for TB<br>**Additional pharmacovigilance activities:**<br>STELARA UC/CD PASS using Swedish Registers<br>Final study report due date: 31 December 2028<br>STELARA UC PASS using SNDS<br>Final study report due date: 31 December 2027 |
| Malignancy | **Routine risk minimisation measures:**<br>SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects)<br>PL section 2<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>TOI TFUQ for Malignancies (including Lymphoma, Second and Secondary Malignancies)<br>**Additional pharmacovigilance activities:**<br>STELARA UC/CD PASS using Swedish Registers<br>Final study report due date: 31 December 2028<br>STELARA UC PASS using SNDS<br>Final study report due date: 31 December 2027 |
| Cardiovascular events | **Routine risk minimisation measures:**<br>None<br>**Additional risk minimisation measures:** | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>TOI TFUQ for CV Events |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | None | **Additional pharmacovigilance activities:**<br>STELARA UC/CD PASS using Swedish Registers (MACE only)<br>Final study report due date:<br>31 December 2028<br>STELARA UC PASS using SNDS (MACE only)<br>Final study report due date:<br>31 December 2027 |
| Serious depression including suicidality | **Routine risk minimisation measures:**<br>SmPC section 4.8 (Undesirable Effects)<br>PL section 4<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>None |
| Venous thromboembolism | **Routine risk minimisation measures:**<br>None<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>TOIQ for VTE<br>**Additional pharmacovigilance activities:**<br>STELARA UC/CD PASS using Swedish Registers<br>Final study report due date:<br>31 December 2028<br>STELARA UC PASS using SNDS<br>Final study report due date:<br>31 December 2027 |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Long-term safety in paediatric psoriasis patients 6 years and older | **Routine risk minimisation measures:**<br>None<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>CNTO1275PSO4056 (Paediatric Psoriasis Registry)<br>Final study report due date:<br>31 March 2033 |
| Long-term impact on growth and development in paediatric psoriasis patients 6 years and older | **Routine risk minimisation measures:**<br>None<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>CNTO1275PSO4056 (Paediatric Psoriasis Registry)<br>Final study report due date:<br>31 March 2033 |
| Long-term safety in adult patients with moderately to severely active Crohn's disease | **Routine risk minimisation measures:**<br>None<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>STELARA UC/CD PASS using Swedish Registers<br>Final study report due date:<br>31 December 2028 |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Long-term safety in adult patients with moderately to severely active ulcerative colitis | **Routine risk minimisation measures:**<br>None<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>STELARA UC/CD PASS using Swedish Registers<br>Final study report due date:<br>31 December 2028<br>STELARA UC PASS using SNDS<br>Final study report due date:<br>31 December 2027 |
| Long-term safety in paediatric patients ~~weighing at least 40 kg~~ **2 years and older** with moderately to severely active Crohn's disease | **Routine risk minimisation measures:**<br>None<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>CNTO1275ISD3001 (UNITED) LTE<br>Final study report due date:<br>31 January 2030 |

## *2.8. Update of the Product Information*

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of BE, DE, IE, LU, NL, SLO.

### 2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Only minor changes to the PL are proposed. The design and layout of the Stelara IV and SC PLs will be unchanged and the existing Stelara SC PL design and layout is in accordance with the applicable EU guidelines. No changes that may affect its readability are expected.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

In both children and adults, Crohn's disease is a chronic inflammatory condition with a relapsing and remitting course. It is characterised by asymmetric, transmural and granulomatous inflammation affecting any portion of the intestinal tract. Symptoms and physical examination findings in adults and children are similar - abdominal cramps, diarrhoea, cachexia, fever, anaemia, right lower quadrant mass and perianal fistulae (Gajendran 2018; Rosen 2015; Torres 2017). Intestinal and extraintestinal complications and manifestations of Crohn's disease are also similar in adults and children (excluding children with underlying monogenic disease) (Lichtenstein 2022). In children, Crohn's disease is also characterised by delayed puberty and growth retardation.

### 3.1.2. Available therapies and unmet medical need

The current standard of medical care for paediatric Crohn's disease patients involves anti-inflammatory therapeutic approaches, which include corticosteroids, thiopurines (AZA, 6-MP), MTX, and anti-TNF agents. Currently, the anti-TNF agents' infliximab and adalimumab are the only approved biologic therapies for the treatment of paediatric Crohn's disease. In both the adult and paediatric Crohn's disease patient populations, the overall goal of treatment is to induce remission in acute, active disease and to maintain disease remission over time. While agents used to treat mild Crohn's disease are well-tolerated and have infrequent severe AEs, as the disease severity of Crohn's disease increases, medications required to manage moderate and/or severe disease are associated with a wider range and higher risk of severe SAEs. In addition, many patients cannot tolerate and/or do not attain, or subsequently lose, clinical benefit even with combinations of these therapies.

### 3.1.3. Main clinical studies

The main study supporting this extension of indication is Study CRD3004. This was a Phase 3, multicentre interventional study consisting of an open-label induction period with a single IV ustekinumab induction dose followed by a maintenance period with a randomised, double blind, parallel-group 2-arm study design, exploring 2 different SC Ustekinumab maintenance dose regimens in paediatric participants ages 2 to <18 years with moderately to severely active Crohn's disease (defined by a PCDAI score >30).

## *3.2. Favourable effects*

In the pivotal phase 3 trial CRD3004, 46.5% and 54% of patients were in clinical remission at week 8 and week 52. The numbers of patients who maintained clinical remission throughout the study remained steady over time and was roughly consistent across both dosing frequencies. 84% and 60% of patients experienced a clinical response at week 8 and week 52. 53% of patients were in corticosteroid free remission at week 8 and week 52. 28% of patients had endoscopic responses at the end of the trial (week 52). Similar positive results were also observed with a reduction in CRP, faecal calprotectin and faecal lactoferrin levels, and an increase in QoL scores throughout the trial. There were also small increases in the average BMI z-scores for both sexes by the end of the study. For the Exposure Optimisation Substudy (EOS) analyses where patients were treated every 4 weeks, results demonstrated

that 16 weeks after entering the sub study, 19/20 (95%) and 10/20 (50%) of subjects were in clinical response and clinical remission, broadly in line with results from the main study population treated q8w or q12w.

Comparable results were also observed in the phase 1 trial CRD1001 in clinical, and endoscopic outcomes, and inflammatory biomarkers. In addition, the LTE of the phase 1 study also provided limited efficacy data for up to 224 weeks. When looking at ustekinumab serum concentrations, a positive exposure-response (E-R) relationship was observed for clinical response and improvement of PCDAI scores at week 8.

When comparing the pivotal phase 3 paediatric trial to adult data, at induction week 8, the rate of clinical remission was higher in the paediatric patients (46.5%) when compared with adult patients (30% (the 2 induction studies combined)). For the induction phase at week 8, the rate of clinical response was also higher in the paediatric patients (84%) when compared with adult patients (38% (CRD3001) and 58% (CRD3002). Similar trends were also observed when looking at reductions from baseline in faecal calprotectin levels with a greater reduction in the paediatric study compared to the corresponding adult studies. Clinical remission and response rates in paediatric and adult patients who were non-biologic failures was generally stronger compared with those who were biologic failures. For the maintenance phase, results demonstrated that levels of clinical remission, clinical response and corticosteroid-free clinical remission were higher or comparable across the paediatric and adult studies. For CRP and faecal calprotectin levels, there were greater reductions in paediatric patients compared to adult studies.

In the RWE observational study  a direct, within study, comparison of the targeted paediatric population compared to adults showed that 23% of paediatric patients were in clinical remission (sPCDAI) at week 52 comparable with 22% of young adults. These results compare favourably to 8% of placebo patients in clinical remission in adults (data taken from study CRD3001, biologic-failure population). Other outcomes demonstrated that at week 52, the percentage of patients in clinical response and PGA clinical remission was higher in paediatric patients (2 to <18 years of age) compared to young adults, 51 v 40% (clinical response) and 34.5 v 27.5% (PGA remission). A similar percentage of patients were in corticosteroid-free clinical remission (21 v 20% for paediatrics v young adults).

Overall, data from the phase 3 trial demonstrates positive efficacy to support the use of ustekinumab in paediatric patients (2 to <18 years of age) with moderately to severely active Crohn's disease for up to 1 year of treatment, results across the phase 1 and 3 trials are broadly comparable particularly in the maintenance phase. Results are also broadly comparable to ustekinumab in the adult pivotal trials, again particularly in the maintenance phase, and these results are also supported by RWE demonstrating similar head to head results in paediatric patients (2 to <18 years of age) and young adults after one year of treatment.

## *3.3. Uncertainties and limitations about favourable effects*

The main limitations of both the paediatric clinical trials include the small sample size, especially in the infants with weight <30kg. For the pivotal phase 3 study there were only 2 (2%) patients recruited who were 2-5 years old and 18 (17.8%) patients 6-11 years old. The study recruited 29 (28.7%) patients who weighed less than 40kg, including 11 (10.9%) subjects who weighed less than 30kg, this is reflected in the SmPC, section 5.1. CD in the youngest paediatric patient group is a rare condition and the feasibility of including this patient group is limited. It is also described that disease burden and effect of treatment is less favourable in the youngest patients. However, it is expected that the pathophysiology of the disease and the mechanism of action for monoclonal antibodies in different age subsets is sufficiently similar to derive data by extrapolation. The lack of a placebo or comparator group also prohibited formal statistical analyses and as such results are mainly presented by descriptive statistics.

Within the pivotal trial, when using different scoring systems (PCDAI <10, CDAI and sPCDAI), induction clinical response rates were not comparable and varied from 42% to 89% warranting cautious interpretation of comparisons between the paediatric and adult studies which used different scoring systems for many of the endpoints.

The updates to the product information section 4.2 recommending dosing every 4 weeks for patients who lose clinical response and have low ustekinumab exposure have been implemented. This dosing frequency is not approved in adult patients, it is however based on data from 26 paediatric CD patients, data from the RWE study and PK modelling.

For the phase 1 PK LTE study CRD1001, the induction dosing was weight based and not BSA based as proposed in the SmPC or used in the phase 3 trial; also, the numbers of patients that completed the LTE was very low with 76.5% of patients having discontinued treatment. When looking at ustekinumab serum concentrations, no positive exposure-response (E-R) relationship was observed for clinical remission at week 8.

Across the two paediatric clinical trials, and when comparing the pivotal phase 3 paediatric trial to adult data there are a number of methodological differences limiting interpretation of comparisons between the trials. Similarly, results from the RWE need to be interpreted with caution due to, e.g. limited data capture (outpatient appointments only and not hospitalisations), wide timeframe in which time-specific outcomes were measured or enrollemnt of young adults aged 18 to 26 rather than a wider range of adult ages.

Notwithstanding the methodological aspects mentioned above the extrapolation of the ustekinumab efficacy to paediatric patients with moderately to severely active Crohn's disease from the age of 2 years and older has been confirmed by the pivotal trial and supportive data.

## *3.4. Unfavourable effects*

Overall, there were high rate of AEs in both CRD1001 and CRD3004 for the induction period (approx. 63% in both each study's induction) and higher again for maintenance periods (79.1% for CRD1001 and 86.6% for CRD3004).

SAEs rates are also relatively high, for example, 13.4 % of patients during the maintenance phase of CRD3004 had at least one SAE in CRD3004, and 23% in CRD1001.

There were no deaths across any of the paediatric Crohn's studies.

No AESIs of malignancy, active TB or opportunistic infection in any of the studies.

In both studies, and both phases, the AEs are driven by gastrointestinal AEs and Infections/Infestations AEs. Gastrointestinal AEs appear to be driven by Crohn's Disease, abdominal pain, diarrhoea, nausea and vomiting, nausea and vomiting- and Infections/infestations are largely driven by URTI, gastroenteritis, nasopharyngitis, rhinitis. Anaemia, headache and arthralgia also have occurred commonly.

Comparing the q8w arm and q12w of CRD3004's maintenance phase there is no signal of increased toxicity at the more frequent q8w frequency.

The overall breakdown of the AEs in terms of SOC/PT mirrors the trends seen in the main part of CRD3004, most AEs coming from Gastrointestinal and Infections/infestations, with most of the AEs appearing to be associated with CD.

Generally, both the overview of AEs and breakdown of AEs is in line with the adult CD data for ustekinumab. There are no apparent new safety signals not already identified in the SmPC, hence no new additions were proposed to Section 4.8.

## 3.5. Uncertainties and limitations about unfavourable effects

The main limitations of both the paediatric clinical trials include the small sample size, and the fact that neither study included a placebo or comparator group preventing direct within study comparisons.

Safety data from the phase 1 PK LTE study CRD1001 can be considered as supportive in this assessment, given that the weight based, not BSA based dosing regime was used in the study, and some subjects in CRD1001 had only a low induction dose (3 mg/kg for subjects <40 kg or 130 mg for subjects ≥40 kg - about half of the proposed induction dose).

Safety data in the youngest patients is limited. In total, 145 paediatric participants were recruited to CRD3004 and CRD1001. Of these, only 30 were aged >2 to 12 years, and only 2 were aged >2 to 6 years; about 80% of the subjects were adolescents.

Results from the registry studies have limitations including limited data capture with potential information missing on AEs and AESI as well as missing information on severity and relationship of (S)AEs to ustekinumab.

Comparison to paediatric use of ustekinumab for paediatric plaque psoriasis is limited as study designs, dosing regimens, study population, and disease indications are different.

Overall, due to the limited number of children recruited, there is a need for long-term safety data to be collected post-approval; this is being addressed in the RMP. Longterm safety in children from age 2 years is a Missing Information in the Summary of Safety Concerns.

Safety data in relation to the proposed q4w interval is limited and is derived from open label data. However, comparing the overall AE profile in the 16-week EOS versus the maintenance phase of CRD3004, no significant differences are evident.

## 3.6. Effects Table

**Table 101: Effects Table for ustekinumab, paediatric (2 to <18 years of age) Crohn's disease**

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Clinical remission Week 8<br><br>Week 52 - q12w and q8w combined | ≤10 points PCDAI (Max 100 points) | n/N (%) | 47/101 (46.5%)<br><br>46/85 (54.1%) | - | No active control | Phase 3 trial CRD3004 |
| Clinical response Week 8<br><br>Week 52 - q12w and q8w combined | ≥12.5 points PCDAI (and total score not more than 30) (Max 100 points) | n/N (%) | 85/101 (84.2%)<br><br>51/85 (60.0%) | - | No active control | Phase 3 trial CRD3004 |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| Endoscopic response<br>Week 16<br><br>Week 52 - q12w and q8w combined | A reduction in the SES-CD score of ⩾50% OR<br><br>SES-CD score ⩽2, in participants with a baseline SES-CD score of ⩾3. | n/N (%) | 34/94 (36.2%)<br><br>23/83 (27.7%) | - | No active control | Phase 3 trial CRD3004 |
| CRP<br>Week 8<br><br>Week 52 - q12w and q8w combined | Inflammatory marker, mean change from baseline | mg/L (SD) | -8.71 (20.626)<br><br>-6.65 (18.609) | - | No active control | Phase 3 trial CRD3004 |
| Faecal calprotectin<br>Week 8<br><br>Week 52 - q12w and q8w combined | Inflammatory marker, mean change from baseline | mg/kg (SD) | -1143.1 (4711.04)<br><br>-716.9 (2597.66) | - | No active control | Phase 3 trial CRD3004 |
| Clinical remission<br>16 weeks after entering sub study | ≤10 points PCDAI (Max 100 points) | n/N (%) | 10/20 (50%) | - | No active control | EOS Phase 3 CRD3004 |
| Clinical response<br>16 weeks after entering sub study | ≥12.5 points PCDAI (and total score not more than 30) (Max 100 points) | n/N (%) | 19/20 (95%) | - | No active control | EOS Phase 3 CRD3004 |
| **Unfavourable Effects** | | | | | | |
| AE | Induction phase | n(%) | 63/101 (62.4%) | | No active control | CRD3004 |
| AE | Maintenance phase- q12w and q8w combined | n(%) | 84/101 (86.6%) | | No active control | CRD3004 |
| SAE | Induction phase | n(%) | 3/101 (3%) | | No active control | CRD3004 |
| SAE | Maintenance phase- q12w and q8w combined | n(%) | 13/101 (13.4%) | | No active control | CRD3004 |
| Infections | Induction phase | n(%) | 30/101 (29.7%) | | No active control | CRD3004 |
| Infections | Maintenance phase- q12w | n(%) | 61/101 (62.9%) | | No active control | CRD3004 |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| | and q8w combined | | | | | |
| Serious Infections | Induction phase | n(%) | 1/101 (1%) | | No active control | CRD3004 |
| Serious Infections | Maintenance phase- q12w and q8w combined | n(%) | 4/101 (4.1%) | | No active control | CRD3004 |
| Active TB infection | all phases | n(%) | 0 | | No active control | CRD3004 |
| Opportunistic infections | all phases | n(%) | 0 | | No active control | CRD3004 |
| Death | all phases | n(%) | 0 | | No active control | CRD3004 |
| Malignancy | all phases | n(%) | 0 | | No active control | CRD3004 |
| AE | EOS substudy- of CRD3004- q4w dose interval | n(%) | 19/26 (73.1%) | | Open label, no control | EOS CRD3004 |
| SAE | EOS substudy- of CRD3004- q4w dose interval | n(%) | 3/26 (11.5%) | | Open label, no control | EOS CRD3004 |
| AE considered reasonably related | EOS substudy- of CRD3004- q4w dose interval | n(%) | 2/26 (7.7%) | | Open label, no control | EOS CRD3004 |
| Serious Infections | EOS substudy- of CRD3004- q4w dose interval | n(%) | 3/26 (11.5%) | | Open label, no control | EOS CRD3004 |
| Opportunistic infections | EOS substudy- of CRD3004- q4w dose interval | n(%) | 1/26 (3.8%) | | Open label, no control | EOS CRD3004 |
| Death | EOS substudy- of CRD3004- q4w dose interval | n(%) | 0 | | Open label, no control | EOS CRD3004 |

Abbreviations: EOS- Exposure Optimisation Substudy of CRD3004

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

This extension of indication application to paediatric patients with Crohn's disease age 2 years and older is based on extrapolation of efficacy and safety based on similar exposure as in adults where efficacy and safety have been established. The efficacy is in line with the proven efficacy in adults. There is an unmet need for treatments for this cohort of patients. The main limitations of both the paediatric clinical trials include the small sample size, neither study included a placebo or comparator group preventing direct within study comparisons, but extensive data is available from the adult population and the use of uncontrolled studies are considered acceptable. The lack of a placebo or comparator group also prohibited formal statistical analyses and as such results are mainly presented by descriptive statistics. The similar pathophysiology of the disease and mechanism of action for monoclonal antibodies in different age subsets justify this approach.

Sufficient PK data were submitted to establish an overall similarity of exposure between children below and above 40 kg and adult patients. However, as very few children below the age of 9 were included in the clinical trials, additional model-based simulations, across the expected body weight range, in paediatric patients weighing <40 kg were presented. These provided further support for the view that the proposed posology for paediatric CD patients (≥2 years), across the expected body weight range, will likely result in ustekinumab exposures that are comparable to those established to be safe and effective in the adult CD population. See Clinical Pharmacology for further details.

There were no new safety signals observed during the study period. The most commonly reported adverse events were infections and gastrointestinal disorders, the latter likely representing a disease manifestation. The observed safety profile is consistent with the known safety profile of ustekinumab. Although the exposure of paediatric CD patients is limited, the use of ustekinumab in adult CD and other paediatric indications is large and knowledge on the safety profile from these indications is considered supportive for this new indication. Due to the limited number of children recruited, there is a need for long-term safety data to be collected post-approval; this is being addressed in the RMP. Longterm safety in children from age 2 years is included as Missing Information in the Summary of Safety Concerns.

As described above, LOR to ustekinumab 12-weekly dosing is managed by empirical dose escalation to 8 weekly dosing. Loss of response on 8-weekly dosing, with exposure-based assessment confirming low drug levels (<1.4 µg/mL), can be managed by shortening the dosing interval to every 4 weeks.

### 3.7.2. Balance of benefits and risks

Overall, data from the phase 3 trial demonstrates positive efficacy to support the use of ustekinumab in paediatric patients (2 to <18 years of age) with moderately to severely active Crohn's disease for up to 1 year of treatment, results across the phase 1 and 3 trials are broadly comparable particularly in the maintenance phase. Results are also broadly comparable to ustekinumab in the adult pivotal trials, again particularly in the maintenance phase, and these results are also supported by RWE demonstrating similar head-to-head results in paediatric patients (2 to <18 years of age) and young adults after one year of treatment.

The efficacy of ustekinumab in the claimed indication is in line with the proven efficacy in adults which is based on substantial data as well as long-term use outside of clinical trials in a large CD patient population.

The safety profile in children from age 2 years observed in the paediatric studies is consistent with the known safety profile of ustekinumab and no new safety signals were observed. Given the low number of paediatric patients recruited, the long-term safety in children from age 2 years will require further characterisation and be followed up post-authorisation as described in the RMP.

### *3.8. Conclusions*

The overall B/R of ustekinumab is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

| Variation accepted | | Type |
|---|---|---|
| C.I.6.a | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II |

Extension of indication to include treatment of moderately to severely active Crohn's disease in paediatric patients from the age of 2 years and older, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy, based on final results from the Phase 3 open-label CNTO1275CRD3004 study and the supportive results from the Phase 1 PK CNTO1275CRD1001 study. Study CNTO1275CRD3004 is a Phase 3 study of the efficacy, safety, and pharmacokinetics of ustekinumab as open-label intravenous induction treatment followed by randomised double-blind subcutaneous ustekinumab maintenance in paediatric participants 2 to <18 years of age with moderately to severely active Crohn's disease. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are being updated. The Package Leaflet is updated accordingly. The RMP version 32.1 has also been approved. In addition, the MAH took the opportunity to introduce editorial, formatting and administrative changes to the PI, bringing it in line with the latest QRD template. In addition, the MAH updated the list of local representatives in the Package Leaflet.

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

NA