27 February 2025
EMA/121491/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stelara

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/000958/II/0108

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
DBL	database lock
EMA	European Medicines Agency
ERAS EMA	Randomized Analysis Set
EOS	Exposure Optimisation Substudy
EU	European Union
GCP	Good Clinical Practices
GHAS	Global Histology Activity Score
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
ICE	Intercurrent Current Event
ICF	Informed Consent Form
IgG1k	immunoglobulin G1 kappa
IL	interleukin
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)
PKERAS EMA	PK Analysis Set
q4w	every 4 weeks
q8w	every 8 weeks
q12w	every 12 weeks
QoL	quality of life
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

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 2 July 2024 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderately to severely active Crohn's disease in paediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy or have medical contraindications to such therapies for STELARA, based on final results from study CNTO1275CRD3004. This 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 with Moderately to Severely Active Crohn’s Disease. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 29.1 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics 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.

Scientific advice

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).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jayne Crowe Co-Rapporteur: N/A

PRAC Rapporteur: Rhea Fitzgerald

Timetable	Actual dates
Submission date	2 July 2024
Start of procedure:	20 July 2024
CHMP Rapporteur Assessment Report	13 September 2024
PRAC Rapporteur Assessment Report	13 September 2024
PRAC Outcome	3 October 2024
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2024
Request for supplementary information (RSI)	17 October 2024
CHMP Rapporteur Assessment Report	23 December 2024
PRAC Rapporteur Assessment Report	23 December 2024
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur Assessment Report	23 January 2025
Request for supplementary information (RSI)	30 January 2025
CHMP Rapporteur Assessment Report	12 February 2025
PRAC Rapporteur Assessment Report	12 February 2025
CHMP members comments	n/a
PRAC members comments	n/a
Updated CHMP Rapporteur Assessment Report	19 February 2025
Updated PRAC Rapporteur Assessment Report	19 February 2025
Opinion	28 February 2025

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 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
- 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 claimed therapeutic indication is:

Paediatric Crohn's disease

STELARA is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy, or have medical contraindications to such therapies.

The MAH had originally claimed the above-mentioned indication, however as requested by the CHMP, has agreed to remove the text, "or have medical contraindications to such therapies" to align with indication wordings as agreed by CHMP in recent Crohn's Disease approvals:

STELARA is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.

2.1.2. The development programme

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 an 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 Crohn's disease, ages 18 years of age or older. The target population is paediatric participants (2 to <18 years of age) with moderately to severely active Crohn's disease, weighing ≥40 kg.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

With this variation, the MAH seeks to add a new indication for the treatment of paediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease.

The clinical development program for ustekinumab in 'Paediatric Crohn's disease' consists of;

- Paediatric Crohn's disease clinical studies
    - Phase 3 open label Study CRD3004 (UNITI Jr.)
    - Phase 1 PK Study CRD1001 (UNISTAR)

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 randomized withdrawal maintenance Study CRD3003 (IM-IMUNITI).
- 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).
- Post- authorisation safety study 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 (Remicade) and collects data on other medical therapies for IBD as part of routine clinical care (C0168Z02 (DEVELOP)).
- Real-world observational, noninterventional paediatric RWE Study CRD3010 (REALITI).

<u>Paediatric Crohn's disease clinical studies</u>

The phase 3 study CRD3004 (UNITI Jr.), is an ongoing study which evaluates efficacy, safety, and pharmacokinetics of ustekinumab dosing in paediatric participants between 2 to <18 years of age. Enrolment has completed and the main study is anticipated to be completed in November 2024. The submitted CSR provides the results of an EMA submission interim analysis of data from 48 randomised participants with body weight ≥40 kg who completed the Induction Week I-8 and Maintenance Week M-44

visit (or terminated the study participation prior to Week M-44). This submission aims to fulfil the agreed European Union (EU) Paediatric Investigation Plan (PIP) (P/0341/2023).

The study consists of an 8-week open-label IV induction treatment period followed by randomised double-blind 44-week SC ustekinumab maintenance period. Induction was weight tiered which is the similar to the adult dosing regimen (≥40 kg to ≤55kg: 260mg, >55kg to ≤85kg: 390mg, >85kg: 520mg). For randomised participants with body weight ≥40 kg, in the maintenance period, participants either received 90 mg ustekinumab SC q8w or 90 mg ustekinumab SC q12w.

Study CRD3004 also includes an Exposure Optimisation Sub study (EOS), which was an optional open-label exposure optimisation sub study of minimum 16 weeks duration, with dose interval adjustment to q4w. Participants who had a confirmed LOR and had low steady-state trough ustekinumab concentrations (low exposure) were eligible to participate in the optional EOS and received a modified dosing regimen of 90 mg SC q4w.

The randomised double-blind Phase 1 PK Study CRD1001 (UNISTAR) aimed to demonstrate PK, efficacy, and safety in paediatric patients ages 2 to <18 years. Patients were randomised in a 1:1 ratio into 1 of 2 treatment groups stratified by weight (<40 kg, ≥40 kg) and by previous tumour necrosis factor (TNF) antagonist exposure status. Subjects in each treatment group received a single IV induction dose of ustekinumab at Week 0:

- Treatment Group 1: 3 mg/kg for subjects <40 kg or 130 mg for subjects ≥40 kg.
- Treatment Group 2: 9 mg/kg for subjects <40 kg or 390 mg for subjects ≥40 kg.

Following their single IV induction dose at Week 0, all subjects received a SC maintenance dose of ustekinumab at Week 8:

- 2 mg/kg for subjects <40 kg
- 90 mg for subjects ≥40 kg

The final safety assessment was at week 28. At Week 16, all participants were eligible to enter the long-term extension (LTE, phase 1) to continue receiving maintenance doses of SC q8w provided that the participant was receiving benefit from ustekinumab maintenance therapy as, determined by the investigator.

Table 1: The 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 Maintenance- Week 8 to Week 16 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 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) • Randomized, Double-blind Period Week 0 to Week 16 (n=44) • LTE Period (Week 16 to Week 240) (n=34) • 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 • To evaluate the safety and immunogenicity of ustekinumab in this population • 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 Maintenance- Week 8 to Week 44 LTE- Transitioned to CNTO1275ISD3001 for Week 44 to Week 240	Total population (n=48) • q12w (n=25) • q8w (n=23) • 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 • 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 • To evaluate the safety profile of ustekinumab in pediatric participants with moderately to severely active Crohn's disease • To evaluate ustekinumab exposure (PK)

Efficacy and Safety Non-interventional Clinical Studies: Crohn's Disease					
CNTO1275CRD3010 REALITI Non-interventional real-world study NA Synopsis Start of data collection 21 March 2022 (start of chart reviews). End of data collection 22 May 2023 (Database lock).	USA: 51	Phase 3 Retrospective, single arm, non-interventional, observational, real-world evidence study Pediatric subjects (ages ≥2 to <18) and young adults (ages 18 to <26) with moderately to severely active Crohn's disease. 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 Cohort 2: 31 Cohort 3:145 Cohort 4: 204 Cohort 5:56 Cohort 6: 348 Cohort 7 (Young Adults [Reference]): 51 Cohort 8: 91 Cohort 9: 131

Safety Uncontrolled Clinical Studies: Inflammatory Bowel Disease				
C0168Z02 (North America) DEVELOP™ NA Start of data collection 31 May 2007 (first patient dosed with ustekinumab on 17 December 2010 End of data collection Ongoing. Data cutoff for this report 30 June 2022	BEL, CAN, DEU, DNK, FRA, GBR, ITA, NLD, USA: 82	Registry Multicenter, prospective, observational registry 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. 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 Ustekinumab

GCP

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH GCP guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

2.3.2. Pharmacokinetics

Two paediatric studies (CRD1001 and CRD3004) have been conducted to support an indication of moderately to severely active Crohn's disease (CD) in paediatric patients (≥40 kg body weight). Paediatric and adult patients with CD have similar pathophysiology, clinical manifestations, and response to other treatments. It is thus expected that paediatric patients with CD would have a similar clinical response to ustekinumab treatment as adults. Therefore, a key objective of the development program was to determine a paediatric dose regimen that would provide systemic exposure to ustekinumab similar to that observed in adults receiving the approved dose for CD.

Studies CRD1001 and CRD3004 used the following presentations of ustekinumab:

- Ustekinumab 90 mg/mL liquid in vial (LIV), supplied as a 2mL vial for intravenous (IV) infusion or subcutaneous (SC) administration at a dose strength of 45 mg/0.5 mL
- Ustekinumab 5 mg/mL LIV supplied as a single-use 30 mL vial for IV infusion
- Ustekinumab 90 mg/mL pre-filled syringe (PFS) supplied as 90 mg/mL or 45 mg/0.5 mL.

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.

Phase 1 Crohn's Disease Study in Paediatric Participants (CRD1001)

CRD1001 was a Phase 1, randomised, double-blind PK study of IV ustekinumab induction followed by SC ustekinumab maintenance in paediatric participants with moderately to severely active CD.

The weight-based ustekinumab dosages that were studied in this paediatric population were:

- Treatment Group 1: 3 mg/kg for participants <40 kg or 130 mg for participants ≥40 kg
- Treatment Group 2: 9 mg/kg for participants <40 kg or 390 mg for participants ≥40 kg

Following the IV induction at Week 0, all participants received a SC maintenance dose of ustekinumab at Week 8 (2 mg/kg for participants <40 kg or 90 mg for participants ≥40 kg). All participants who completed the safety and efficacy evaluations at Week 16 and who received benefit from ustekinumab maintenance therapy had the opportunity to participate in the long term extension (LTE) period of the study. In the LTE period, all participants continued receiving maintenance doses of SC ustekinumab q8w at the same dose as they received at Week 8 (i.e., 2 mg/kg for participants <40 kg or 90 mg for participants ≥40 kg).

Serum Ustekinumab Concentrations Through Week 16

A total of 44 participants (59.1% female, 81.8% White) with a median body weight of 42.9 kg (range: 19.5 to 70.1 kg) and a median age of 13.0 years (range: 6.0 to 17.0 years) were enrolled and treated with ustekinumab.

After a single IV administration of the low-induction dose (3 mg/kg or 130 mg) or the high-induction dose (9 mg/kg or 390 mg) of ustekinumab, mean and median serum ustekinumab concentrations were approximately dose proportional at all sampling timepoints through Week 8.

Median (mean) peak serum ustekinumab concentrations 1 hour after the Week 0 infusion were 50.51 µg/mL (51.25 µg/mL) and 150.22 µg/mL (148.71 µg/mL) for the low- and high-induction doses, respectively. At the end of induction at Week 8, median (mean) serum ustekinumab concentrations were 1.18 µg/mL (1.56 µg/mL) and 2.53 µg/mL (4.76 µg/mL) for the low- and high-induction doses, respectively.

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

Serum ustekinumab concentrations were generally comparable between participants in the baseline age subgroups (2 to 11 years versus 12 to 17 years) in the low- and high-induction dose groups from Week 0 through Week 8. Serum ustekinumab concentrations were generally comparable between participants in the baseline body weight subgroups (<40 kg versus ≥40 kg) for the low-induction dose group. 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.

Serum Ustekinumab Concentrations During the LTE

Of the 40 paediatric participants who completed participation through Week 16, 34 entered the LTE period (approximately 4 years): 18 participants from the low-induction dose group and 16 participants from the high-induction dose group. Of these participants, 61.8% were female and 85.3% were White, with a median body weight of 41.05 kg (range: 19.5 to 70.1 kg) and a median age of 13.0 years (range: 6.0 to 17.0 years).

Because both the high and low dose induction treatment groups began receiving the same maintenance dose regimen from Week 8, the impact of the different induction doses on serum ustekinumab concentrations had diminished by Week 16. Therefore, serum ustekinumab concentrations were assessed for the combined treatment group during the LTE period.

Based on the visits with a sample size of ≥ 10 participants in the combined treatment group during the LTE period, median and mean serum trough ustekinumab concentrations ranged from 0.98 µg/mL to 1.86 µg/mL and from 1.58 µg/mL to 2.03 µg/mL, respectively. After maintenance treatment with ustekinumab SC q8w, starting at Week 8 and continuing in the LTE for up to 4 years, mean serum ustekinumab concentrations were generally consistent over time during the LTE period.

Comparison of Observed Serum Ustekinumab Concentrations between Paediatric Study CRD1001 and Adult Studies CRD3001, CRD3002, and CRD3003

Serum ustekinumab concentrations observed in the overall paediatric CD population in CRD1001 were generally comparable to those observed in the reference adult CD population. However, a pattern towards lower median or mean serum ustekinumab concentrations was observed in participants in the <40 kg body weight subgroup compared with participants in the ≥40 kg body weight subgroup and compared with the reference adult Crohn's disease population. Median, or mean serum ustekinumab concentrations in the ≥40 kg body weight subgroup were generally comparable with those in the reference adult population.

Immunogenicity

Of the 42 ustekinumab-treated participants with appropriate samples, none were positive for antibodies to ustekinumab through Week 16. During the LTE period, 1 (2.9%) of the 34 ustekinumab-treated participants with appropriate samples were positive for antibodies to ustekinumab through the final safety visit with a peak titre of 1:100. The 1 participant was positive for NAb.

Phase 3 Crohn's Disease Study in Paediatric Participants (CRD3004)

CRD3004 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. Participants had to have an inadequate response and/or intolerance to biologic therapy and/or to conventional therapies or be dependent upon corticosteroids.

Induction period

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

For participants with body weight <40 kg:

- 250 mg/m2 IV

For participants with body weight ≥40 kg:

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

Maintenance period

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

- **Ustekinumab q8w:** 90 mg SC for ≥40 kg body weight or 60 mg/m2 SC for <40 kg body weight.
- **Ustekinumab q12w:** 90 mg SC for ≥40 kg body weight or 60 mg/m2 SC for <40 kg body weight.

Beginning at Week M-8 for induction responders and beginning at Week M-16 for delayed responders (i.e., induction non-responders who were in clinical response at Week M-8), 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.

A total of 48 participants (56.3% male, 91.7% White) with a median body weight of 53.8 kg (range: 41 to 85 kg) and a median age of 15.0 years (range: 10 to 17 years) were randomised.

Serum Ustekinumab Concentrations through Week I-8

After a single IV administration of the approximately 6 mg/kg weight-tiered fixed dose of ustekinumab, median (mean) peak serum ustekinumab concentration observed 1 hour after the end of the infusion at Week 0 was 91.8 µg/mL (97.9 μg/mL). At Week 8, the time of the main efficacy assessment, median (mean) serum ustekinumab concentration was 3.38 µg/mL (4.40 µg/mL).

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 2.77 (3.35) µg/mL and 3.38 (5.45) µg/mL in the ustekinumab 90 mg q12w, and ustekinumab 90 mg q8w groups, respectively. Participants randomised to ustekinumab 90 mg q8w or 90 mg q12w had sustained serum ustekinumab concentrations through Week M-44.

Steady-state concentrations appeared to have been 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 ustekinumab 90 mg 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 1.38 (2.08) µg/mL to 1.74 (2.32) µg/mL. In the ustekinumab 90 mg 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 0.67 (0.65) µg/mL.

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. For example, at Week M-24, the only concurrent pre-administration timepoint during maintenance for both ustekinumab randomised maintenance treatment groups, the median (mean) trough serum ustekinumab concentration was 1.38 (2.08) µg/mL in the ustekinumab 90 mg q8w group and 0.51 (0.59) µg/mL in the ustekinumab 90 mg q12w group.

At Week M-44 (i.e., 4 weeks and 8 weeks from the previous dose for the ustekinumab 90 mg q8w group and the ustekinumab 90 mg q12w group, respectively), where key maintenance efficacy endpoints (e.g., clinical remission) were assessed in this study, median (mean) serum ustekinumab concentrations were 6.11 (5.92) µg/mL in the ustekinumab 90 mg q8w group and 1.76 (1.75) µg/mL in the ustekinumab 90 mg q12w group.

The sample size of participants who had a dose adjustment was too small, hence no conclusion could be reached on the impact of dose adjustment on ustekinumab concentrations. Only 2 participants dose

adjusted from the ustekinumab q12w dose regimen: (1) one participant at Week M-32 to q8w (by Week M-36, serum ustekinumab concentration was below the limit of quantification) and (2) one participant at Week M-36 to the exposure optimisation sub study.

Five participants on the q12w dose regimen and 7 participants on the q8w dose regimen entered the exposure optimising sub study. Dose adjustment to the q4w regimen in paediatric participants who lost response and had low ustekinumab levels (i.e., 8 weeks post-dose steady-state concentration <1.4 µg/mL) led to increased ustekinumab concentrations. Nevertheless, the resulting ustekinumab exposure following this dose adjustment to q4w still fell within the range of exposures observed in adult participants with CD.

Comparison of Observed Serum Ustekinumab Concentrations between Paediatric Study CRD3004 and Adult Studies CRD3001, CRD3002, and CRD3003

Overall, serum ustekinumab concentrations in paediatric participants in CRD3004 fell within the range of the concentrations observed in adult participants with CD who received the same ustekinumab induction or maintenance doses.

Through Week I-8, median or mean serum ustekinumab concentrations were generally comparable between the paediatric CD population ≥40 kg and adult participants with CD who received the same induction dose:

- Among those who received the 260 mg IV induction dose, median (mean) serum ustekinumab concentration at post-infusion Week I-0 was 89.6 (88.1) µg/mL among paediatric participants compared with 101.3 (100.7) µg/mL among adult participants. Likewise, at Week I-8, median (mean) serum ustekinumab concentration was 3.49 (4.00) µg/mL among paediatric participants compared with 4.08 (4.39) µg/mL among adult participants.
- Among those who received the 390 mg induction dose, median (mean) serum ustekinumab concentration at post-infusion Week I-0 was 109.9 (109.6) µg/mL among paediatric participants compared with 129.4 (127.4) µg/mL among adult participants. Likewise, at Week I-8, median (mean) serum ustekinumab concentration was 3.14 (4.85) µg/mL among paediatric participants compared with 6.82 (7.49) µg/mL among adult participants.

During maintenance, median (mean) steady-state concentrations were generally comparable between paediatric participants in CRD3004 and adult participants with CD.

- Following the 90 mg SC q8w regimen in CRD3004, median steady-state serum ustekinumab concentrations ranged between 1.38 to 1.74 µg/mL (mean: 2.08 to 2.57 µg/mL) among paediatric participants with body weight ≥40 kg. In comparison, median steady-state serum ustekinumab concentrations ranged between 1.97 to 2.24 µg/mL (mean: 2.39 to 2.83 µg/mL) among adult participants.
- Following the 90 mg SC q12w regimen in CRD3004, median steady-state serum ustekinumab concentrations ranged between 0.41 to 0.67 µg/mL (mean: 0.58 to 0.65 µg/mL) among paediatric participants with body weight ≥40 kg. In comparison, median steady-state serum ustekinumab concentrations ranged between 0.61 to 0.76 µg/mL (mean: 0.86 to 1.13 µg/mL) among adult participants.

Immunogenicity

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 (2.1%) of 48 participants was positive for antibodies to ustekinumab through Week I-8 with a peak titer of 1:200. The 1 participant was positive for NAb.

From Week M-0 through Week M-44

Among participants in CRD3004 who received ustekinumab during both induction and maintenance, 1 (2.2%) of 46 participants was positive for antibodies to ustekinumab through Week M-44. This participant was also positive for antibodies to ustekinumab through Week M-44. The 1 participant was positive for NAb.

The incidence of antibodies to ustekinumab in paediatric participants ≥40 kg (2.4%) was 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.

Population PK analysis in participants with Crohn's Disease

A popPK model was established to characterise the PK of ustekinumab in paediatric participants with moderately to severely active CD, using nonlinear mixed effects modelling methods as implemented in NONMEM (Version 7.3 or later). The developed model was used to simulate and compare the systemic exposure to ustekinumab across different ranges of body weight between the paediatric patients (≥40 kg) and adult CD populations.

A previously developed adult popPK model was updated by re-estimating parameter estimates with adult data from Phase 3 studies CRD3001, CRD3002, and CRD3003 only and with standard allometric scaling exponents fixed to the values of 0.75 for CL and Q and 1 for V2 and V3. This updated adult PopPK model was based on 11,196 ustekinumab concentrations from 1,196 adult participants with CD. The parameters of the updated adult PopPK model were adequately estimated with RSE <30% for most of the structural model parameters (Table 2). Visual predictive checks (VPCs) indicated adequate performance of the final updated adult model (Figure 1). The typical value for CL in participants with a standardised body weight of approximately 70 kg was 0.18 L/day while V2 was estimated to be 2.86 L. The typical value of ka was approximately 0.15 day-1 and the typical value of F1 was 75%.

Table 2: Parameter Estimates of Ustekinumab for the Updated Adult PopPK Model in Adults With Moderately to Severely Active Crohn's Disease

Parameter, unit	Estimate[a]	RSE (%)	Shrinkage (%)
CL (L/day)[b]	0.18	1%	
CL-BWT	0.75 Fixed		
CL-BALB	-1.18	5.50%	
CL-SEX=M	0.132	14.10%	
CL-RACE=A	0.142	21.20%	
CL-FTNF	0.0557	29.30%	
CL-BCRP	0.0572	11%	
CL-IRPT	0.195	62.10%	
V2 (L)[c]	2.86	1.10%	
V2-BWT	1 Fixed		
V2-BALB	-0.416	12%	
V2-SEX	0.0705	23.10%	
Q (L/day)[d]	0.18	4.80%	
Q-BWT	0.75 Fixed		
V3 (L)[e]	1.64	6.50%	
V3-BWT	1 Fixed		
ka (day^{-1})	0.15	2.30%	
F1	0.75	6.40%	
IIV of CL (%CV)	31.20%	2.30%	5%
Correlation between IIV of CL and V2 (%CV)	55.30%	14.60%	
IIV of V2 (%CV)	19.70%	4.50%	26%
Correlation between IIV of CL and V3 (%CV)	-44.70%	11.30%	
IIV of V3 (%CV)	42.90%	6.20%	21%
IIV of Q (%CV)	55.60%	11.10%	58%
IIV of ka (%CV)	62.1%	5.20%	44%
IIV of F1 (%CV)	120.2%	5.60%	34%
ADD ERR	0.00835	10%	15%
PROP ERR	0.0292	2%	15%

Abbreviations: A=Asian; ADD ERR=additive error term; BALB=baseline albumin (g/dL); BCRP=baseline C-reactive protein (mg/dL); BWT=baseline body weight (kg); CL=clearance; CV=coefficient of variation ($\sqrt{\exp(variance^2) - 1} \times 100\%$); exp=exponential; F1=subcutaneous bioavailability; FTNF=tumor necrosis factor failure (0=non-failure, 1=failure); IIV=inter-individual variability; IRPT=immune response status over time; ka=first-order absorption rate constant; M=male; PK=pharmacokinetic; PopPK=population pharmacokinetic; PROP ERR=proportional error term; Q=inter-compartmental flow; RSE=relative standard error; TNF=tumor necrosis factor; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

[a] The transformed estimate to the standard PK scale

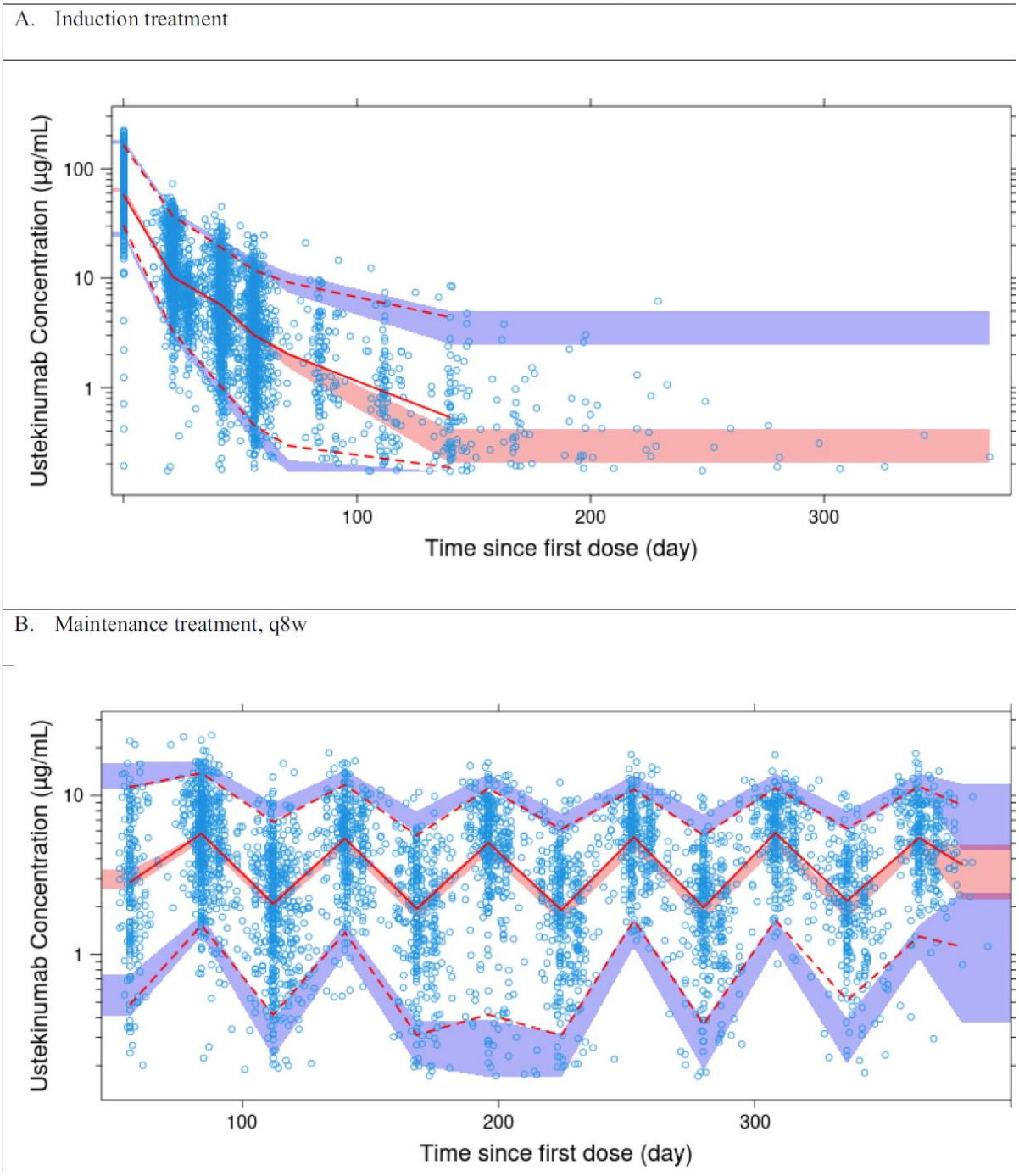
[b] $CL(L/day) = 0.18 \times \left(\frac{BWT}{68.7}\right)^{0.75} \times \left(\frac{BALB}{3.7}\right)^{-1.18} \times \left(\frac{BCRP}{0.93}\right)^{0.0572} \times \exp(0.132 \times SEX = M) \times \exp(0.142 \times RACE = A) \times \exp(0.0557 \times TNF) \times \exp(0.195 \times IRPT)$

[c] $V2\ (L) = 2.86 \times \left(\frac{BWT}{68.7}\right)^{1} \times \left(\frac{BALB}{3.7}\right)^{-0.416} \times \exp(0.0705 \times SEX = M)$

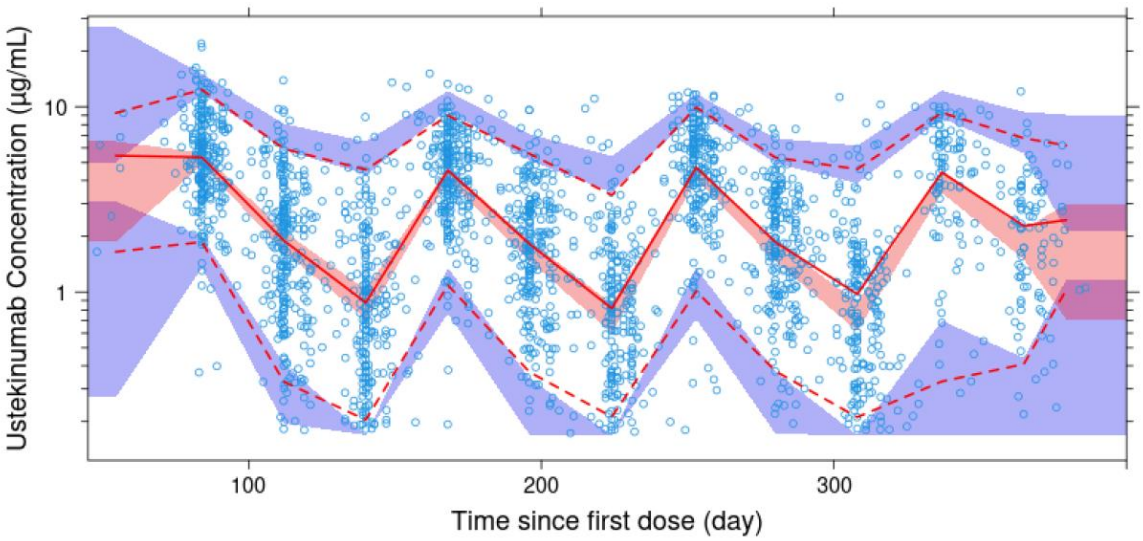
[d] $Q(L/day) = 0.18 \times \left(\frac{BWT}{68.7}\right)^{0.75}$

[e] $V3\ (L/day) = 1.64 \times \left(\frac{BWT}{68.7}\right)^{1}$

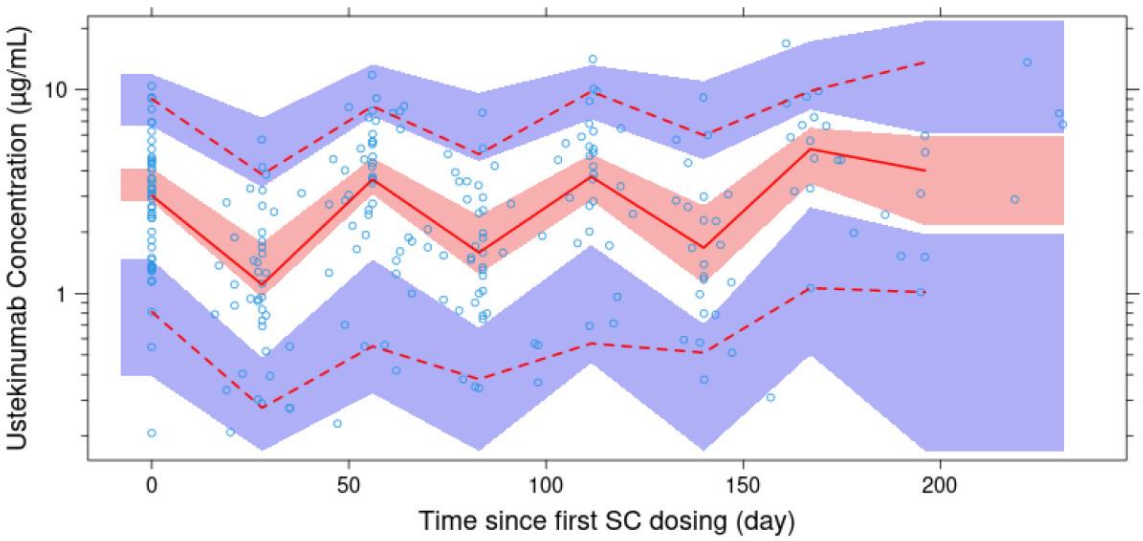
Figure 1: VPC for Updated Adult PopPK Model, Stratified by Treatment Phase and Regimen



C. Maintenance treatment, q12w



D. Maintenance treatment, other treated participants



Abbreviations: CI=confidence interval; LOR=loss of response; PopPK=population pharmacokinetic; qXw=every X weeks; SC=subcutaneous; VPC=visual predictive check.

Results of an external model evaluation indicated that the updated adult model overpredicted the ustekinumab concentrations over time in paediatric participants from Studies CRD1001 and CRD3004 following both induction and maintenance treatment. Therefore, parameters from the updated adult model were re-estimated using paediatric PK data from Studies CRD1001 and CRD3004. 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 (tumour necrosis factor [TNF] antagonist failure status, anti-ustekinumab antibodies, baseline albumin, baseline CRP levels, sex, and race [Asians versus non-Asians]). The allometric scaling exponents on CL, Q, V2 and V3 were fixed to standard values, as in the updated adult popPK model.

The final paediatric model was based on 995 ustekinumab concentrations from 92 paediatric participants with CD (73 post-dose concentrations [6.8%, 73/1,068] were BQL and excluded, and no concentrations were identified as outliers).

Descriptive statistics of baseline continuous and categorical covariates are presented in Table 3 and Table 4, respectively.

Table 3: Demographic and Baseline Characteristics of Pooled Study Data (Continuous Covariates)

Study No	CRD3004	CRD1001	CRD3001	CRD3002	Pediatric Studies (CRD1001 and CRD3004)	Adult Studies (CRD3001 and CRD3002)
N	48	44	681	536	92	1217
Weight (kg)						
Mean (SD)	56.4 (12.8)	43.1 (12.1)	69.5 (18.3)	73.2 (20.5)	50.1 (14.1)	71.1 (19.4)
Median	53.8	42.9	66.8	70.5	47.8	68.4
Range	(41.0-84.7)	(19.5-70.1)	(35.0-173)	(35.0-184)	(19.5-84.7)	(35.0-184)
Age (Years)						
Mean (SD)	14.7 (1.62)	13.4 (2.74)	37.4 (12.0)	39.5 (13.5)	14.1 (2.31)	38.3 (12.7)
Median	15	13	36	37	14	37
Range	(10.0-17.0)	(6.00-17.0)	(18.0-71.0)	(18.0-75.0)	(6.00-17.0)	(18.0-75.0)
Baseline Albumin (g/dL)						
Mean (SD)	4.16 (0.349)	3.95 (0.479)	3.43 (0.525)	3.63 (0.512)	4.06 (0.427)	3.52 (0.529)
Median	4.05	4	3.5	3.7	4	3.6
Range	(3.50-4.80)	(3.00-4.90)	(1.50-4.60)	(1.20-5.10)	(3.00-4.90)	(1.20-5.10)
Baseline CRP (mg/L)						
Mean (SD)	25.7 (30.7)	23.1 (28.8)	18.6 (23.6)	16.2 (21.4)	24.5 (29.7)	17.6 (22.7)
Median	11.4	12.9	9.93	8.13	11.9	9.15
Range	(0.100-122)	(0.100-112)	(0.100-157)	(0.100-137)	(0.100-122)	(0.100-157)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations: CRP=C-reactive protein; SD=standard deviation; N=number of participants.

Table 4: Demographic and Baseline Characteristics of Pooled Study Data (Categorical Covariates)

Study No	CRD3004	CRD1001	CRD3001	CRD3002	Pediatric Studies (CRD1001 and CRD3004)	Adult Studies (CRD3001 and CRD3002)
N	48	44	681	536	92	1217
Sex						
Male	27 (56.2%)	18 (40.9%)	288 (42.3%)	249 (46.5%)	45 (48.9%)	537 (44.1%)
Female	21 (43.8%)	26 (59.1%)	393 (57.7%)	287 (53.5%)	47 (51.1%)	680 (55.9%)
Race						
Caucasian	44 (91.7%)	36 (81.8%)	580 (85.2%)	452 (84.3%)	80 (87.0%)	1032 (84.8%)
Black	1 (2.1%)	0 (0.0%)	21 (3.1%)	17 (3.2%)	1 (1.1%)	38 (3.1%)
Asian	3 (6.2%)	0 (0.0%)	55 (8.1%)	44 (8.2%)	3 (3.3%)	99 (8.1%)
Other	0 (0.0%)	2 (4.5%)	10 (1.5%)	17 (3.2%)	2 (2.2%)	27 (2.2%)
Missing	0 (0.0%)	6 (13.6%)	15 (2.2%)	6 (1.1%)	6 (6.5%)	21 (1.7%)
TNF Failure Status						
Otherwise	27 (56.2%)	5 (11.4%)	96 (14.1%)	536 (100.0%)	32 (34.8%)	632 (51.9%)
Failed TNF	21 (43.8%)	39 (88.6%)	585 (85.9%)	0 (0.0%)	60 (65.2%)	585 (48.1%)
Immunogenicity						
Otherwise	47 (97.9%)	43 (97.7%)	665 (97.7%)	525 (97.9%)	90 (97.8%)	1190 (97.8%)
Positive	1 (2.1%)	1 (2.3%)	16 (2.3%)	11 (2.1%)	2 (2.2%)	27 (2.2%)

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

The observed PK profiles of ustekinumab following IV and SC administration to paediatric participants with moderately to severely active CD were adequately described by a 2-compartment model with first-order absorption. The parameters of the final model for paediatric participants are summarised in

Table 5. Model parameters were adequately estimated with RSE <30% for the structural model parameters. The typical value for CL in participants with a standardised body weight of approximately 70 kg was 0.29 L/day while V2 was estimated to be 4.06 L. The typical value of ka was approximately 0.18 day-1 and the typical value of F1 was 81%.

Table 5 Parameter Estimates of Ustekinumab for the Final PopPK Model in Paediatric Participants with Moderately to Severely Active Crohn's Disease

Parameter, unit	Estimate[a]	RSE (%)	Shrinkage (%)
CL (L/day)[b]	0.29	3.70%	
CL-BWT	0.75 Fixed		
CL-BALB	-1.18 Fixed		
CL-SEX=M	0.132 Fixed		
CL-RACE=A	0.142 Fixed		
CL-FTNF	0.0557 Fixed		
CL-BCRP	0.0572 Fixed		
CL-IRPT	0.195 Fixed		
V2 (L)[c]	4.06	1.70%	
V2-BWT	1 Fixed		
V2-BALB	-0.416 Fixed		
V2-SEX	0.0705 Fixed		
Q (L/day)[d]	0.17	9.20%	
Q-BWT	0.75 Fixed		
V3 (L)[e]	2.29	14.10%	
V3-BWT	1 Fixed		
ka (day^{-1})	0.18	11.60%	
F1	0.81	21.80%	
IIV of CL (%CV)	39.90%	8.70%	4%
Correlation between IIV of CL and V2 (%CV)	55.50%	14.60%	
IIV of V2 (%CV)	10.70%	15.80%	30%
Correlation between IIV of CL and V3 (%CV)	-82.70%	11.30%	
IIV of V3 (%CV)	116.80%	11%	7%
IIV of Q (%CV)	55.60% Fixed		
IIV of ka (%CV)	62.1% Fixed		
IIV of F1 (%CV)	120.2% Fixed		
ADD ERR	0.001 Fixed		
PROP ERR	0.0672	6%	

Abbreviations: A=Asian; ADD ERR=additive error term; BALB=baseline albumin (g/dL); BCRP=baseline C-reactive protein (mg/dL); BWT=baseline body weight (kg); CL=clearance; CV=coefficient of variation ($\sqrt{\exp(variance^2) - 1} \times 100\%$); exp=exponential; F1=subcutaneous bioavailability; FTNF=tumor necrosis factor failure (0=non-failure, 1=failure); IIV=inter-individual variability; IRPT=immune response status over time; ka=first-order absorption rate constant; M=male; PopPK=population pharmacokinetic; PROP ERR=proportional error term; Q=inter-compartmental flow; RSE=relative standard error; TNF=tumor necrosis factor; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

[a] The transformed estimate to the standard PK scale.

[b] $CL(L/day) = 0.29 \times \left(\frac{BWT}{68.7}\right)^{0.75} \times \left(\frac{BALB}{3.7}\right)^{-1.18} \times \left(\frac{BCRP}{0.93}\right)^{0.0572} \times \exp(0.132 \times SEX = M) \times \exp(0.142 \times RACE = A) \times \exp(0.0557 \times TNF) \times \exp(0.195 \times IRPT)$

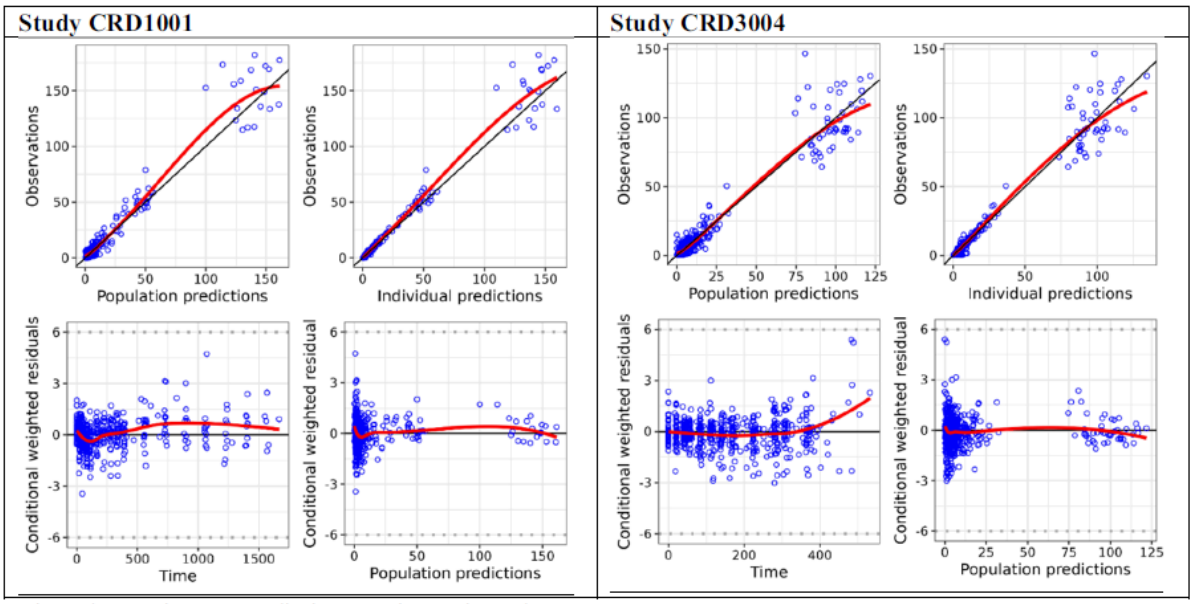
[c] $V2(L) = 4.06 \times \left(\frac{BWT}{68.7}\right)^{1} \times \left(\frac{BALB}{3.7}\right)^{-0.416} \times \exp(0.0705 \times SEX = M)$

[d] $Q(L/day) = 0.17 \times \left(\frac{BWT}{68.7}\right)^{0.75}$

[e] $V3(L/day) = 2.29 \times \left(\frac{BWT}{68.7}\right)^{1}$

Figure 2 shows the basic GOF plots for the final paediatric model. The IPREDs fitted well along the line of identity and the CWRES were generally centred around zero with homogenous variation relative to the PREDs and time.

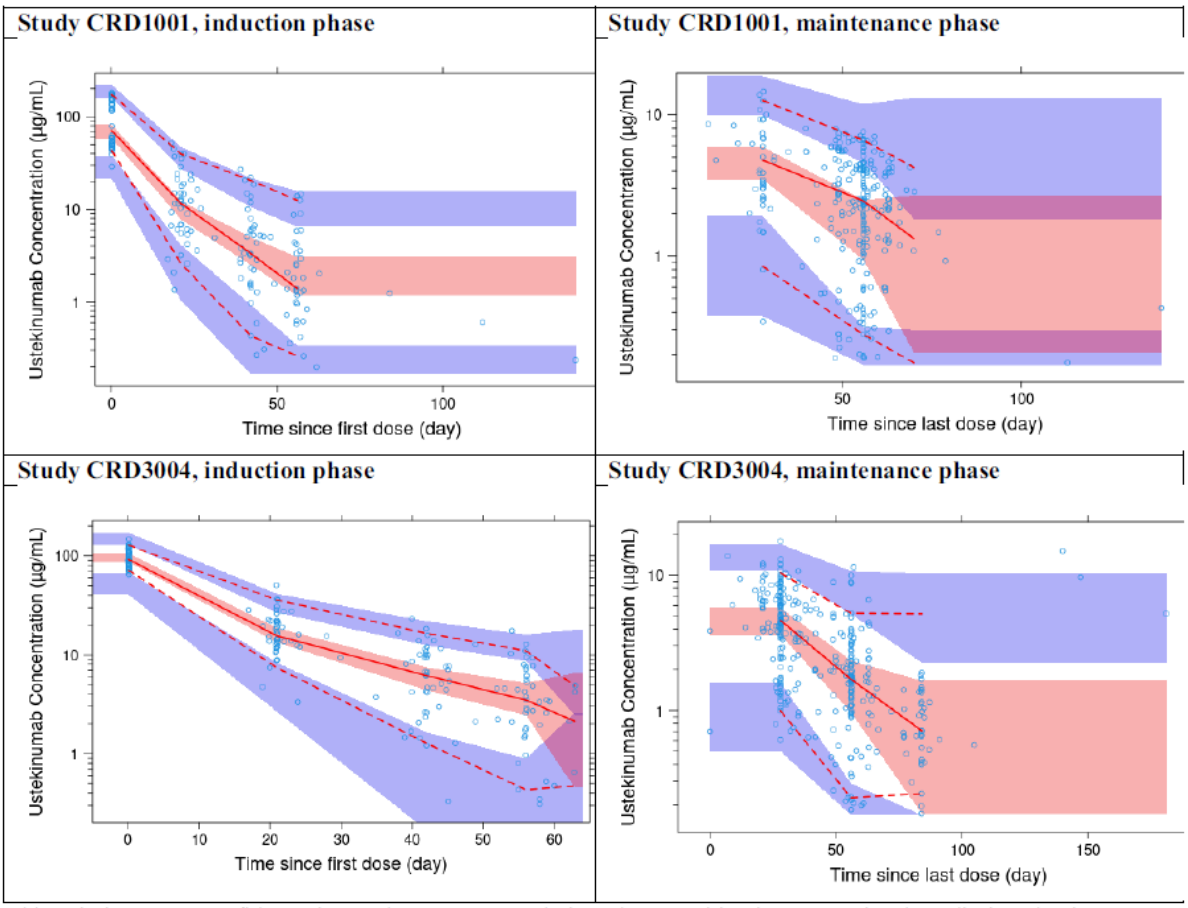
Figure 2: Basic GOF Plots for the Final Paediatric PopPK Model



Units: Observations or predictions=µg/mL; Time=day.
Abbreviations: GOF=Goodness-of-fit; PopPK=population pharmacokinetic.
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 left panels represent Study CRD1001 and the right panels represent Study CRD3004.

The performance of the final model was evaluated using VPCs with stratification by study and treatment phase. As shown in Figure 3, the final model adequately captured the median concentration-time profile of ustekinumab, as well as the associated variabilities, across the studies and treatment phases.

Figure 3: VPC for Final Paediatric PopPK Model

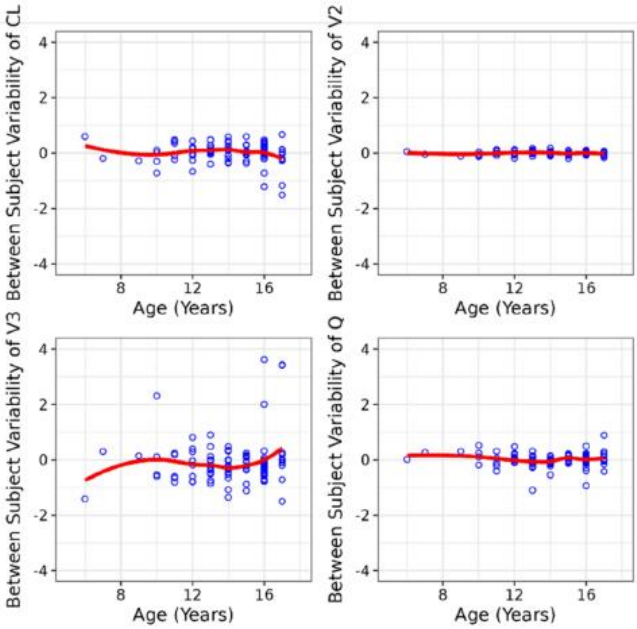


Abbreviations: CI=confidence interval; PopPK=population pharmacokinetic; VPC=visual predictive checks.

Note: the upper panel shows the time course of Study CRD1001 following induction treatment and maintenance treatment, respectively, whereas the lower panel shows the time course of Study CRD3004 following induction treatment and maintenance treatment, respectively. 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 90% CI of the median and the shaded blue areas represent the 90% CI of the 5th and 95th percentiles predicted by the model.

The effect of age in paediatric participants was assessed graphically by plotting the correlation between age and interindividual variability (IIV) on disposition parameters (Figure 4). No correlation was observed between age and IIV on CL, V2, V3, and Q, suggesting that disposition parameters of ustekinumab do not change across age within the paediatric patients.

Figure 4: Scatter Plot of Age Versus ETA on Disposition Parameters for the Final Paediatric Model



Abbreviations: CL=clearance; ETA=individual random effect; Q=distribution clearance; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

12 participants entered into the optional Exposure Optimisation Substudy with documented low ustekinumab exposure (i.e., 8 weeks post-dose steady-state concentration <1.4 µg/mL) and LOR. The median (range) individual *post-hoc* estimate of CL for these 12 participants was 0.304 (0.075 to 0.439) L/day, which is higher compared with those who did not enter the sub study (0.23 [0.064 to 0.554] L/day).

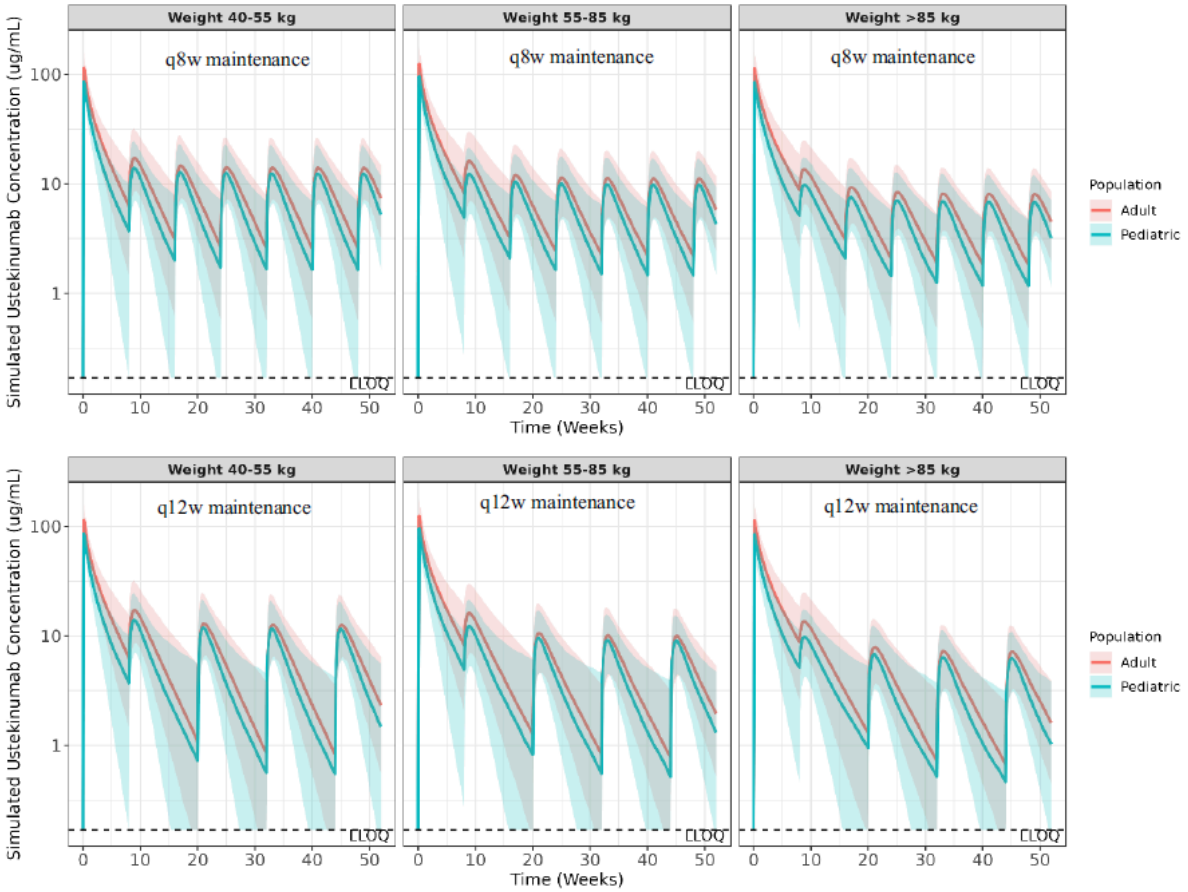
Simulations

Simulated PK profiles were generated in adult and paediatric participants (body weight ≥40 kg) 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 of 260 mg, 390 mg, or 520 mg for each weight group [40 to 55 kg, 55 to 85 kg, and >85 kg, respectively] at Week I-0, and ustekinumab SC maintenance doses of 90 mg q8w or q12w starting from Week I-8).

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

Figure *5*. The concentration-time profiles of ustekinumab in paediatric participants largely overlapped with those in adult participants, where predicted Ctrough in approximately 75% of paediatric participants fell within the 90% prediction interval of adult exposures following either induction or maintenance treatment across weight groups. Any numerical differences between the adult and paediatric exposures are likely not clinically meaningful.

Figure 5: Comparison of the Predicted Serum Concentration-time Profiles of Ustekinumab in Paediatric and Adult Participants by Weight Group



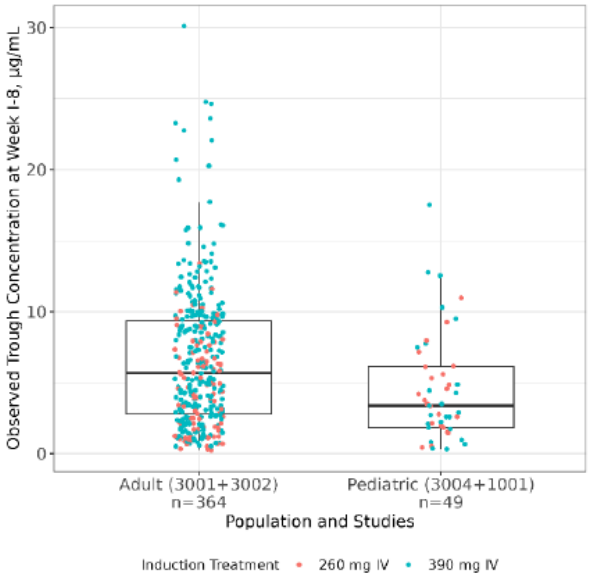
Abbreviations: IV=intravenous; LLOQ=lower limit of quantification; PK=pharmacokinetic(s); qXw=every X weeks.

Note: lines represent medians of the simulated values. Shaded regions represent the 5th to 95th percentile ranges. The upper and lower panel shows 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 pediatric or adult participants.

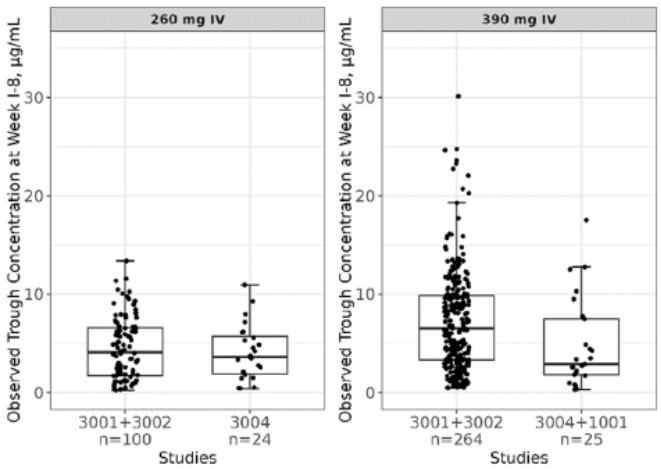
Figure 6 and Figure 7 show the observed Ctrough in adult and paediatric participants (body weight ≥40 kg) after the same induction treatment and maintenance treatment, respectively. Following the single 260 mg IV induction dose, and the 90 mg SC q12w or q8w maintenance dose regimens, serum trough ustekinumab concentrations were generally comparable between paediatric and adult participants. While serum trough ustekinumab concentrations were lower in paediatric participants who received the 390 mg IV induction dose, the range of concentrations in paediatric participants following this induction dose were within the concentration range observed in adults receiving approved induction IV doses of 260 mg and 390 mg.

Figure 6: Boxplots of Observed C_{trough} Between Adult Studies CRD3001 and CRD3002 and Paediatric Studies CRD3004 and CRD1001 at Week 8 after 260mg or 390mg IV Induction Treatment

A: Overall Induction Treatment

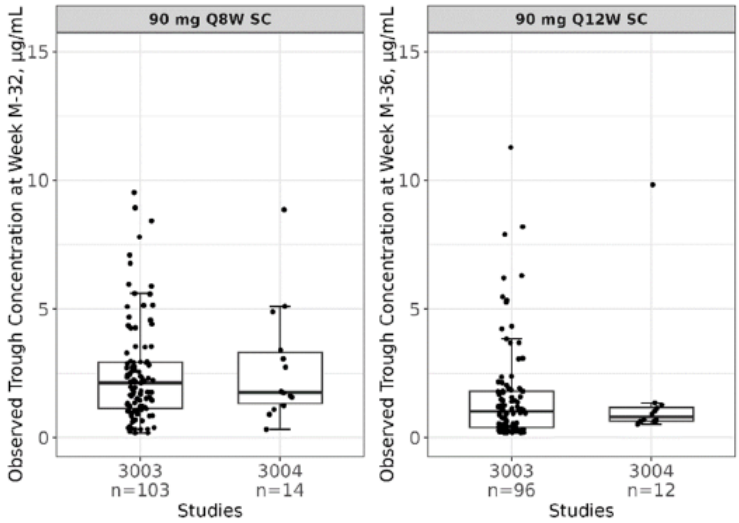


B: Stratified by Induction Treatment



Abbreviations: C_{trough}=trough concentration; I=induction; IV=intravenous; n=number of participants.
Note: black dots are the observed individual C_{trough} at Week I-8. Plot A presents the pooled distribution of observed C_{trough} after 260 mg and 390 mg induction treatment in adult and pediatric participants; plot B presents the separate distribution of observed C_{trough} stratified by induction treatment. The numbers of participants (40 kg ≤weight ≤55 kg) with available C_{trough} following 260 mg IV induction treatment from adult Studies CRD3001 and CRD3002 and pediatric study CRD3004 are 100 and 24, respectively. The numbers of participants (55 kg <weight ≤85 kg) with available C_{trough} following 390 mg IV induction treatment from adult Studies CRD3001 and CRD3002 and pediatric Studies CRD3004 and CRD1001 are 264 and 25, respectively.

Figure 7: Boxplots of Observed C_{trough} in Induction Responders From Adult Study CRD3003 and Paediatric Study CRD3004 at Week M-32 with q8w Maintenance Treatment and at Week M-36 with q12w Maintenance Treatment



Abbreviations: C_{trough}=trough concentration; M=maintenance; n=number of participants; qXw=every X weeks; SC=subcutaneous.

Note: black dots are the observed individual C_{trough} at Week M-32 for q8w maintenance treatment or at Week M-36 for q12w maintenance treatment. Comparisons were made in induction responders. The numbers of induction responders with available C_{trough} at Week M-32 following 90 mg SC maintenance treatment from adult Study CRD3003 and pediatric Study CRD3004 are 103 and 14, respectively. The numbers of induction responders with available C_{trough} at Week M-36 following 90 mg SC maintenance treatment from adult Study CRD3003 and pediatric Study CRD3004 are 96 and 12, respectively.

2.3.3. Pharmacodynamics

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

Mechanism of action

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

2.3.4. PK/PD modelling

Exposure-response analysis in participants with Crohn's Disease

The exposure-response (E-R) analysis for efficacy in paediatric participants (body weight ≥40 kg) with CD was performed to explore the relationships between ustekinumab exposure metrics and 3 efficacy endpoints, including clinical remission and clinical response at Week I-8 in relation to Ctrough, weekI8 and clinical remission at Week M-44 in relation to Ctrough, weekM44. The primary endpoint of clinical remission at Week I-8 was the focus of the paediatric E-R analysis for efficacy. The analysis methods for each efficacy endpoint are provided in **Table *6***.

Table 6: Summary of E-R Analysis for Efficacy Endpoints

Efficacy Endpoint	Study	Analysis Method
Clinical remission at Week I-8	CRD3004 (CRD1001 was included for modelling analysis)	Graphical exploratory analysis and modelling analysis
Clinical response at Week I-8	CRD3004	Graphical exploratory analysis
Clinical remission at Week M-44	CRD3004	Graphical exploratory analysis

Abbreviations: E-R=exposure response; I=induction; M=maintenance.

For the induction endpoints, 48 paediatric participants from Study CRD3004 were included in the E-R modelling and graphical exploratory analysis, while 45 paediatric participants who were induction responders from Study CRD3004 were used for exploratory E-R analysis for maintenance endpoints. Additionally, 23 paediatric participants from Study CRD1001 with body weight ≥40 kg were included in the E-R modelling for clinical remission at Week I-8. To evaluate the E-R similarity, historical adult E-R data were used, including 1,386 adult participants from Studies CRD3001 and CRD3002 and 387 adult participants who were induction responders from Study CRD3003. To compare clinical remission rate at Week I-8, data from 458 adult participants who received ustekinumab 6 mg/kg in Studies CRD3001 and CRD3002.

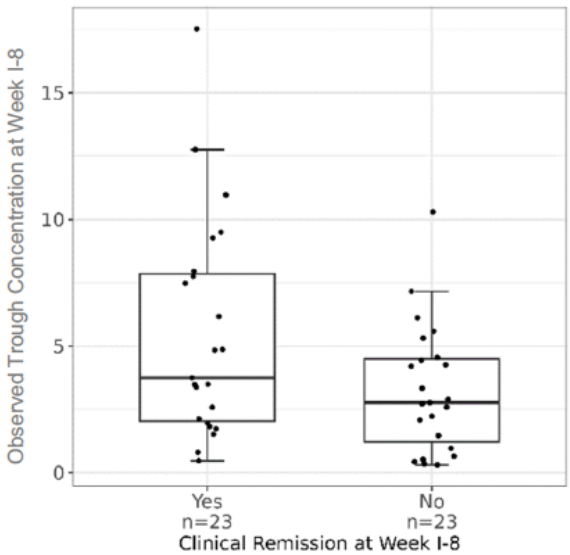
Individual exposure metrics for the E-R analyses, including predicted Ctrough at Week I-8 (Ctrough,weekI8) and the most recent predicted Ctrough prior to Week M-44 (i.e., Ctrough,weekM40 q8w and Ctrough,weekM36 q12w), were generated from simulations based on the final paediatric popPK model using actual individual dosing information.

Clinical remission at Week I-8

Exploratory graphical analysis

Figure *8* shows the distribution of observed Ctrough in paediatric participants (body weight ≥40 kg) with and without clinical remission at Week I-8 from Study CRD3004. The observed Ctrough at Week I-8 overlapped between paediatric participants with and without clinical remission, with numerically higher median Ctrough observed in those with clinical remission.

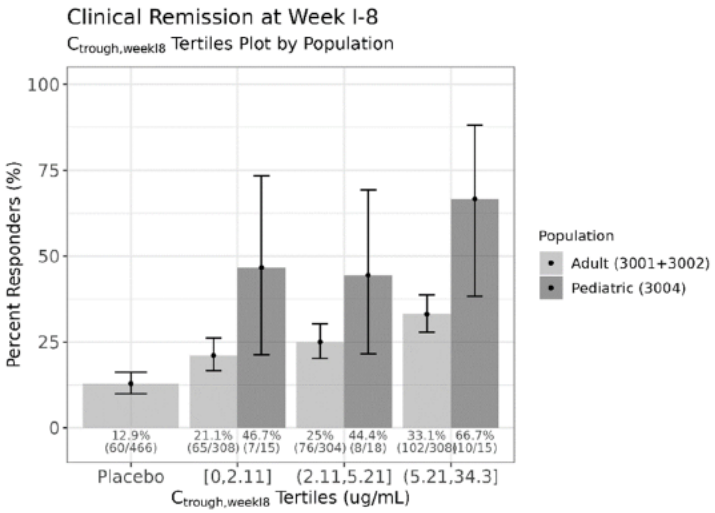
Figure 8: E-R Relationship for Clinical Remission at Week 1-8 in Paediatric Study CRD3004



Abbreviations: CI=confidence interval; E-R=exposure-response; I=induction; n=number of participants.
Note: error bars are the 95% CI of response rates in the respective exposure tertile groups.
Note: black dots are the observed individual trough concentration at Week I-8. The number of participants with available trough concentrations in clinical remission and not in clinical remission at Week I-8 are 23 and 23, respectively.

Figure *9* shows the E-R relationship of paediatric participants (body weight ≥40 kg) from Study CRD3004 in comparison with adult participants from Studies CRD3001 and CRD3002. A similar positive E-R trend was observed in clinical remission at Week I-8 in relation to predicted Ctrough, weekI8 in adult and paediatric participants, with a higher (but more variable) clinical remission rate in paediatric participants in each predicted Ctrough, weekI8 tertile group. Overall, the clinical remission rate at Week I-8 in paediatric participants was higher compared to that in adult participants (52.1% [25/48 participants] in Study CRD3004 and 29.7% [136/458 participants] in Studies CRD3001 and CRD3002).

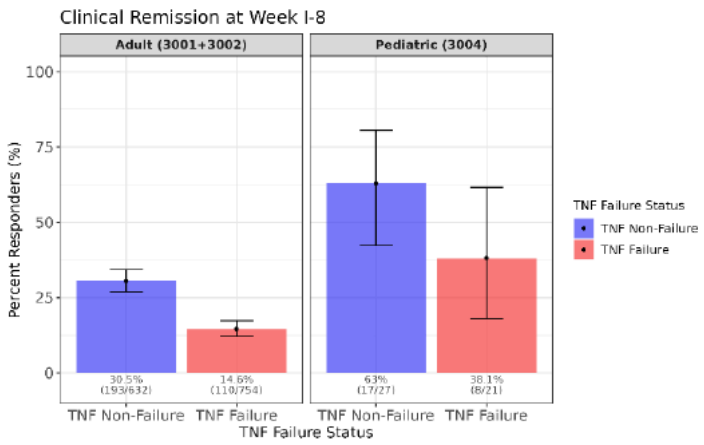
Figure 9: E-R Relationship of Clinical Remission at Week I-8 Versus Predicted $C_{trough,\ week\ 18}$ in Paediatric Study CRD3004 and Adult Studies CRD3001 and CRD3002



Abbreviations: CI=confidence interval; $C_{trough,week18}$=trough concentration at Week I-8; E-R=exposure-response; I=induction; N=number of participants.
Note: error bars are the 95% CI of response rates 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 Studies CRD3001 and CRD3002 (N=1,386). E-R relationship in pediatric participants was summarized in participants who received ustekinumab ~6 mg/kg at Week I-0 from Study CRD3004 (N=48). Exposure tertile cutoffs for $C_{trough,week18}$ were based on pooled data from pediatric Study CRD3004 and adult Studies CRD3001 and CRD3002.

Similar to adults, the clinical remission rate at Week I-8 was higher in the TNF non-failure population compared to the TNF failure population in paediatric participants, as presented in Figure 10.

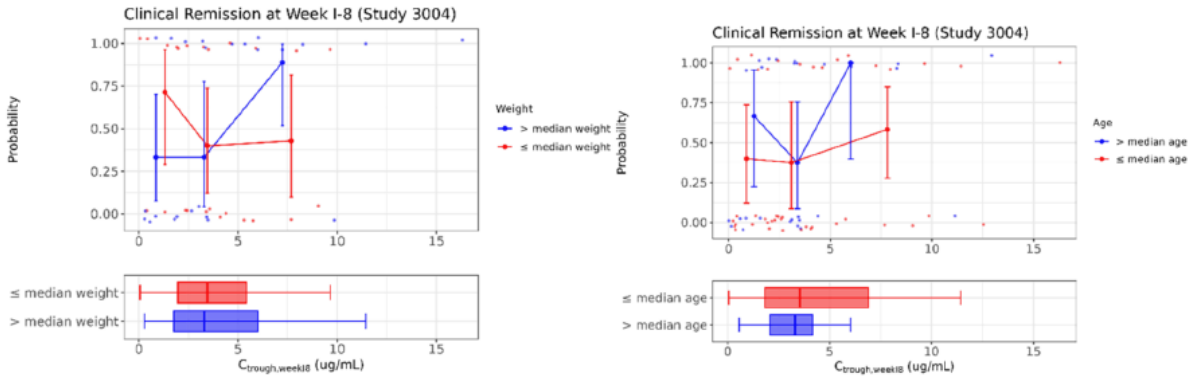
Figure 10: Clinical Remission at Week I-8 in Paediatric Study CRD3004 and Adult Studies CRD3001 and CRD3002, stratified by TNF Failure Status



Abbreviations: CI=confidence interval; I=induction; N=number of participants; TNF=tumor necrosis factor.
Note: error bars are the 95% CI of response rates 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 Studies CRD3001 and CRD3002 (N=1,386). Clinical remission at Week I-8 in pediatric was summarized in participants who received ustekinumab ~6 mg/kg at Week I-0 from Study CRD3004 (N=48).

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

Figure 11: E-R Relationship of Clinical Remission at Week I-8 Versus the Predicted $C_{trough, week\ 18}$ in Paediatric Study CRD3004, Stratified by Age Group or Weight Group



Abbreviations: CI=confidence interval; $C_{trough,weekI8}$=trough concentration at Week I-8; E-R=exposure-response; I=induction; N=number of participants; PopPK=population pharmacokinetic.

Note: connected dots with error bars are the observed median and 95% CI 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 actual dose regimen and individual PopPK model parameter estimates in pediatric participants who received ~6 mg/kg ustekinumab at Week I-0 from Study CRD3004 (N=48). Box plots in the bottom represent the distribution of the individual model predicted exposure metrics in subgroups.

E-R modelling

E-R model-based analysis was performed for clinical remission at Week I-8 in paediatric participants with body weight ≥40 kg using logistic regression. Covariate relationships that were identified as significant in the previously run adult E-R model for clinical remission at Week I-8 were explored, including TNF failure status, baseline Crohn's Disease Activity Index (CDAI) score, and baseline CRP. In the paediatric E-R analysis, baseline Paediatric Crohn's Activity Index (PCDAI) score was explored as baseline CDAI score was not available in most paediatric participants. The previous adult E-R model for clinical remission at Week I-8 was refitted with the E-R data from paediatric Studies CRD3004 and CRD1001. This was done by fixing the placebo effect (the intercept in logistic regression) to the value of adult as there is no placebo data in Studies CRD3004 and CRD1001. Covariate relationships that were not evident in the graphical analysis of the paediatric data were not included. The effects of TNF failure status on placebo effect and EC50 were retained from the previously established adult model.

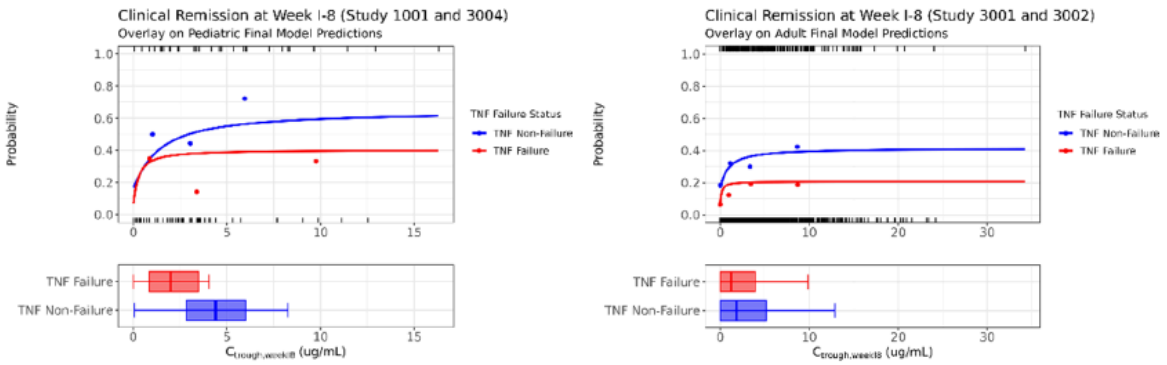
The E-R relationship between Ctrough, weekI8 and clinical remission at Week I-8 in paediatric participants (body weight ≥40 kg) with CD was adequately characterised by an Emax model with an additive placebo effect. Parameter estimates from the E-R model are presented in **Table *7***. A GOF plot of the final model comparing observed and predicted clinical remission rates at Week I-8 in the predicted Ctrough, weekI8 tertile bins is shown in **Figure *12***. The large RSE for EC50 was likely due to the limited sample size for paediatric data (n=71). The estimated EC50 in the paediatric E-R model was 1.12 µg/mL, which is close to the value of 0.712 µg/mL from the previous adult E-R model. This suggests that the E-R relationship between Ctrough, weekI8 and clinical remission at Week I-8 in paediatric participants (body weight ≥40 kg) was similar to the E-R relationship in adults.

Table 7: Clinical Remission at Week I-8 E-R Final Model Parameter Estimates With Fixed TNF Failure Status

Parameter	Estimate (RSE%)
Placebo Effects (β)	
β_0	-1.60 Fixed
TNF Failure	-0.996 Fixed
Emax	
Emax,0	2.21 (16%)
EC50 (ug/mL)	
EC50,0	1.12 (81%)
TNF Failure	-1.98 Fixed

Abbreviations: β_0=logit probability for remission; EC50=half maximal effective concentration; Emax=maximum drug effect; E-R=exposure-response; I=induction; RSE=relative standard error; TNF=tumor necrosis factor.

Figure 12: GOF Plots of Final Paediatric Model and Final Adult Model for Clinical Remission at Week I-8 in Paediatric Participants ⩾40kg from Studies CRD1001 and CRD3004 and Adult Participants From Studies CRD3001 and CRD 3002, Stratified by TNF Failure Status



Abbreviations: $C_{trough,weekI8}$=trough concentration at Week I-8; E-R=exposure-response; GOF=Goodness-of-fit; I=induction; N=number of participants; PopPK=population pharmacokinetic; TNF=tumor necrosis factor.

Note: dots are the observed median of 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 actual dose regimen and individual PopPK model parameter estimates in pediatric participants (body weight ≥40kg) who received ~6 mg/kg ustekinumab at Week I-0 from Studies CRD1001 and CRD3004 (N=71, left panel) or adult participants who received 130 mg or ~6 mg/kg ustekinumab or placebo at Week I-0 in Studies CRD3001 and CRD3002 (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.

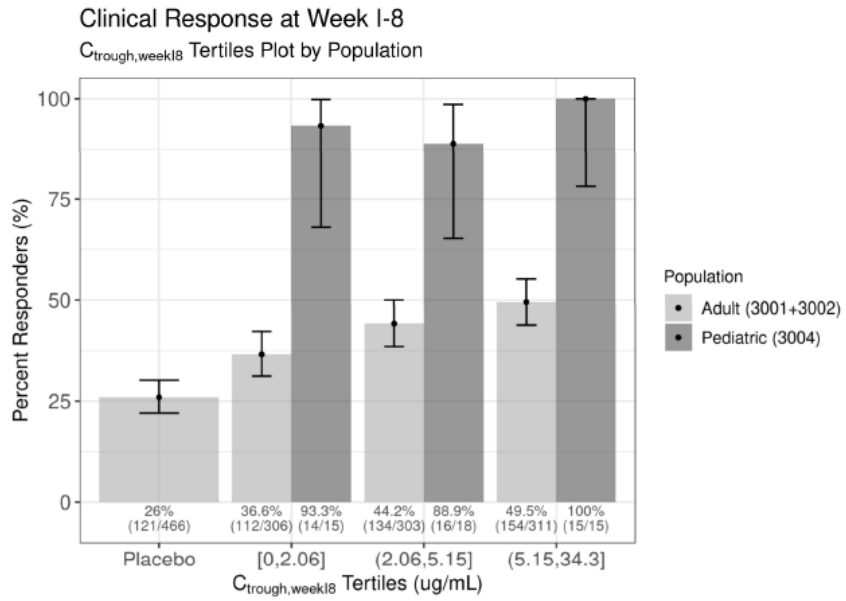
Sensitivity analyses were performed by estimating the placebo effect or the effect of TNF failure status on EC50. The model with estimated placebo effect was not stable and estimation for Emax and EC50 was unreasonably large as no placebo data were available in paediatric data to support the estimation of placebo effect. The model with estimated effect of TNF failure status on EC50 resulted in large RSE on EC50 and the effect of TNF failure status on EC50 (greater than 100%). Sensitivity analyses suggest that fixing the placebo effect and the covariates effect of TNF failure status on EC50 in the paediatric E-R model to the historical adult E-R model is necessary.

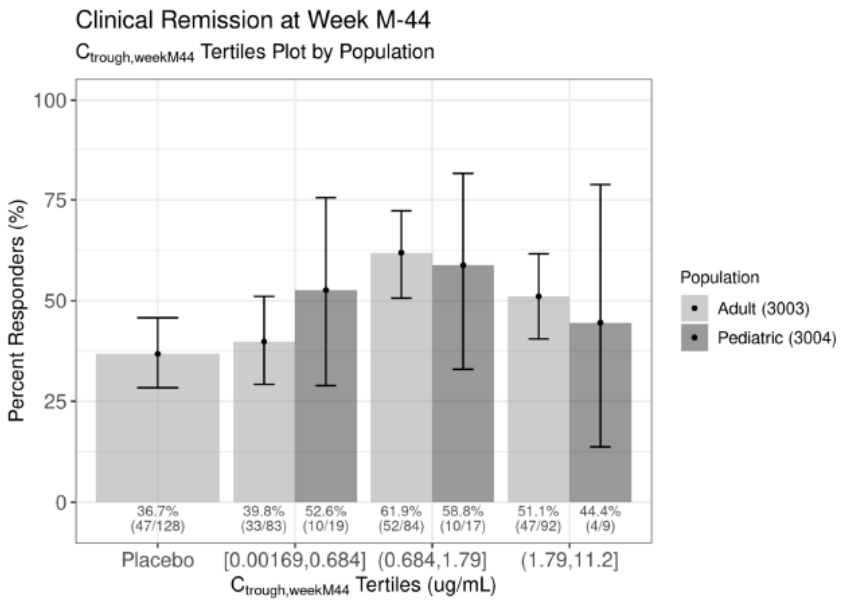
Other Efficacy Endpoints (Clinical Response at Week I-8 and Clinical Remission at Week M-44)

Figure *13* shows the exploratory E-R analysis for clinical response at Week I-8 and clinical remission at Week M-44 in paediatric participants (body weight ⩾40 kg) from Study CRD3004 and its comparison with adult participants from Studies CRD3001 and CRD3002 or Study CRD3003, respectively. No clear E-R relationship was observed between clinical response at Week I-8 and predicted Ctrough, weekI8, mainly

because the overall response rate was very high (45/48 participants [93.8%]). A similar E-R trend was observed for clinical remission at Week M-44 versus predicted Ctrough, weekM44 in adult participants from Study CRD3003 and paediatric participants from Study CRD3004. In paediatric study CRD3004, the remission rates of both the q8w and q12w maintenance treatments were high, with overlapping confidence intervals in participants (Figure 14).

Figure 13: E-R Relationship of Clinical Response at Week I-8 and Clinical Remission at Week M-44 in Paediatric Study CRD3004 and Adult Studies CRD3001, CRD3002, and CRD3003



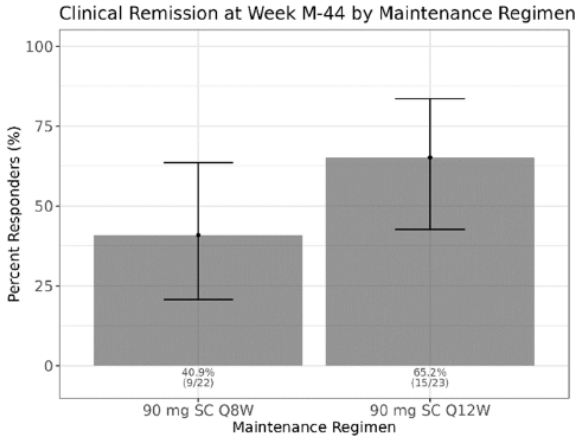


Abbreviations: CI=confidence interval; $C_{trough,weekI8}$=trough concentration at Week I-8; $C_{trough,weekM44}$=trough concentration at Week M-44; E-R=exposure-response; I=induction; M=maintenance; qXw=every X weeks; SC=subcutaneous.

Note: error bars are the 95% CI of response rates in the respective exposure tertile groups.

Note: the exposure tertile cutoffs for $C_{trough,weekI8}$ and $C_{trough,weekM44}$ were based on pooled data from pediatric Study CRD3004 and adult Studies CRD3001, CRD3002, and CRD3003. Clinical response at Week I-8 was summarized in pediatric participants (body weight ≥40 kg) who received ~6 mg/kg ustekinumab at Week I-0 from Study CRD3004 and in adult participants who received 130 mg or ~6 mg/kg ustekinumab or placebo at Week I-0 in Studies CRD3001 and CRD3002. Clinical remission at Week M-44 was summarized in inductior responders who received at least 1 administration of 90 mg SC q8w or q12w ustekinumab or placebo during maintenance in adult maintenance Study CRD3003 and pediatric Study CRD3004.

Figure 14: Clinical Remission at Week M-44 in Induction Responders From Paediatric Study CRD3004, Stratified by Maintenance Regimen



Abbreviations: CI=confidence interval; M=maintenance; qXw=every X weeks; SC=subcutaneous.
Note: error bars are the 95% CI of response rates in the respective maintenance regimen.
Note: clinical remission at Week M-44 was summarized in induction responders who received at least 1 administration of 90 mg SC q8w or q12w ustekinumab in pediatric Study CRD3004.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics in the target population (Study 3004)

Observed serum ustekinumab concentrations following the dose regimens employed for paediatric participants ≥40 kg in the Phase 3 Study 3004 were generally within the range of concentrations observed in adult participants with CD receiving the approved dose regimen for this indication.

For paediatric participants who lost response and had low ustekinumab levels, dose adjustment to q4w dosing led to a higher steady-state than the q12w and q8w dose regimens and provided exposures that fell within the range of ustekinumab concentrations observed in adults with CD. However, as acknowledged by the applicant, this observation is based on a small number of participants (n=12). Therefore, no conclusions can be made about the impact of dose adjustment on ustekinumab concentrations based on these data alone.

Population PK analysis

The popPK analysis was based on new data from the paediatric studies (CRD1001 and CRD3004). The developed model was used to simulate and compare the systemic exposure to ustekinumab between the paediatric patients (≥40 kg) and adult CD populations.

A previously developed adult popPK model was updated by re-estimating parameter estimates with adult data from 3 Phase 3 studies in adults with CD and with standard allometric scaling exponents fixed to 0.75 and 1 for clearance and volume parameters, respectively. This approach is endorsed. Parameters of the updated adult model were estimated with adequate precision, diagnostic plots showed that the model described the adult data reasonably well, and VPCs indicated satisfactory predictive performance of the final adult model.

For the paediatric model, parameters from the updated adult model were re-estimated using paediatric data and covariate relationships from the adult model were retained as fixed values. This approach is considered acceptable given the limited paediatric data. Further, the PK of ustekinumab in paediatric patients with CD ≥40 kg is not expected to differ significantly from adults with CD provided that the impact of body weight is appropriately included in the model. 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.

The final paediatric popPK model was a 2-compartment model with first-order absorption. All model parameters were estimated with good precision and model diagnostics showed good agreement between observed and model-predicted ustekinumab concentrations. The VPCs indicated that the predictive performance of the model was adequate. As such, the paediatric popPK model is deemed fit for performing simulations.

The simulated PK profiles largely overlapped between the adult and paediatric populations following the same induction and maintenance treatment across weight groups (≥40 kg). Further, the observed Ctrough following induction treatment and 90 mg SC maintenance dose (either q8w or q12w) in paediatric participants were within the range of those in adult participants. This provides support for the proposed dose regimens for paediatric patients with CD.

The 12 paediatric participants that entered the optional Exposure Optimisation Sub study due to low ustekinumab exposure and loss of response had higher ustekinumab clearance compared with those who did not enter the sub study. This suggested that children who lose effect may benefit from a switch to q4w posology. As requested by the CHMP, the applicant performed simulations to compare ustekinumab exposure between all paediatric participants receiving q4w dosing, regardless of loss of response and adult participants receiving q8w dosing. The results predicted higher exposures in paediatric participants than those in adult participants receiving the highest approved dose. The applicant provided also justification for q4w dosing based on paediatric clinical practice (Pujol-Muncunill 2024) and published adult literature. These RWE studies did not use TDM or concentrations to adjust the dose, however. Furthermore, a summary of adult trial data with q4w dosing was presented (STARDUST study CRD3005). No new safety concerns were identified but exposure data were not available, and no further assessment of safety was provided. Of note, q4w dosing remains unauthorised in adult patients with CD. In summary, the limited safety data presented in the response were considered insufficient evidence to support q4w dosing in paediatric CD patients. Therefore, a recommendation to switch paediatric patients with loss of response to q4w dosing is not presently justified since it is based on a limited number of participants.

Immunogenicity

Consistent with adult patients with CD, the incidence of antibodies to ustekinumab was low in paediatric participants with CD. Therefore, the impact of immunogenicity on the PK, efficacy, or safety of ustekinumab in paediatric patients could not be evaluated.

Pharmacodynamics

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

PK/PD modelling

The E-R analysis for efficacy in paediatric participants (≥40 kg) with CD was conducted to explore relationships between ustekinumab trough concentrations and 3 efficacy endpoints - clinical remission at induction Week 8, clinical response at induction Week 8, and clinical remission at maintenance Week 44.

All 3 endpoints were explored graphically. The primary endpoint of clinical remission at induction Week 8 was the focus of the paediatric E-R analysis and this endpoint was also explored using E-R modelling. Individual ustekinumab trough concentrations were derived from simulations of the final paediatric popPK model.

In the graphical analysis of clinical remission at induction Week 8, a positive E-R trend was observed in paediatric participants with CD treated with ustekinumab. The E-R relationship for clinical remission at

induction Week 8 appeared to be similar between paediatric participants and adult participants. However, overall clinical remission rates were higher in paediatric participants compared to adults.

For the E-R modelling analysis, nonlinear logistic regression models with additive placebo and Emax drug effects adequately described clinical remission rates at induction Week 8 in paediatric participants treated with ustekinumab. The placebo effect was fixed to the previously established adult model and the effects of TNF failure status on the placebo effect and EC50 were also retained from the previously established adult model. This approach was justified with sensitivity analyses.

The modelling analysis demonstrated a positive E-R trend between ustekinumab trough concentrations and clinical remission at induction Week 8. The E-R relationship for clinical remission at induction Week 8 was not affected by age or body weight within the paediatric participants. TNF failure status was an influential covariate on both placebo and drug parameters, resulting in lower clinical remission rates at Week I-8 for participants who had previously failed on TNF-antagonist therapy relative to the TNF non-failure subpopulation.

No clear E-R trend was observed for clinical response at induction Week 8 mainly because the response rate was very high (94%). The E-R trend of clinical remission at maintenance Week 44 in relation to ustekinumab trough concentrations was similar in adult and paediatric participants. The dose response analysis demonstrated that the proportions of participants achieving clinical remission following treatment with the 90 mg q8w and q12w maintenance regimens were high, with overlapping CIs in paediatric participants.

2.3.6. Conclusions on clinical pharmacology

The totality of the observed and model-simulated data suggests that the ustekinumab doses used for paediatric participants (≥40 kg body weight) with CD, will likely result in PK profiles and E-R relationships that are comparable to those in adult participants with CD. As such, these data support the proposed dose regimens for paediatric participants (≥40 kg body weight) with CD.

2.4. Clinical efficacy

2.4.1. Study CRD3004, phase 3

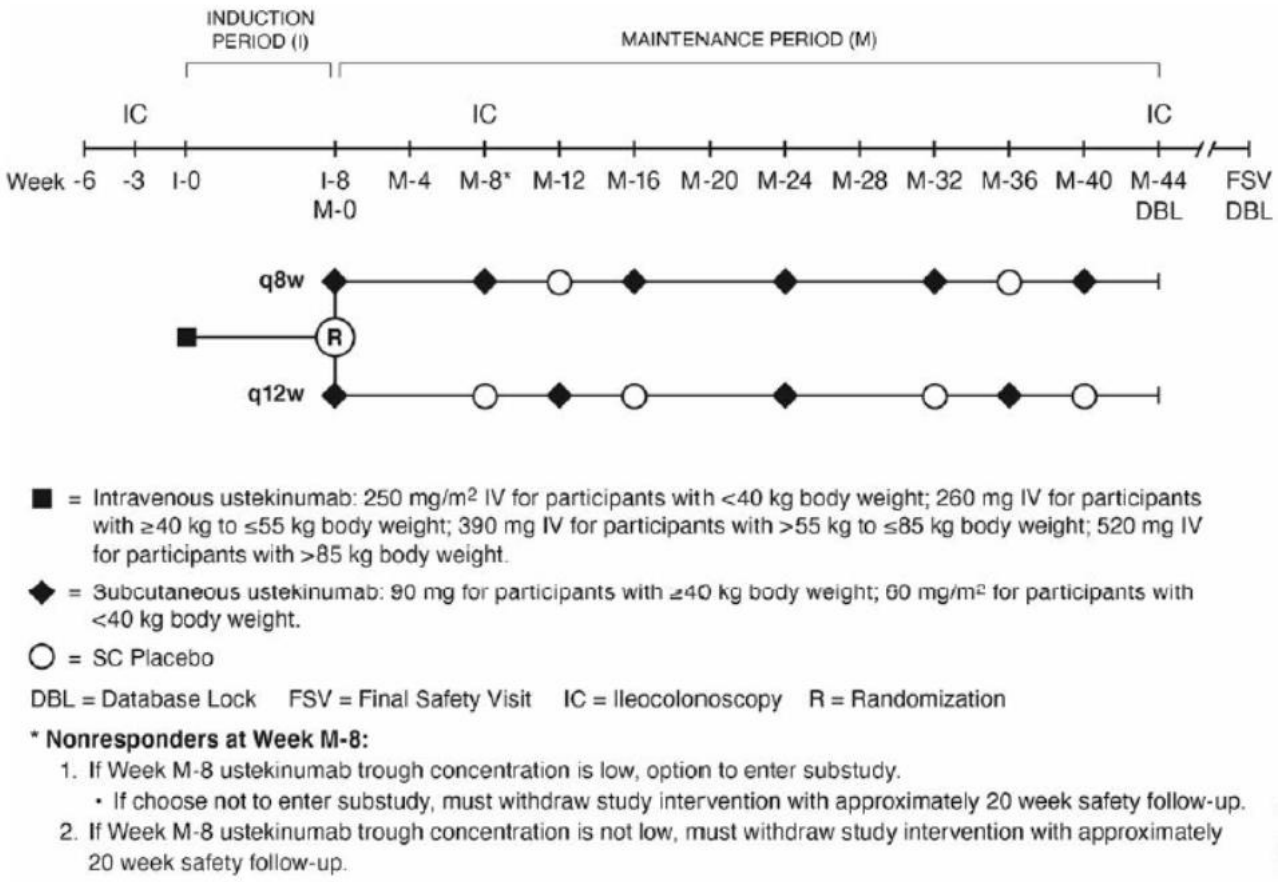
Title of Study: A Phase 3 Study of the Efficacy, Safety, and Pharmacokinetics of Ustekinumab as Open label Intravenous Induction Treatment Followed by Randomized Double blind Subcutaneous Ustekinumab Maintenance in Paediatric Participants with Moderately to Severely Active Crohn's Disease

Study Number: CNTO1275CRD3004

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., TNFα 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 15: 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 fistulising 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.

Subsequent PIP modification included these data, justifying a reduction in the data needed amongst participants weighing at least 40 kg, while maintaining sample size requirements for those <40 kg. Therefore, an interim analysis of the data has been performed when at least 36 randomised participants with body weight ≥40 kg at Week I-0 and Week M-0 had completed the Week M-44 visit or terminated the main study participation prior to Week M-44. The interim analysis results are presented in this CSR and will be used for the EMA submission of participants with body weight ≥40 kg. At the time of the interim analysis, the treatment regimen was unblinded for the participants who were included in the interim analysis (i.e., at least 36 randomised participants with body weight ≥40 kg who have completed the Week M-44 visit or terminated the main study participation prior to Week M-44). The treatment information for the remainder of the randomised participants not included in the interim analysis remained blinded.

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 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 this 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.

Study population was defined as the EMA Randomised Analysis Set for Participants with Body Weight ≥40 kg (ERAS), i.e. all participants who had body weight ≥40 kg at Week I-0 and Week M-0, received at least 1 administration of study intervention during maintenance, and completed Week M-44 visit or terminated the main study prior to Week M-44 at the EMA DBL, including participants who entered the sub study.

Results

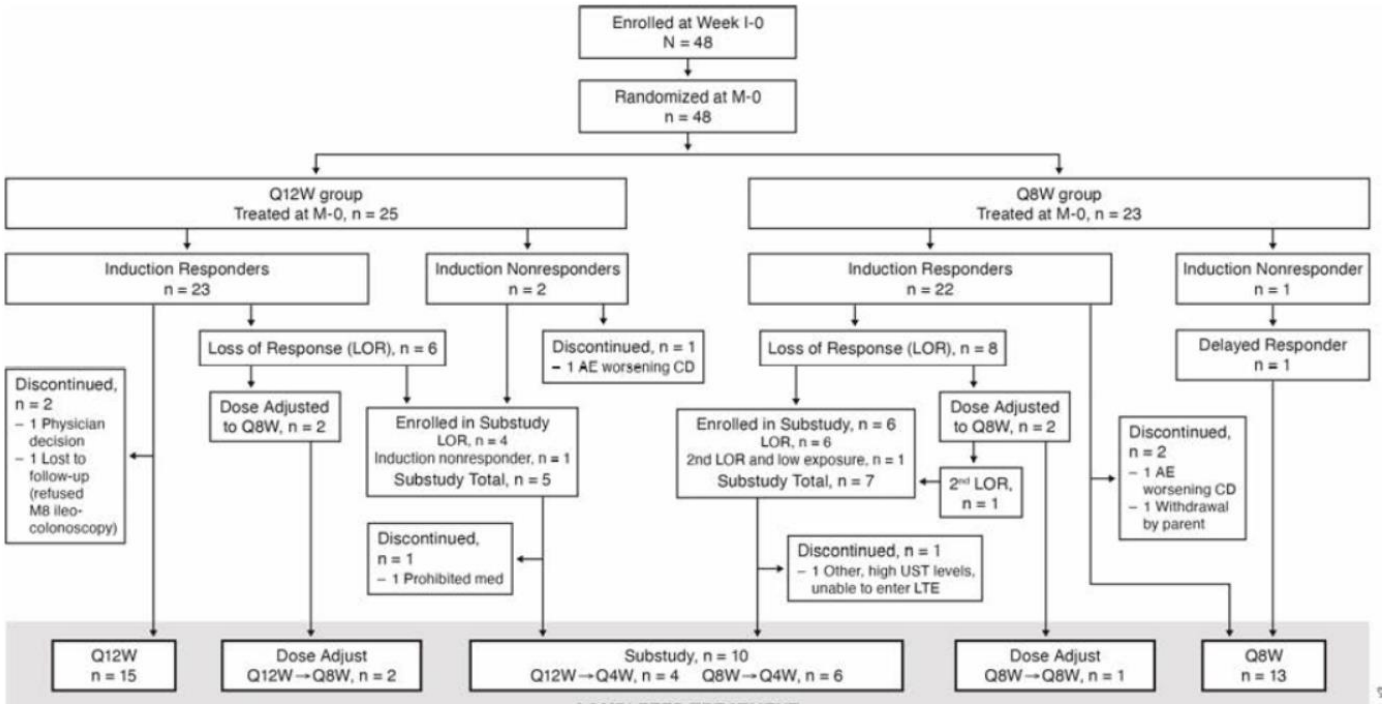
Participant flow

The disposition of participants from the ERAS by study intervention from Induction Week I-0 through Week M-44 is shown in **Figure *16***.

All participants from the ERAS (48 [100%] of 48 participants) were randomised and treated at Week I-0 and Week M-0.

All participants were randomised in 16 centres across 7 countries (Poland [60.4%], Hungary [8.3%], Belgium [20.8%], Germany [2.1%], the United Kingdom [2.1%], USA [4.2%], and Japan [2.1%]).

Figure 16: Disposition of Randomised Participants



There were no participants who discontinued study intervention during the induction period and 5 (10.4%) of 48 participants discontinued study intervention between Week M-0 and Week M-44 (

Table *8*).

The proportions of participants discontinuing study intervention prior to completing maintenance dosing were low for both the ustekinumab 90 mg SC q12w (3 of 25 participants [12.0%]) and the ustekinumab 90 mg SC q8w (2 of 23 participants [8.7%]) dosing regimen groups. In the q12w group, 1 participant discontinued study intervention due to AE of worsening of Crohn's disease, 1 discontinued due to lost to follow-up, and the other participant discontinued due to physician decision. In the q8w group, one participant discontinued study intervention due to AE of worsening of Crohn's disease and one following study withdrawal by their parents or guardians. No participant discontinued study intervention due to COVID-19 related reasons.

Table 8: Treatment Disposition From Week M-0 Through Week M-44; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: EMA Randomized	25	23	48
Subjects randomized at Week M-0	25 (100.0%)	23 (100.0%)	48 (100.0%)
Subjects treated at Week M-0	25 (100.0%)	23 (100.0%)	48 (100.0%)
Subjects entered into substudy	5 (20.0%)	7 (30.4%)	12 (25.0%)
Discontinued study treatment through Week M-44	3 (12.0%)	2 (8.7%)	5 (10.4%)
Reason for termination			
Adverse event of worsening of Crohn's disease	1 (4.0%)	1 (4.3%)	2 (4.2%)
Adverse event other than worsening of Crohn's disease	0	0	0
Death	0	0	0
Lack of efficacy	0	0	0
Lost to follow-up	1 (4.0%)	0	1 (2.1%)
Non-compliance with study drug	0	0	0
Physician decision	1 (4.0%)	0	1 (2.1%)
Pregnancy	0	0	0
Initiated prohibited medication	0	0	0
Product quality complaint	0	0	0
Protocol deviation	0	0	0
Site terminated by sponsor	0	0	0
Study terminated by sponsor	0	0	0
Weight is less than 10 kg for 2 consecutive visits	0	0	0
Withdrawal by parent or guardian	0	1 (4.3%)	1 (2.1%)
Withdrawal by subject	0	0	0
Other	0	0	0
Covid-19 related	0	0	0

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

Conduct of the study

During the study, from Week I-0 through Week M-44 in the ERAS, 7 participants had a major protocol deviation:

- One participant received the wrong medication kit, subsequently determined to be placebo; participant returned to site and received the intended medication kit (with proper study intervention), without missing a dose or breaking the treatment blind.
- One participant-initiated rescue medication therapy prior to confirmation of loss of response; the incorrect Week I-8 PCDAI score was entered into IWRS resulting in the participant being incorrectly categorised in IWRS as an induction responder; treatment was not impacted.
- The remaining major PDs were related to either missing PCDAI diary information or missing laboratory results.

One participant enrolled under protocol version 5, had protocol deviation (past medical history of cytomegalovirus colitis) related to the exclusion criterion #15 (*medical history of or current*

nontuberculous mycobacterial infection or clinically significant opportunistic infection [e.g., pneumocystosis, invasive aspergillosis, progressive multifocal leukoencephalopathy] at any time). Subsequently, protocol version 6 was amended to remove a past cytomegalovirus colitis as an example of a clinically significant opportunistic infection and an exclusion criterion, as these are commonly described infections in the refractory IBD population.

Treatment Compliance

All participants from the ERAS (48 [100%]) received the scheduled IV induction dose at Week I-0 and received at least 1 SC dose of study intervention during the maintenance period. No participants missed any study intervention administration during the study.

Baseline data

Baseline demographic characteristics, with the exception of sex, were generally balanced across treatment groups in the ERAS (

Table *9*). The median age was 15.0 years (range 10 to 17 years). The majority of participants were white (44 [91.7%] of 48 participants) and male (27 [56.3%] of 48 participants). There was a greater proportion of males (69.6%) than females (30.4%) in the q8w treatment group. The median weight was 53.8 kg (range 41 to 85 kg) with BMI z-score median (range) -0.16 (-1.7; 4.1). However, some minor differences were observed:

- BMI z-score median for female was 0.17 (-0.7; 2.6) and -0.26 (-1.7; 4.1) for male.
- The greater proportion of males with the lower BMI-z-scores among males overall in this population (Becker 2015).

Table 9: Summary of Demographics at Baseline; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: EMA			
Randomized	25	23	48
Age, years			
N	25	23	48
Mean (SD)	14.7 (1.52)	14.7 (1.76)	14.7 (1.62)
Median	14.0	15.0	15.0
Range	(11; 17)	(10; 17)	(10; 17)
IQ range	(14.0; 16.0)	(14.0; 16.0)	(14.0; 16.0)
2-11 years	1 (4.0%)	1 (4.3%)	2 (4.2%)
2-5 years	0	0	0
6-11 years	1 (4.0%)	1 (4.3%)	2 (4.2%)
12-17 years	24 (96.0%)	22 (95.7%)	46 (95.8%)
Sex			
N	25	23	48
Female	14 (56.0%)	7 (30.4%)	21 (43.8%)
Male	11 (44.0%)	16 (69.6%)	27 (56.3%)
Race			
N	25	23	48
American Indian or Alaska Native	0	0	0
Asian	2 (8.0%)	1 (4.3%)	3 (6.3%)
Black or African American	1 (4.0%)	0	1 (2.1%)
Native Hawaiian or			

Other Pacific Islander	0	0	0
White	22 (88.0%)	22 (95.7%)	44 (91.7%)
Multiple	0	0	0
Weight, kg			
N	25	23	48
Mean (SD)	55.6 (13.65)	57.4 (11.98)	56.4 (12.77)
Median	47.8	55.4	53.8
Range	(41; 83)	(42; 85)	(41; 85)
IQ range	(45.0; 67.4)	(47.5; 61.8)	(45.5; 63.2)
≥40 kg	25 (100.0%)	23 (100.0%)	48 (100.0%)
≥40 - ≤55 kg	15 (60.0%)	11 (47.8%)	26 (54.2%)
>55 - ≤85 kg	10 (40.0%)	12 (52.2%)	22 (45.8%)
>85 kg	0	0	0
Body mass index, kg/m2			
N	25	23	48
Mean (SD)	19.8 (3.69)	20.3 (3.53)	20.0 (3.58)
Median	18.7	19.7	19.5
Range	(14; 29)	(16; 30)	(14; 30)
IQ range	(17.0; 22.9)	(18.4; 21.4)	(17.2; 21.7)
Underweight <18.5	12 (48.0%)	6 (26.1%)	18 (37.5%)
Normal 18.5-<25	11 (44.0%)	15 (65.2%)	26 (54.2%)
Overweight 25-<30	2 (8.0%)	1 (4.3%)	3 (6.3%)
Obese ≥30	0	1 (4.3%)	1 (2.1%)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Body mass index Z scorea			
N	25	23	48
Mean (SD)	0.01 (0.941)	0.18 (1.243)	0.09 (1.088)
Median	-0.26	0.08	-0.16
Range	(-1.7; 2.6)	(-1.3; 4.1)	(-1.7; 4.1)
IQ range	(-0.63; 0.76)	(-0.59; 0.55)	(-0.63; 0.67)

[a] Age and sex-specific

The clinical disease characteristics at baseline for the primary population were generally well balanced across treatment groups and are representative of a population with moderately to severely active Crohn's disease. Overall, at baseline:

- The median duration of Crohn's disease was 2.0 years.
- The median PCDAI score was 40.
- The median CDAI score was 365.30.
- The median SES-CD score was 11.5.
- The mean (SD) faecal calprotectin level was 3198.1 (3765.31) mg/kg.
- The mean (SD) CRP concentration was 25.73 (30.714) mg/L.

Faecal calprotectin was >250 µg/g in 91.5% of participants and CRP was >3 mg/L in 77.1% of participants. At baseline, 20 (64.5%) of 48 participants had received EEN therapy as a primary therapy for Crohn's disease.

Concomitant Crohn's disease medications for participants in the ERAS are presented in

Table *10*. The proportions of participants receiving concomitant Crohn's disease medications, including corticosteroids, immunomodulators, and aminosalicylates were generally well balanced across treatment groups. Among the EMA participants, at baseline:

- 72.9% were receiving Crohn's disease-related medications.
- 29.2% were receiving corticosteroids (including budesonide and beclomethasone dipropionate).
- 37.5% were receiving immunomodulators.
- 43.8% were receiving 5-aminosalicylates.

Table 10: Summary of Crohn's disease-related Concomitant Medications at Baseline; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: EMA Randomized	25	23	48
Any Crohn's disease-related Concomitant Medication	18 (72.0%)	17 (73.9%)	35 (72.9%)
Antibiotic	1 (4.0%)	0	1 (2.1%)
Corticosteroids	6 (24.0%)	8 (34.8%)	14 (29.2%)
Budesonide	3 (12.0%)	6 (26.1%)	9 (18.8%)
Beclomethasone dipropionate	1 (4.0%)	0	1 (2.1%)
Hydrocortisone	0	0	0
Methylprednisolone	0	2 (8.7%)	2 (4.2%)
Prednisolone	1 (4.0%)	0	1 (2.1%)
Prednisone	1 (4.0%)	0	1 (2.1%)
Other	0	0	0
Immunomodulatory drugs	9 (36.0%)	9 (39.1%)	18 (37.5%)
6-Mercaptopurine	0	0	0
Azathioprine	7 (28.0%)	8 (34.8%)	15 (31.3%)
Methotrexate	2 (8.0%)	1 (4.3%)	3 (6.3%)
5-Aminosalicylate (5-ASA)	11 (44.0%)	10 (43.5%)	21 (43.8%)

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

A total of 34 (70.8%) of 48 participants had a history of inadequate response, intolerance, or dependence to corticosteroids and immunomodulators (

Table *11*). Proportions were similar across treatment groups.

Table 11: Summary of Corticosteroid and Immunomodulator Prior Failure Status; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: EMA Randomized	25	23	48
Subjects with inadequate response, intolerance, or dependence to corticosteroids and/or 6-MP/AZA/MTX	17 (68.0%)	17 (73.9%)	34 (70.8%)
Corticosteroids			
Subjects with inadequate response, intolerance or dependence to corticosteroids	9 (36.0%)	12 (52.2%)	21 (43.8%)
Subjects with inadequate response	8 (32.0%)	10 (43.5%)	18 (37.5%)
Subjects intolerant	0	2 (8.7%)	2 (4.2%)
Subjects dependent	2 (8.0%)	6 (26.1%)	8 (16.7%)
Immunomodulators (AZA, 6-MP or MTX)			
Subjects with inadequate response or intolerance to immunomodulators (6-MP/AZA/MTX)	13 (52.0%)	10 (43.5%)	23 (47.9%)
Subjects with inadequate response	11 (44.0%)	9 (39.1%)	20 (41.7%)
Subjects intolerant	4 (16.0%)	2 (8.7%)	6 (12.5%)

A total of 19 (39.6%) of 48 participants had a history of biologic failure (

Table *12*). Proportions were similar across treatment groups.

Table 12: Summary of Crohn's disease-related Biologic Medication History; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab SC Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: EMA Randomized	25	23	48
Subjects without a history of biological failure	16 (64.0%)	13 (56.5%)	29 (60.4%)
Biologic-naive	15 (60.0%)	12 (52.2%)	27 (56.3%)
Biologic-experienced, but not documented failure	1 (4.0%)	1 (4.3%)	2 (4.2%)
Subjects with a history of biological failure	9 (36.0%)	10 (43.5%)	19 (39.6%)
Primary nonresponse, secondary nonresponse, or intolerance to			
Only anti-TNF (NOT to vedolizumab)	9 (36.0%)	9 (39.1%)	18 (37.5%)
Primary nonresponse	3 (12.0%)	3 (13.0%)	6 (12.5%)
Secondary nonresponse	7 (28.0%)	6 (26.1%)	13 (27.1%)
Intolerance	0	3 (13.0%)	3 (6.3%)
At least one anti-TNF (regardless of vedolizumab)	9 (36.0%)	10 (43.5%)	19 (39.6%)
Primary nonresponse	3 (12.0%)	4 (17.4%)	7 (14.6%)
Secondary nonresponse	7 (28.0%)	6 (26.1%)	13 (27.1%)
Intolerance	0	3 (13.0%)	3 (6.3%)
Any anti-TNF and vedolizumab	0	1 (4.3%)	1 (2.1%)
Primary nonresponse	0	1 (4.3%)	1 (2.1%)
Secondary nonresponse	0	0	0
Intolerance	0	0	0
Vedolizumab (regardless of anti-TNF)	0	1 (4.3%)	1 (2.1%)
Primary nonresponse	0	1 (4.3%)	1 (2.1%)
Secondary nonresponse	0	0	0
Intolerance	0	0	0

All participants used Crohn's disease medication prior to Week I-0.

A total of 31 (64.5%) of 48 participants previously received nutritional treatments for Crohn's disease. Of those participants who received nutritional therapies, exclusive enteral nutrition therapy was the most common therapy (64.5%), given to 20 of 31 participants as primary Crohn's disease therapy. Past dietary therapies were followed to improve Crohn's disease by 22 participants. The most frequently followed diet was Crohn's Disease Exclusion Diet (59.1%) and partial or total liquid diet (31.8%), followed by lactose free diet (18.2%) and gluten free diet (9.1%).

Numbers analysed

Population used for all efficacy analysis in this maintenance Week M-44 study report included 48 randomised participants with body weight ≥40 kg at Week I-0 and Week M-0, who received at least 1 administration of study intervention during maintenance and completed the Week M-44 visit or terminated the main study participation prior to Week M-44 (ERAS).

Outcomes and estimation

Primary endpoint

The primary endpoint (Global Primary Estimand 1) was clinical remission at Week I-8 defined as PCDAI score ≤10 points. At Week I-8, the number of participants who achieved clinical remission was 25 (52.1%) of 48 (95% CI: 38.3%, 65.5%) (**Table *13***). No ICEs were observed through Week I-8. Furthermore, due to completeness of the PCDAI data, the supplementary and sensitivity analyses produced identical results as the primary estimand. A total of 9 (18.8%) of 48 participants had 1 PCDAI sub score missing.

Table 13: Primary Endpoint Analysis (Global Primary Estimand 1): Number of Subjects in Clinical Remission at I-8; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab IV
Analysis set: EMA Randomized	48
Week I-8	
N	48
Subjects in clinical remission[a,b,c,d]	25 (52.1%)
95% CI for proportion of subjects in clinical remission[e]	(38.3%, 65.5%)

[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.

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 in clinical remission at Week I-8 was numerically greater in male participants (66.7% [18 of 27]) than in female participants (33.3% [7 of 21]).
- The proportion of participants in clinical remission at Week I-8 was 65.2% of participants with severe Crohn’s disease (PCDAI >40) and 40.0% with PCDAI scores lower than the severe cutoff value.
- The proportions of participants in clinical remission at Week I-8 were 62.1% in those without a history of failure to treatment with biologics (failed conventional therapy) at baseline and 36.8% in participants with history of biologic failures at baseline.

Other subgroups analyses inferences and comparisons are of limited value due to their very small sample size(s).

Secondary endpoints

Clinical remission at Week I-6 was defined as sPCDAI score of ≤10 points. At Week I-6, 21 (43.8%) of 48 participants (95% CI: 30.7%, 57.7%) achieved clinical remission (**Table *14***).

Clinical response was defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30. At Week I-8, 45 (93.8%) of 48 participants (95% CI: 83.2%, 97.9%) achieved clinical response (**Table *14***).

Clinical response was defined as a reduction from baseline in the sPCDAI score of ≥10. At Week I-6, 46 (95.8%) of 48 participants (95% CI: 86.0%, 98.8%) achieved clinical response (**Table *14***).

Endoscopic response at Week M-8* as assessed by SES-CD was evaluated 8 weeks after completion of induction period at Week M-8, to allow for adequate time for mucosal healing prior to repeat endoscopic assessment. Endoscopic response was 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-8, 14 (29.8%) of 47 participants (95% CI: 18.7%, 44.0%) achieved endoscopic response (**Table *14***).

Clinical response at Week M-8 was evaluated 8 weeks after the start of the maintenance period; however, the objective is to evaluate induction response and allow for an additional 8 weeks of treatment (to include M-8 delayed induction responders). At Week M-8, 43 (89.6%) of 48 participants (95% CI: 77.8%, 95.5%) achieved clinical response (**Table *14***).

Table 14: Summary of the Results of Secondary Endpoint Analyses (Global Secondary Estimand 1 to 5) through Week M-8; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab IV
Analysis set: EMA Randomized	48
Week I-6	
N	48
Subjects in clinical remission[a,b,c,d]	21 (43.8%)
95% CI for proportion of subjects in clinical remission[e]	(30.7%, 57.7%)
Week I-6	
N	48
Subjects in clinical response[i,b,j,k]	46 (95.8%)
95% CI for proportion of subjects in clinical response[e]	(86.0%, 98.8%)
Week I-8	
N	48
Subjects in clinical response[f,b,g,h]	45 (93.8%)
95% CI for proportion of subjects in clinical response[e]	(83.2%, 97.9%)
Subjects with baseline SES-CD score >= 3	47 (97.9%)
Week M-8	
N	47
Subjects in endoscopic response[l,b,m,n]	14 (29.8%)
95% CI for proportion of subjects in endoscopic response[e]	(18.7%, 44.0%)
Week M-8	
N	48
Subjects in clinical response[f,b,o,p]	43 (89.6%)
95% CI for proportion of subjects in clinical response[e]	(77.8%, 95.5%)

[a] Clinical remission is defined as sPCDAI 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-6 are considered not to be in clinical remission at Week I-6 (ie, composite strategy). Subjects with ICE 4 prior to Week I-6 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-6.

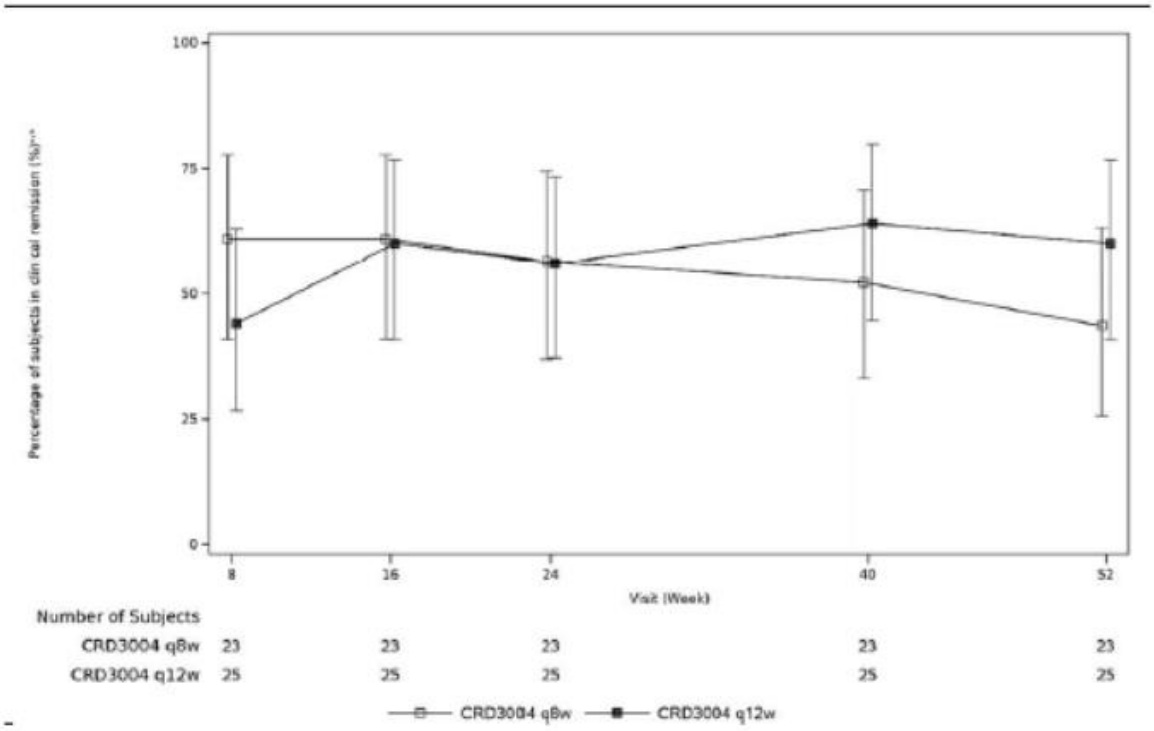
[e] The confidence intervals are based on the Wilson statistic.
[f] Clinical response is defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30.
[g] ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 are considered not to be in clinical response at Week I-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing clinical response data from the time of the event onward (ie, hypothetical strategy).
[h] After accounting for the ICEs, subjects who have missing clinical response are considered not to be in clinical response at Week I-8.
[i] Clinical response is defined as a reduction from baseline in the sPCDAI score of ≥10.
[j] ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-6 are considered not to be in clinical response at Week I-6 (ie, composite strategy). Subjects with ICE 4 prior to Week I-6 are considered to have missing clinical response data from the time of the event onward (ie, hypothetical strategy).
[k] After accounting for the ICEs, subjects who have missing clinical response are considered not to be in clinical response at Week I-6.
[l] 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.
[m] ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 are considered not to be in endoscopic response at Week M-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing endoscopic response data from the time of the event onward (ie, hypothetical strategy).
[n] After accounting for the ICEs, subjects who have missing endoscopic response are considered not to be in endoscopic response at Week M-8.

[o] ICEs strategies: Subjects with ICEs 1-3, and 5 prior to Week I-8 are considered not to be in clinical response at Week M-8 (ie, composite strategy). Subjects with ICE 4 prior to Week I-8 are considered to have missing clinical response data from the time of the event onward (ie, hypothetical strategy).
[p] After accounting for the ICEs, subjects who have missing clinical response are considered not to be in clinical response at Week M-8.

Maintenance Period

The proportion of participants who achieved clinical remission at Week I-8 was high over time through Week M-44 (**Figure *17***).

Figure 17: Line Plot of Percentage of Subjects Achieving Clinical Remission by Visit Through Week M-44 Among Subjects Weighing at Least 40kg; Full Analysis Set (Study CNTO1275CRD3004)



[a] Clinical remission is defined as a PCDAI score ≤10 points.
[b] 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.
Note: CRD3004 includes visits: Week I-8 (Week 8), M-8 (Week 16), M-16 (Week 24), M-32 (Week 40), and M-44 (Week 52).

At Week M-44, 25 (52.1%) of 48 participants (95% CI: 38.3%, 65.5%) achieved clinical remission (PCDAI score ⩽10 points) (

Table *15*). A total of 21 (43.8%) of 48 participants experienced at least one ICE through Week M-44. A total of 10 (20.8%) of 48 participants who had PCDAI scores ≤10 had at least 1 ICE, leading to a non-responder status at Week M-44. Of the 10 participants, 9 had the ICE of eligibility for dose adjustment. A total of 6 (12.5%) of 48 participants discontinued study intervention prior to Week M-44 and were missing PCDAI sub scores, thus their remission status was imputed as not in remission.

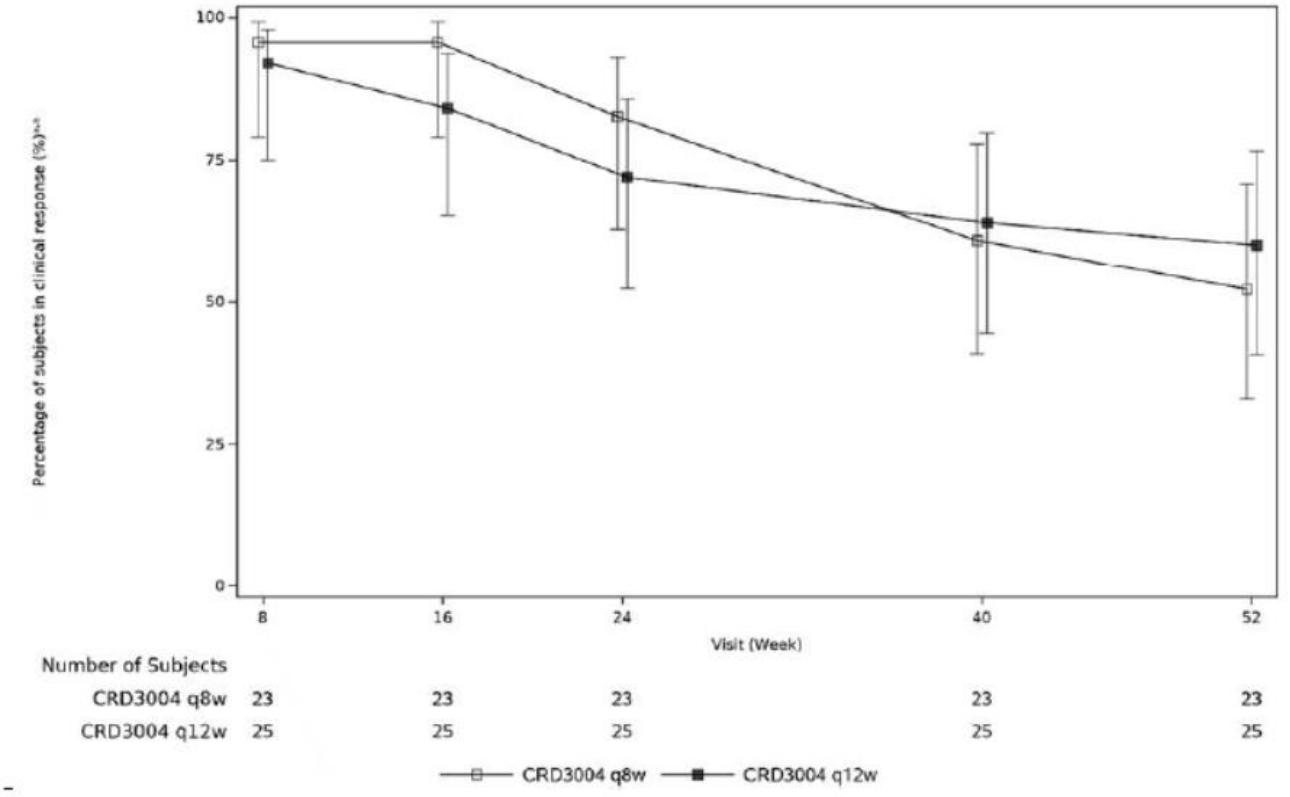
Endoscopic response at Week M-44 as assessed by SES-CD At Week M-44, 12 (25.5%) of 47 participants (95% CI: 15.3%, 39.5%) achieved endoscopic response (

Table *15*).

The proportion of participants who achieved clinical response at Week I-8 was high over time through Week M-44 (

Figure *18*).

Figure 18: Line Plot of Percentage of Subjects Achieving Clinical Response by Visit Through Week M-44 Among Subjects Weighing at Least 40kg; Full Analysis Set (Study CNTO1275CRD3004)



[a] 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] 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.

Note: CRD3004 includes visits: Week I-8 (Week 8), M-8 (Week 16), M-16 (Week 24), M-32 (Week 40), and M-44 (Week 52).

At Week M-44, 27 (56.3%) of 48 participants (95% CI: 42.3%, 69.3%) achieved clinical response (

Table *15*).

At Week M-44, 25 (52.1%) of 48 participants (95% CI: 38.3%, 65.5%) achieved corticosteroid free clinical remission (

Table *15*).

Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8 was, 6 (54.5%) of 11 participants (95% CI: 28.0%, 78.7%) in the q12w treatment group and 9 (64.3%) of 14 participants (95% CI: 38.8%, 83.7%) in the q8w treatment group achieved clinical remission (

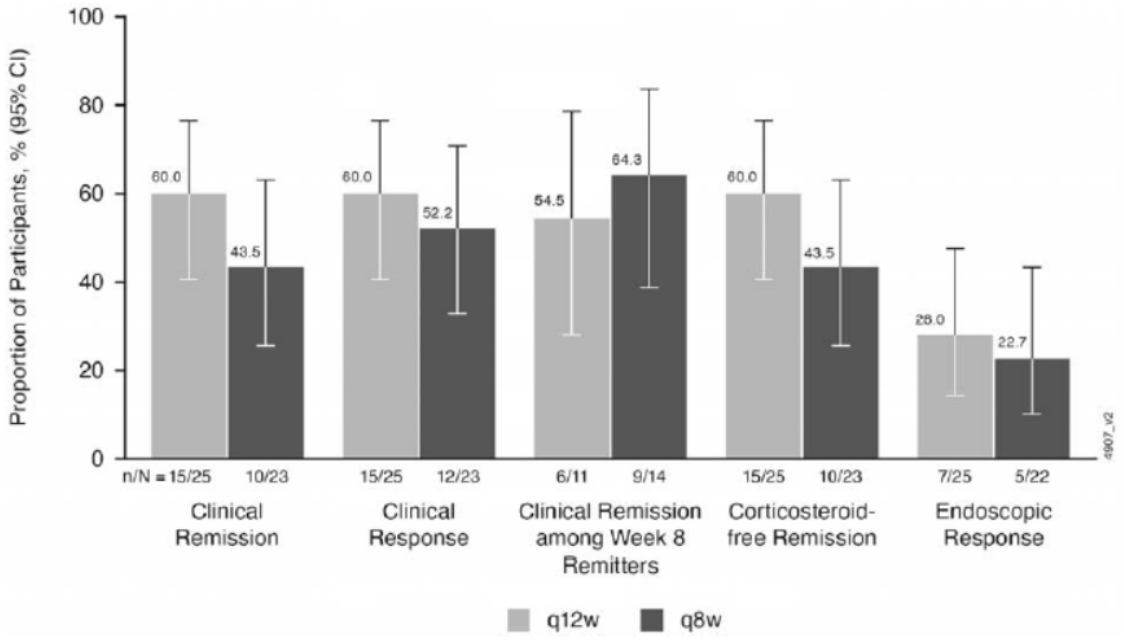
Table *15*).

Table 15: Summary of the Results of Secondary Endpoint Analyses (Global Secondary Estimand 6 to 10) through Week M-44; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: EMA Randomized	25	23	48
Week M-44			
N	25	23	48
Subjects in clinical remission[a,b,c,d]	15 (60.0%)	10 (43.5%)	25 (52.1%)
95% CI for proportion of subjects in clinical remission[e]	(40.7%, 76.6%)	(25.6%, 63.2%)	(38.3%, 65.5%)
Difference in proportion (95% CI)[f]		-16.5% (-44.4%, 11.4%)	
Subjects with baseline SES-CD score >= 3	25 (100.0%)	22 (95.7%)	47 (97.9%)
Week M-44			
N	25	22	47
Subjects in endoscopic response[g,b,h,i]	7 (28.0%)	5 (22.7%)	12 (25.5%)
95% CI for proportion of subjects in endoscopic response[e]	(14.3%, 47.6%)	(10.1%, 43.4%)	(15.3%, 39.5%)
Difference in proportion (95% CI)[f]		-5.3% (-30.1%, 19.6%)	
Week M-44			
N	25	23	48
Subjects in clinical response[j,b,k,l]	15 (60.0%)	12 (52.2%)	27 (56.3%)
95% CI for proportion of subjects in clinical response[e]	(40.7%, 76.6%)	(33.0%, 70.8%)	(42.3%, 69.3%)
Difference in proportion (95% CI)[f]		-7.8% (-35.9%, 20.2%)	
Week M-44			
N	25	23	48
Subjects in corticosteroid-free clinical remission[m,b,n,o]	15 (60.0%)	10 (43.5%)	25 (52.1%)
95% CI for proportion of subjects in corticosteroid-free clinical remission[e]	(40.7%, 76.6%)	(25.6%, 63.2%)	(38.3%, 65.5%)
Difference in proportion (95% CI)[f]		-16.5% (-44.4%, 11.4%)	
Subjects who are in clinical remission at Week I-8	11 (44.0%)	14 (60.9%)	25 (52.1%)
Week M-44			
N	11	14	25
Subjects in clinical remission at Week M-44 among those in clinical remission at Week I-8[a,b,c,d]	6 (54.5%)	9 (64.3%)	15 (60.0%)
95% CI for proportion of subjects in clinical remission[e]	(28.0%, 78.7%)	(38.8%, 83.7%)	(40.7%, 76.6%)
Difference in proportion (95% CI)[f]		9.7% (-28.9%, 48.4%)	

[a] Clinical remission is defined as PCDAI score ≤10 points.
[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 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).
[d] After accounting for the ICEs, subjects who have missing clinical remission data are considered not to be in clinical remission at Week M-44.
[e] The confidence intervals are based on the Wilson statistic.
[f] The confidence intervals are based on the Wald statistic.
[g] 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.
[h] ICEs strategies: Subjects that have ICEs 1-5, and 7 prior to Week M-44 are not considered to be in endoscopic response at Week M-44 (ie. composite strategy). Subjects with ICE 6 prior to Week M-44 are considered to have missing endoscopic response data from the time of the event onward (ie. hypothetical strategy).
[i] After accounting for the ICEs, subjects who have missing endoscopic response data are considered not to be in endoscopic response at Week M-44.
[j] 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.
[k] ICEs strategies: Subjects that have ICEs 1-5, and 7 prior to Week M-44 are not considered to be in clinical response at Week M-44 (ie. composite strategy). Subjects with ICE 6 prior to Week M-44 are considered to have missing clinical response data from the time of the event onward (ie, hypothetical strategy).
[l] After accounting for the ICEs, subjects who have missing clinical response data are considered not to be in clinical response at Week M-44.
[m] 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.
[n] ICEs strategies: Subjects that have ICEs 1-5, and 7 prior to Week M-44 are not considered to be in corticosteroid-free clinical remission at Week M-44 (ie, composite strategy). Subjects with ICE 6 prior to Week M-44 are considered to have missing corticosteroid-free clinical remission data from the time of the event onward (ie. hypothetical strategy).
[o] After accounting for the ICEs, subjects who have missing corticosteroid-free clinical remission data are considered not to be in corticosteroid-free clinical remission at Week M-44.

Figure 19: Summary of Secondary Endpoints Through Week M-44

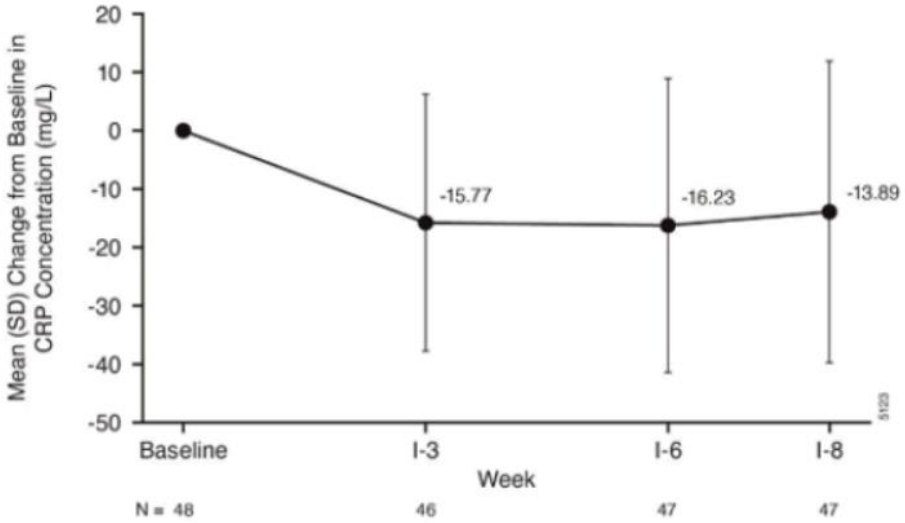


Tertiary endpoints

C-Reactive Protein

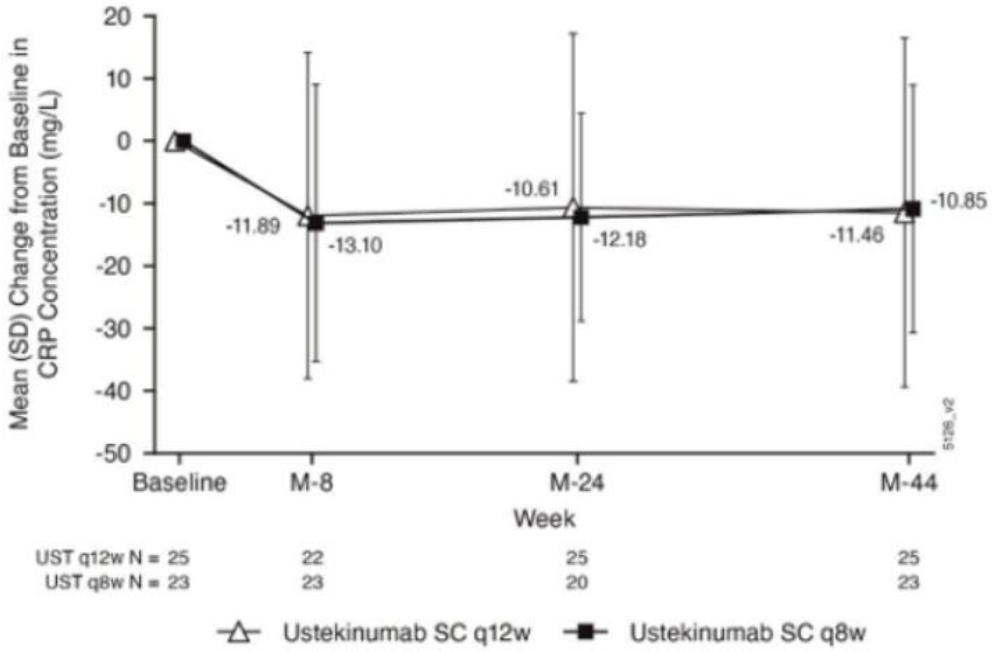
The mean change (SD) from baseline in CRP concentrations at Week I-8 was -13.89 mg/L (25.825) (**Figure *20***).

Figure 20: Mean Change from Baseline in CRP concentration through Week I-8



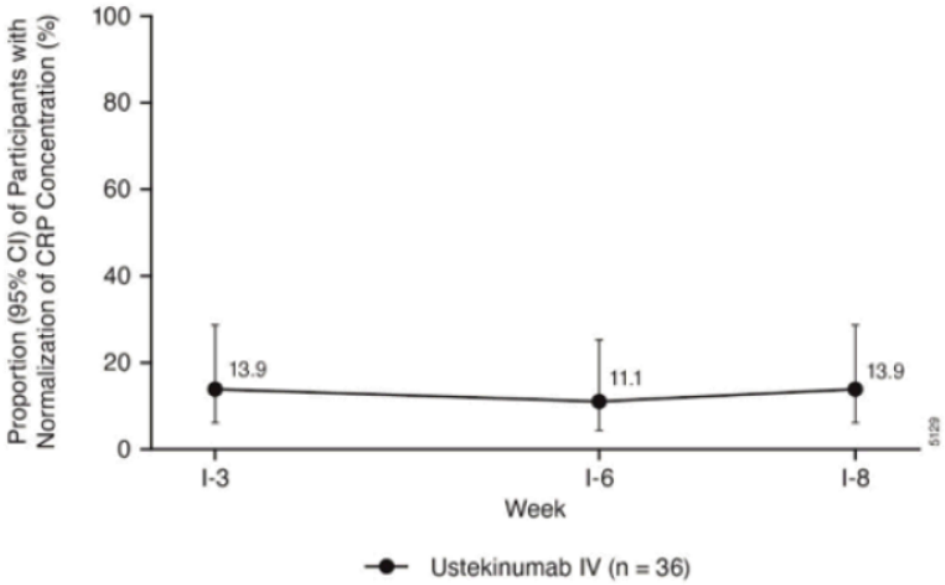
The decreases in CRP concentrations observed at Week M-0 (from baseline) were maintained through Week M-44 with a mean change (SD) in CRP concentrations of -10.85 mg/L (19.832) in q8w group and -11.46 mg/L (27.969) in q12w group (**Figure *21***).

Figure 21: Mean Change from Baseline in CRP concentration From Week M-0 Through M-44



At Week I-8, among 36 participants with elevated CRP levels (>3 mg/L) at baseline, 5 (13.9% [95% CI: 6.1%, 28.7%]) had normalised CRP levels (≤3 mg/L) (**Figure *22***).

Figure 22: Number of Subjects with Normalisation of CRP concentration (≤3 mg/L) Through Week I-8

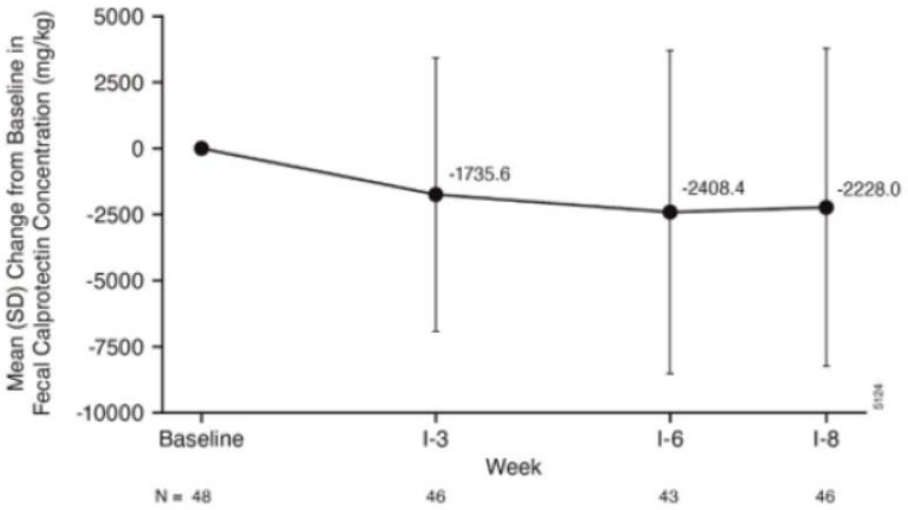


Among 36 participants with elevated CRP levels (>3 mg/L) at baseline, 2 (10.5%) of 19 participants in the q12w group and 3 (17.6%) of 17 participants in the q8w group had normalised CRP levels (≤3 mg/L) at Week M-44.

Faecal Calprotectin

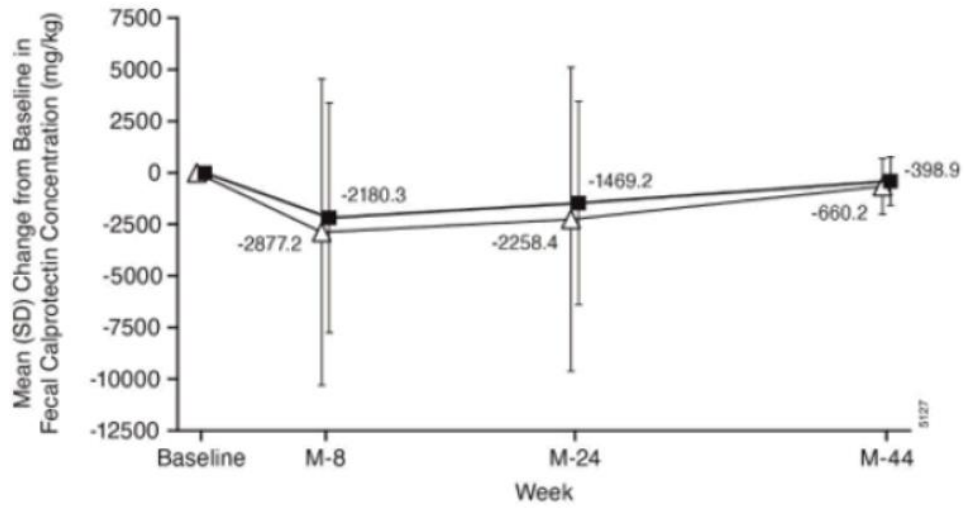
At Week I-8, the mean change (SD) from baseline in faecal calprotectin was -2228 mg/kg (6008) (**Figure *23***).

Figure 23: Mean Change from Baseline in Fecal Calprotectin Concentration through Week I-8



At Week M-44, the mean change (SD) from baseline in faecal calprotectin was -660.2 mg/kg (1358.2) in the q12w group and -398.9 mg/kg (1181.6) in the q8w group (**Figure *24***).

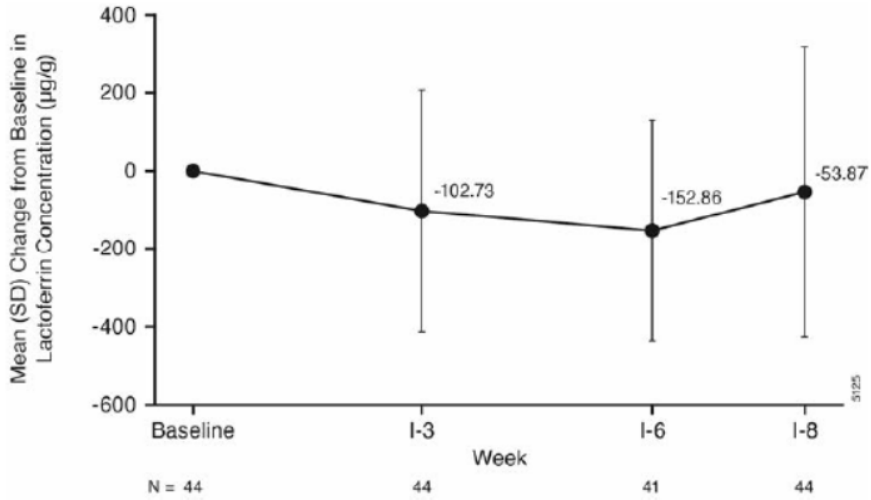
Figure 24: Mean Change from Baseline in Fecal Calprotectin Concentration From Week M-0 Through M-44



Lactoferrin

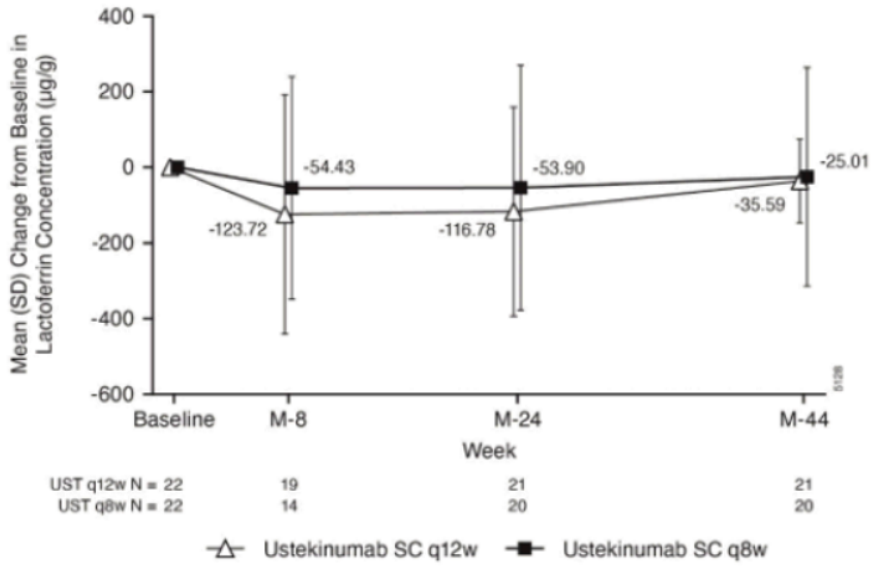
At Week I-8, the mean change (SD) from baseline in lactoferrin was -53.869 µg/g (371.9) (**Figure *25***).

Figure 25: Mean Change from Baseline in Lactoferrin Concentration through Week I-8



At Week M-44, the mean change (SD) from baseline in lactoferrin was -35.594 mg/kg (111.25) in the q12w group and -25.013 mg/kg (289.23) in the q8w group (**Figure *26***).

Figure 26: Mean Change from Baseline in Lactoferrin Concentration From Week M-0 Through M-44



Growth

At Week I-8, there was an increase from baseline in BMI z-scores mean (SD): females, 0.19 (0.241); males, 0.10 (0.321). At Week I-8, BMI z-scores for males ranged lower than -1.0.

At Week M-44 there was a small increase from baseline mean BMI z-scores, among males and females and across the q12w and q8w treatment group. At Week M-44, the BMI z-score in females was within the normal range (BMI z-score >-1), in the q12w treatment group and q8w treatment. However, compared

with females there was a greater proportion of males with the lower BMI z-scores, notably within the q12w treatment group, contributing to the numerically lower BMI z-scores and negative z-score values detected within the lower range of the q12w treatment group. The low z-score is an indication of mild malnutrition (defined as BMI z-score -1 to -1.9) among males overall and specifically within the q12w treatment group (Becker 2015).

Nutritional parameters

The mean (SD) Vit D concentration was 66.951 (33.3) nmol/L at baseline and 71.273 (32.96) nmol/L at Week M-44. At Week M-44, Vit D shifted from normal (≥20.0 ng/mL) to low (<20.0 ng/mL) for 9/27 participants. Note: the central laboratory reference normal range for 2 to18 years was ≥20.0 ng/mL.

Methylmalonic acid (MMA) values stayed normal (0-378 nmol/L) at Week M-44 for 27 participants, 2 participants had a shifted values from high to normal.

Iron serum values shifted from low to normal for 13 of 25 participants.

IMPACT-III Scores

The IMPACT-III total score ranges from 35 to 175 (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 good overall HRQoL. Alternatively, a lower score indicates that the disease has negatively affected patient HRQoL.

Table *16* presents IMPACT-III raw and transformed total score baseline values and change to Week M-44 for study CRD3004 (q12w, q8w and combined treatment groups). Raw mean change scores overall (i.e., increase by 20.6 points; SD 29.86) and for q12w and q8w indicate that HRQoL improved with ustekinumab treatment over 44 weeks (respectively, 11.4 points [SD 18.66] and 29.8 points [SD 36.18]).

Table 16: 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; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: EMA Randomized	25	23	48
Subjects ≥10 years of age at Week I-0	25 (100.0%)	23 (100.0%)	48 (100.0%)
IMPACT-III scores			
Baseline[a]			
N	22	19	41
Mean (SD)	102.6 (25.05)	98.6 (22.57)	100.7 (23.72)
Median	101.0	96.0	100.0
Range	(40; 143)	(63; 132)	(40; 143)
Week M-44 Change from baseline[b,c]			
N	18	18	36
Mean (SD)	11.4 (18.66)	29.8 (36.18)	20.6 (29.86)
Median	0.0	11.5	0.0
Range	(-3; 57)	(0; 96)	(-3; 96)
IMPACT-III Transformed[d] Scores			
Baseline[a]			
N	22	19	41
Mean (SD)	48.3 (17.89)	45.4 (16.12)	47.0 (16.95)
Median	47.1	43.6	46.4
Range	(4; 77)	(20; 69)	(4; 77)
Week M-44 Change from baseline[b,c]			
N	18	18	36
Mean (SD)	8.1 (13.33)	21.3 (25.84)	14.7 (21.33)
Median	0.0	8.2	0.0
Range	(-2; 41)	(0; 69)	(-2; 69)

Key: SD = standard deviation

[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.
[d] The transformed scores reflect the scoring methodology proposed by the instrument developer, analogous to that of the PedsQL 4.0). Scores were linearly transformed to a range of 0 to 100; total and domain scores were summed and divided by the number of items answered (Grant 2020).

Table *17*: Tertiary Endpoint Analysis: Summary of Change From Baseline in Three Domains of Impact-III Transformed Score at Week M-44 for Subjects at Least 10 years of Age at Week I-0; EMA Randomised Analysis Set (Study CNTO1275CRD3004)presents more clearly defined subdomains of the IMPACT-III, namely "patient-reported bowel symptoms", "fatigue-related systemic symptoms", and "well-being" (a previously validated parsimonious set of items defined by core symptoms and more proximal functional impairments). To aid in the interpretability of efficacy findings in HRQoL, key stakeholders have identified a 0.5 SD as reasonable threshold for establishing clinically meaningful improvement in HRQoL concepts (Homco 2019; Norman 2003). Mean change scores for the "combined" group indicated that all subdomains improved (exceeding 0.5 SD) with ustekinumab treatment over 44 weeks. Finally, mean subdomain improvements were comparable (range of 18.8 to 20.8) to the mean change observed for IMPACT-III transformed total score (14.7).

Table 17: Tertiary Endpoint Analysis: Summary of Change From Baseline in Three Domains of Impact-III Transformed Score at Week M-44 for Subjects at Least 10 years of Age at Week I-0; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Ustekinumab SC Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: EMA Randomized	25	23	48
Subjects ≥10 years of age at Week I-0	25 (100.0%)	23 (100.0%)	48 (100.0%)
Bowel Symptoms			
Baseline[a]			
N	22	19	41
Mean (SD)	45.1 (20.84)	37.0 (19.39)	41.4 (20.34)
Median	50.0	39.3	39.3
Range	(4; 75)	(4; 79)	(4; 79)
Week M-44 Change from baseline[b,c]			
N	18	18	36
Mean (SD)	10.1 (16.99)	27.6 (33.70)	18.8 (27.75)
Median	0.0	5.4	0.0
Range	(-4; 50)	(0; 82)	(-4; 82)
Systemic Symptoms			
Baseline[a]			
N	22	19	41
Mean (SD)	39.4 (23.74)	34.6 (21.56)	37.2 (22.60)
Median	37.5	25.0	33.3
Range	(0; 100)	(8; 75)	(0; 100)
Week M-44 Change from baseline[b,c]			
N	18	18	36
Mean (SD)	10.6 (19.76)	29.6 (32.99)	20.1 (28.48)
Median	0.0	16.7	0.0
Range	(-17; 50)	(0; 83)	(-17; 83)
Well-being scores			
Baseline[a]			
N	22	19	41
Mean (SD)	41.9 (20.87)	36.3 (19.39)	39.3 (20.14)
Median	43.8	35.4	39.6
Range	(4; 94)	(10; 79)	(4; 94)

	Ustekinumab SC Randomized at Week M-0		
	q12w	q8w	Combined
Week M-44 Change from baseline[b,c]			
N	18	18	36
Mean (SD)	13.2 (20.50)	28.5 (32.71)	20.8 (28.00)
Median	0.0	15.6	0.0
Range	(-6; 52)	(0; 85)	(-6; 85)

Key: SD = standard deviation

[a] Baseline is defined as the last observation prior to or at the time of the first study intervention.

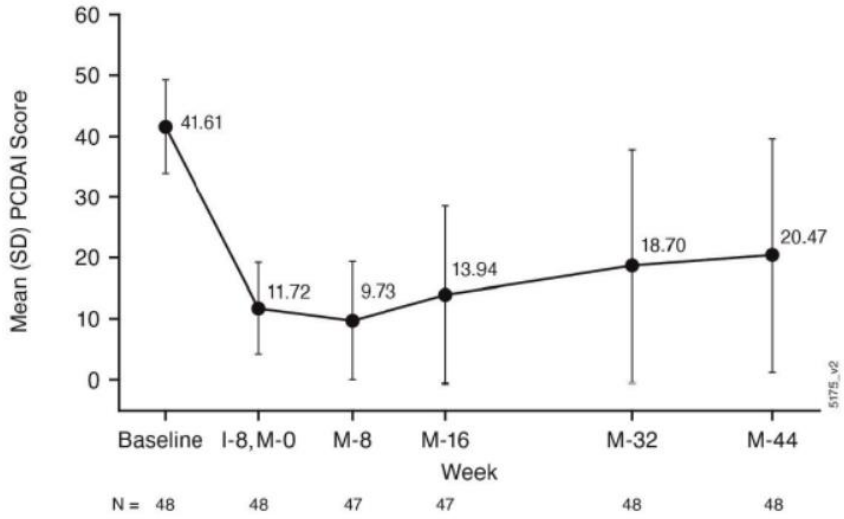
[b] ICEs include: (1) Subjects who had a Crohn's disease-related surgery thought to be a result of lack of efficacy of study intervention, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of Crohn's disease, (3) Had prohibited changes in Crohn's disease medications, (4) 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.

Change from Baseline in PCDAI Scores Over Time

Mean values of PCDAI scores through Week M-44 are presented in **Figure *27***. At Week M-44, improvements in mean change in PCDAI scores were similar between the CRD3004 q8w (-19.02 [19.273]) and q12w (-23.10 [20.275]) groups).

Figure 27: Mean values of PCDAI Scores Through M-44



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

At Week M-44, 8 (57.1%) of 14 participants who received corticosteroids at Week I-0 (95% CI: 32.6%, 78.6%) achieved clinical remission (PCDAI score ≤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

At Week M-8, 8 (17.0%) of 47 participants (95% CI: 8.9%, 30.1%) achieved endoscopic remission as assessed by SES-CD and 9 (19.6%) of 46 participants (95% CI: 10.7%, 33.2%) achieved endoscopic remission as assessed by SEMA-CD (**Table *18***). At Week M-44, 7 (14.9%) of 47 participants (95% CI: 7.4%, 27.7%) achieved endoscopic remission as assessed by SES-CD and 10 (21.7%) of 46 participants (95% CI: 12.3%, 35.6%) achieved endoscopic remission as assessed by SEMA-CD (**Table *18***).

Endoscopic response

At Week M-8, 14 (29.8%) of 47 participants (95% CI: 18.7%, 44.0%) achieved endoscopic response as assessed by SES-CD and 16 (34.8%) of 46 participants (95% CI: 22.7%, 49.2%) achieved endoscopic response as assessed by SEMA-CD (**Table *18***). At Week M-44, 12 (25.5%) of 47 participants (95% CI: 15.3%, 39.5%) achieved endoscopic response as assessed by SES-CD and 14 (30.4%) of 46 participants (95% CI: 19.1%, 44.8%) achieved endoscopic response as assessed by SEMA-CD (**Table *18***).

Clinical meaningful endoscopic improvement

At Week M-8, 29 (61.7%) of 47 participants (95% CI: 47.4%, 74.2%) achieved clinical meaningful endoscopic improvement as assessed by SES-CD and 24 (52.2%) of 46 participants (95% CI: 38.1%, 65.9%) achieved clinical meaningful endoscopic improvement as assessed by SEMA-CD (**Table *18***).

At Week M-44, 17 (36.2%) of 47 participants (95% CI: 24.0%, 50.5%) achieved clinical meaningful endoscopic improvement as assessed by SES-CD and 18 (39.1%) of 46 participants (95% CI: 26.4%, 53.5%) achieved clinical meaningful endoscopic improvement as assessed by SEMA-CD (**Table *18***).

Table 18: Number of Subjects in SEMA-CD and SES-CD Related Endpoints at Week M-8 and at Week M-44; EMA Randomised Analysis Set (Study CNTO1275CRD3004)

	Results: n (%) and 95% CI	
	SEMA-CD	SES-CD
Endoscopic Remission at Week M-8 N Percentage 95% CI	 46 9 (19.6%) (10.7%, 33.2%)	 47 8 (17.0%) (8.9%, 30.1%)
Endoscopic Remission at Week M-44 N Percentage 95% CI	 46 10 (21.7%) (12.3%, 35.6%)	 47 7 (14.9%) (7.4%, 27.7%)
Endoscopic Response at Week M-8 N Percentage 95% CI	 46 16 (34.8%) (22.7%, 49.2%)	 47 14 (29.8%) (18.7%, 44.0%)
Endoscopic Response at Week M-44 N Percentage 95% CI	 46 14 (30.4%) (19.1%, 44.8%)	 47 12 (25.5%) (15.3%, 39.5%)
Clinical meaningful Endoscopic improvement at Week M-8 N Percentage 95% CI	 46 24 (52.2%) (38.1%, 65.9%)	 47 29 (61.7%) (47.4%, 74.2%)
Clinical meaningful Endoscopic improvement at Week M-44 N Percentage 95% CI	 46 18 (39.1%) (26.4%, 53.5%)	 47 17 (36.2%) (24.0%, 50.5%)
Adapted from Attachment tefter17a; Attachment tefter17b.		

Endoscopic Improvement

At Week M-8, 9 (19.6%) of 46 participants (95% CI: 10.7%, 33.2%) 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, 8 (17.4%) of 46 participants (95% CI: 9.1%, 30.7%) achieved endoscopic improvement.

Fistula Related Endpoints Over Time

At Week I-8, 1 (33.3%) of 3 participants (95% CI: 6.1%, 79.2%) who had 1 or more fistulas at baseline achieved complete fistula response. At Week M-44, 1 (33.3%) of 3 participants (95% CI: 6.1%, 79.2%) who had 1 or more fistulas at baseline achieved complete fistula response.

Hospitalisations and Surgeries Over Time

At Week I-8, no participants had Crohn's disease-related hospitalisations or surgeries. At Week M-44, 2 (4.2%) of 48 participants (95% CI: 1.2%, 14.0%) had Crohn's disease-related hospitalisations (no participants had Crohn's disease-related surgeries).

Supplementary Analysis by Responder Status

Only 5 participants were delayed responders at Week M-8. **Table *19*** summarises the supplementary estimand analyses by responder status at Week M-44.

Table 19: Supplementary estimand analyses by responder status

Endpoint (Reference attachment)	Results		
	Ustekinumab SC		
	Clinical responders at Week M-0 (N=41)	Delayed responders at Week M-8 (N=5)	Combined (N=46)
Clinical Remission at Week M-44 (Attachment TEFSUP13)	23 (56.1%)	2 (40.0%)	25 (54.3%)
Endoscopic Response at Week M-44 (Attachment TEFSUP14)	11 (27.5%)	1 (20.0%)	12 (26.7%)
Corticosteroid-free Clinical Remission at Week M-44 (Attachment TEFSUP15)	23 (56.1%)	2 (40.0%)	25 (54.3%)
Clinical Response at Week M-44 (Attachment TEFSUP16)	25 (61.0%)	2 (40.0%)	27 (58.7%)

Adapted from Attachment tefsup13; Attachment tefsup14; Attachment tefsup15; Attachment tefsup16.

Baseline PCDAI score improved through Week I-8 and through M-44.

Supplementary Analysis Excluding COVID-19 Participants

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

Exposure Optimisation Substudy (EOS) Analyses

Five participants in the q12w arm and seven participants in the q8w arm entered the sub study. The overall efficacy results in these participants were as follows:

- The proportion of participants in clinical response at 16 weeks after entering the Substudy is 7 of 7 (100%) with a 95% CI of (64.6%, 100.0%).
- The proportion of participants in clinical remission at 16 weeks after entering the Substudy is 4 of 7 (57.1%) with a 95% CI of (25.0%, 84.2%).
- These data support the potential benefit of dose escalation to q4weeks in participants with low ustekinumab levels after 16 weeks of treatment, who have a loss of response.

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 20: Summary of efficacy for trial CNTO1275CRD3004

Title: A Phase 3 Study of the Efficacy, Safety, and Pharmacokinetics of Ustekinumab as Open label Intravenous Induction Treatment Followed by Randomized Double blind Subcutaneous Ustekinumab Maintenance in Pediatric Participants with Moderately to Severely Active Crohn's Disease			
Study identifier	Study CNTO1275CRD3004 EudraCT Number: 2019-004225-24		
Design	This is a Phase 3, multicenter interventional study consisting of an open-label induction period with a single IV ustekinumab induction dose followed by a maintenance period with a randomized, double-blind, parallel-group 2-arm study design, exploring 2 different SC ustekinumab maintenance dose regimens. Participants will be ages 2 to <18 years with moderately to severely active Crohn's disease (defined by a PCDAI score >30). Participants must have had an inadequate response and/or intolerance to biologic therapy (ie, TNFα antagonist or vedolizumab) and/or conventional therapies (ie, IV or oral corticosteroids or the immunomodulators AZA, 6-MP, and MTX) or be dependent upon corticosteroids.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 Weeks (8 weeks induction, 44 weeks maintenance) Up to 6 weeks screening period Variable
Hypothesis	Exploratory: efficacy is based on totality of evidence from primary and secondary endpoints		
Treatments groups *(maintenance phase)*	Ustekinumab q12w		Ustekinumab 90mg q12w, 44 weeks, 23 participants
	Ustekinumab q8w		Ustekinumab 90mg q8w, 44 weeks, 25 participants
Endpoints and definitions	Primary Efficacy Endpoint	Clinical Remission I-8	The primary endpoint is clinical remission at Week I-8.
	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.
	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.)
	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.
	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.
	Secondary Efficacy Endpoint	C-Free Clinical Remission M-44	Corticosteroid-free clinical remission at Week M-44.(PCDAI score ≤10 points and not receiving corticosteroids for at least 90 days prior to Week M-44)
	Secondary Efficacy Endpoint	Clinical Remission M-44 (I-8)	Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8.

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

Database lock	22 January 2024

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	An interim analysis to support the EMA submission was based on at least 36 randomized participants who had body weight ≥40 kg at Week I-0 and Week M-0 and had completed the Week M-44 visit or terminated study participation prior to Week M-44. For participants who entered the optional exposure-optimization sub-study (EOS), the data from the main study and the data from EOS will be summarized separately. Data were summarized using descriptive statistics. Continuous variables were summarized using the number of observations, mean, SD, median, IQ range, minimum and maximum, as appropriate. Categorical values were summarized 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 (eg, line plots) were also used to summarize the data.		
Descriptive statistics and estimate variability	Treatment group	Ustekinumab q12w	Ustekinumab q8w
	Number of subjects	25	23
	Primary Efficacy Endpoint		
	Clinical Remission I-8 (95% CI)	25/48 (52.1%) (38.3%, 65.5%)	
	Results of Secondary Endpoint Analyses through Week M-8		
	Clinical Remission I-6 (95% CI)	21/48 (43.8%) (30.7%, 57.7%)	

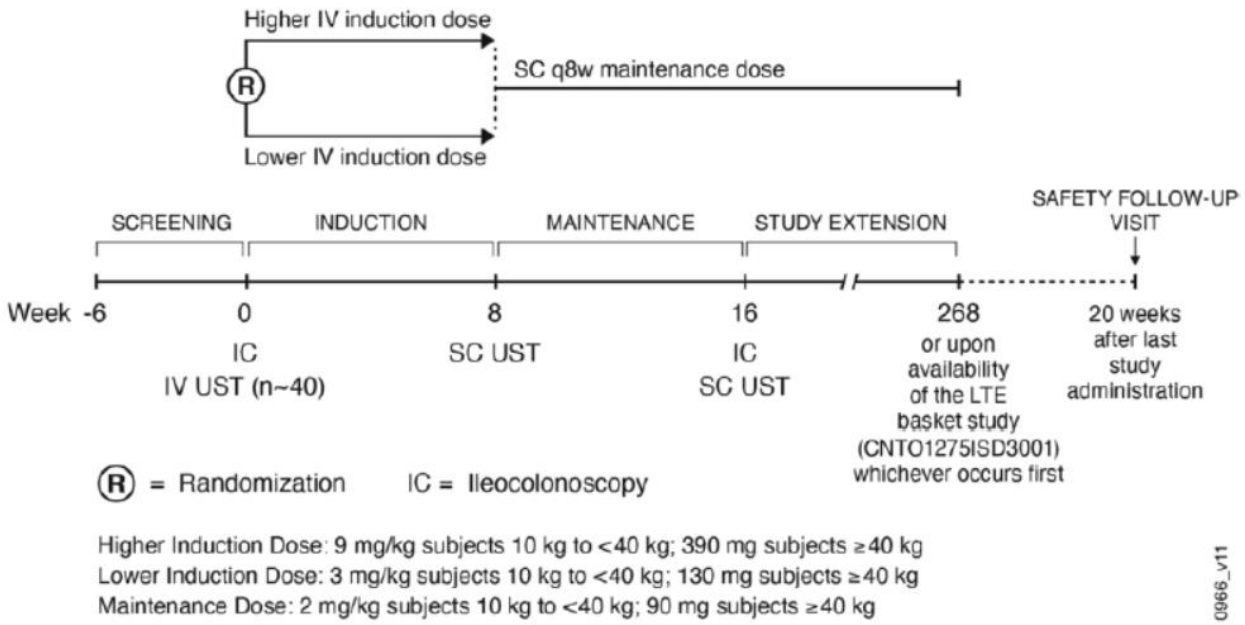
	Clinical Response I-8 (95% CI)	45/48 (93.8%) (83.2%, 97.9%)	
	Clinical Response I-6 (95% CI)	46/48 (95.8%) (86.0%, 98.8%)	
	Endoscopic Response M-8 (95% CI)	14/47 (29.8%) (18.7%, 44.0%)	
	Clinical Response M-8 (95% CI)	43/48 (89.6%) (77.8%, 95.5%)	
	Results of Secondary Endpoint Analyses through Week M-44		
	Clinical Remission M-44 (95% CI)	15/25 (60.0%) (40.7%, 76.6%)	10/23 (43.5%) (25.6%, 63.2%)
	Endoscopic Response M-44 (95% CI)	7/25 (28.0%) (14.3%, 47.6%)	5/22 (22.7%) (10.1%, 43.4%)
	Clinical Response M-44 (95% CI)	15/25 (60.0%) (40.7%, 76.6%)	12/23 (52.2%) (33.0%, 70.8%)
	C-Free Clinical Remission M-44 (95% CI)	15/25 (60.0%) (40.7%, 76.6%)	10/23 (43.5%) (25.6%, 63.2%)
	Clinical Remission M-44 (I-8) (95% CI)	6/11 (54.5%) (28.0%, 78.7%)	9/14 (64.3%) (38.8%, 83.7%)

2.4.2. 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

Figure 28: 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 *21***). 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 21: 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.

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 *22*).

Table 22: 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 21) 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 22) 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 *23***). Clinical response according to the alternative definition was 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 *23***). 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 *23***).

Table 23: 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

CRP

There is an imbalance between the low-induction dose group and high-induction dose group for CRP values at baseline (median [mean] values: 15.60 mg/L [25.88 mg/L] and 8.00 mg/L [20.12 mg/L]), respectively. The median (mean) change from baseline at Week 8 was -0.72 mg/L (-5.62 mg/L) for the low-induction dose group and -0.27 mg/L (-8.70 mg/L) for the high induction dose group. The median (mean) change from baseline at Week 16 was 0.00 mg/L (-3.74 mg/L) for the low-induction dose group and -0.82 mg/L (-7.07 mg/L) for the high induction dose group. Among 18 subjects in the low-induction dose group with abnormal CRP at baseline, 3 (16.7%) subjects achieved normalisation of CRP (≤3 mg/L) at Week 8. Among the 14 subjects in the high-induction dose group with abnormal CRP at baseline, 4 (28.6%) subjects achieved normalisation of CRP (≤3 mg/L) at Week 8. C-reactive protein normalisation was generally maintained through Week 16 for the low-induction and high-induction dose groups.

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 (mean) baseline CRP concentration was 10.43 (17.73) mg/L (study extension efficacy analysis set). The median (mean) CRP concentration at Week 48 was lower than that at baseline, with a median (mean) change from baseline of -0.58 (-7.47) mg/L. 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. Based on the post-hoc analysis of all subjects who entered the LTE, the median (mean) change from baseline at Week 48 was -0.46 (-6.11) mg/L (**Table *24***). The proportion of subjects with abnormal CRP levels at baseline was 70.6% (24/34 subjects) (study extension efficacy analysis set). The effect of ustekinumab observed during the randomised, double-blind period was maintained during the LTE period, with >50% of the subjects with abnormal baseline values having achieved normalisation at the Week 48 and subsequent visits.

Table 24: 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.

Faecal lactoferrin

The median (mean) faecal lactoferrin concentration at baseline was 231.85 µg/g (276.67 µg/g) and 122.79 µg/g (222.65 µg/g) for subjects in the low-induction dose group and the high-induction dose group, respectively. The median (mean) change from baseline at Week 8 was 0.00 µg/g (-26.45 µg/g) and 0.00 µg/g (-4.50 µg/g) for subjects in the low-induction dose group and the high-induction dose group, respectively. At Week 16, the median (mean) change from baseline was 0.00 µg/g (-27.98 µg/g) and 0.00 µg/g (-56.38 µg/g) for subjects in the low-induction dose group and the high-induction dose group, respectively. Among 22 subjects in the low-induction dose group and 20 subjects in the high-induction dose group with abnormal levels of faecal lactoferrin at baseline, 1 (4.5%) subject in the low-induction dose group and 1 (5.0%) subject in the high-induction dose group achieved normalisation of faecal lactoferrin (≤7.24 µg/g) at Week 8. At Week 16, 2 (9.1%) subjects in the low-induction dose group and 2 (10.0%) subjects in the high-induction dose group achieved normalisation of faecal lactoferrin (≤ 7.24 µg/g).

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. In line with the observations for the efficacy analysis set, baseline faecal lactoferrin concentrations in the study efficacy analysis set were high, with a median (mean) value of 163.54 (252.83) µg/mL. The median (mean) faecal lactoferrin concentration at Week 48 was lower than that at baseline, with a median (mean) change from baseline of -106.08 (-143.73) µg/mL. 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. Based on the post-hoc analysis of all subjects who entered the LTE, the median (mean) change from baseline at Week 48 was -48.44 (-72.69) µg/mL (Table 24).

Faecal calprotectin

The median (mean) faecal calprotectin concentration at baseline was 2907.00 mg/kg (4978.17 mg/kg) and 1814.00 mg/kg (2627.16 mg/kg) for subjects in the low-induction dose group and the high-induction dose group, respectively. The median (mean) change from baseline at Week 8 was 0.00 mg/kg (-1703.70 mg/kg) and -37.00 mg/kg (-870.05 mg/kg) for subjects in the low-induction dose group and the high-induction dose group, respectively. The median (mean) change from baseline at Week 16 was 0.00 mg/kg (-2269.65 mg/kg) and 0.00 mg/kg (-570.47 mg/kg) for subjects in the low-induction dose group and the high-induction dose group, respectively. Among 21 subjects in the low-induction dose group and 16 subjects in the high-induction dose group with abnormal levels of faecal calprotectin at baseline, 1 (4.8%) subject in the low induction group and 2 (12.5%) subjects in the high-induction group achieved normalisation of faecal calprotectin (≤250 mg/kg) at Week 8. At Week 16, 3 (14.3%) subjects in the low-induction dose group and 1 (6.3%) subject in the high-induction dose group achieved normalisation of faecal calprotectin (≤250 mg/kg).

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. In line with the observations for the efficacy analysis set, baseline faecal calprotectin concentrations in the study extension efficacy analysis set were high, with a median (mean) value of 2,026.00 (4,160.53) mg/kg. The median (mean) faecal calprotectin

concentration at Week 48 was lower than that at baseline, with a median (mean) change from baseline of -1,011.00 (-2,014.38) mg/kg. Although numbers of remaining subjects at the subsequent visits were small, this effect was maintained after the Week 48 visit in subjects who continued to participate in the study. Based on the post-hoc analysis of all subjects who entered the LTE, the median (mean) change from baseline at Week 48 was -805.00 (-2,655.15) mg/kg (Table 24).

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 25).

Table 25: 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 *26*).

Table 26: 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 *27*). 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 27: 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.

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.

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 *28*).

Table 28: 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

IMPACT-III is a paediatric HRQOL measure specifically developed to assess the HRQOL in subjects with IBD. This questionnaire is validated in subjects 10 to 18 years of age. A higher IMPACT-III score indicates a better HRQOL; a change towards a higher score indicates improvement.

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.

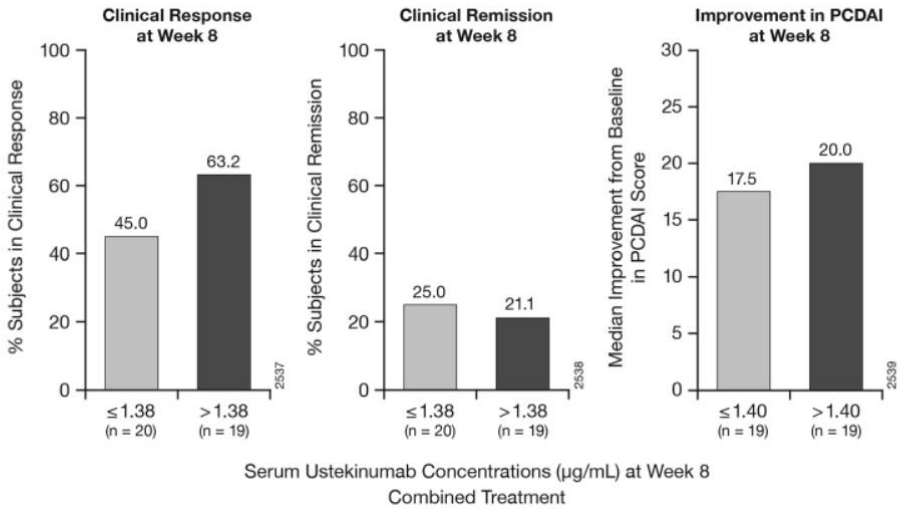
Pharmacokinetic/Pharmacodynamic Relationships

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 29: Bar Chart of Clinical Responses, 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.

2.4.3. 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

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 would be utilised.
- Having at least one ICN visit prior to or at the time of the ICN visit when ustekinumab was 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 *29***).

Table 29: 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:

Figure 30: 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.	

Figure 31: 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

Figure 32: Objectives and Endpoints

Objective	Endpoint
Primary Objective 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 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.	

Endpoints

- Clinical remission at Week 52.
- Clinical response at Week 52.
- 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 hospitalisations. 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

NA

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).

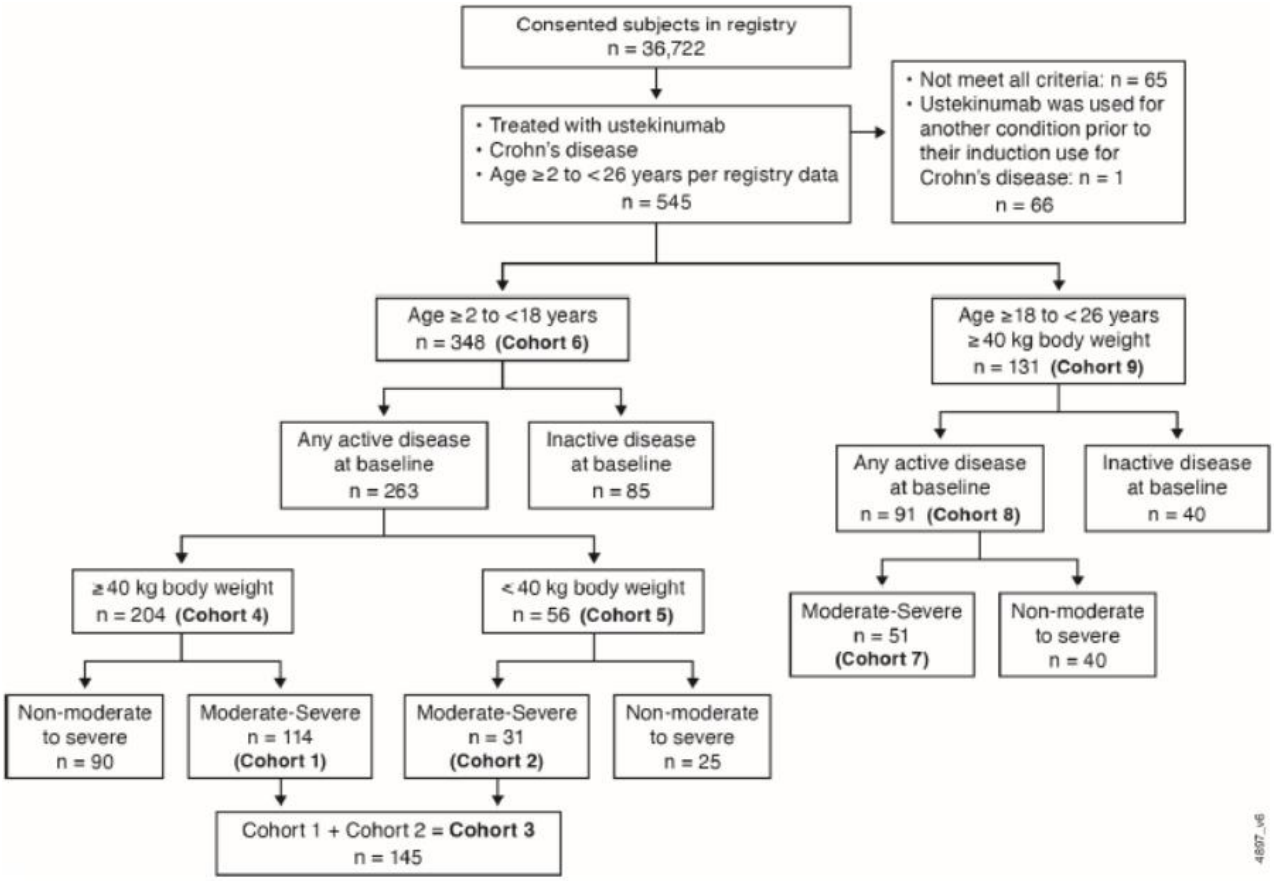
Results

Participant flow

A flowchart shows the number of patients included in this study (

Figure *33*: Study Population Flowchart). 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 33: 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. 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".

Overall, the proportion of patients who discontinued ustekinumab were modest and similar in the Paediatric Patients (Primary Cohort; 25.4%) and the Young Adults (Reference; Cohort 7: 25.5%) (**Table *30***).

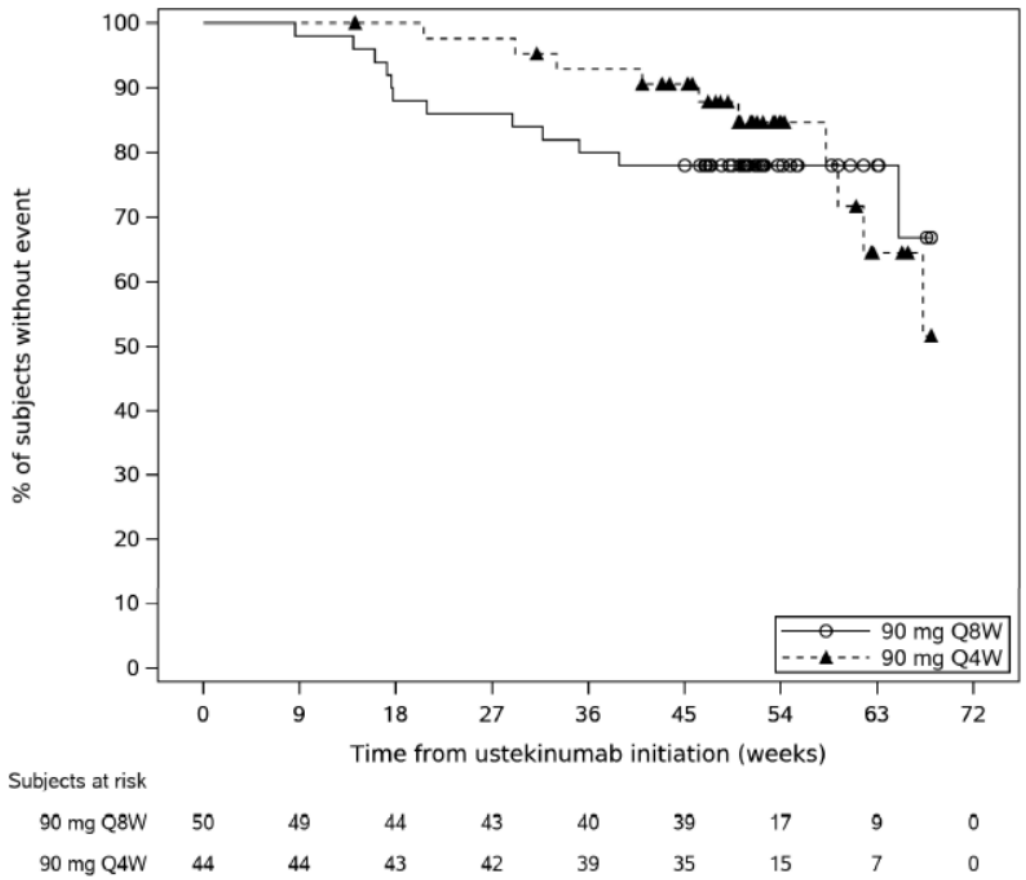
Table 30: Number of Subjects Who Discontinued Ustekinumab Treatment Through Week 52; Primary Cohort and Cohort 7 Full Analysis Set (Study CNTO1275CRD3010

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

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 34. 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, suggesting that a subgroup of patients may benefit from escalation to 90 mg q4w 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).

Figure 34: 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)



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.

Baseline data

Baseline demographic data for the Paediatric Patients (Primary Cohort) and Young Adults (Reference; Cohort 7) are provided in

Table *31*. Within both the Paediatric Patient and Young Adult cohorts there were a group of patients with weight and BMI z-scores suggestive of malnutrition (the lower quartile z-scores ≤-1).

Table 31: Summary of Baseline Demographics; Primary Cohort and Cohort 7 Full Analysis Set (Study CNTO1275CRD3010)

	Pediatric Patients (Primary Cohort)	Young Adults (Cohort 7)
Analysis set: primary cohort full analysis set	114	51
Age at ustekinumab initiation, years		
N	114	51
Mean (SD)	15.4 (1.52)	19.0 (1.22)
Median	16.0	19.0
Range	(11; 17)	(18; 23)
IQ range	(15.0; 16.0)	(18.0; 19.0)
2 - <12 years	4 (3.5%)	0
2 - <6 years	0	0
6 - <12 years	4 (3.5%)	0
12 - <18 years	110 (96.5%)	0
18 - <26 years	0	51 (100.0%)
Sex		
N	114	51
Female	58 (50.9%)	32 (62.7%)
Male	56 (49.1%)	19 (37.3%)
Race		
N	114	51
American Indian or Alaska Native	0	0
Asian	1 (0.9%)	0
Black or African American	9 (7.9%)	3 (5.9%)
Native Hawaiian or other Pacific Islander	0	0
White	93 (81.6%)	43 (84.3%)
Other	4 (3.5%)	3 (5.9%)
Unknown	7 (6.1%)	2 (3.9%)

Weight at baseline, kg		
N	114	51
Mean (SD)	57.61 (14.385)	61.61 (14.482)
Median	54.55	58.60
Range	(40.1; 128.5)	(41.3; 115.5)
IQ range	(45.60; 64.30)	(51.20; 69.80)
Weight z-score at baseline		
N	113	40
Mean (SD)	-0.09 (1.208)	-0.40 (1.374)
Median	0.03	-0.28
Range	(-3.3; 3.0)	(-3.6; 2.5)
IQ range	(-1.00; 0.79)	(-1.26; 0.66)
Height z-score at baseline		
N	112	40
Mean (SD)	-0.11 (1.041)	-0.28 (0.920)
Median	-0.15	-0.38
Range	(-2.2; 2.3)	(-2.4; 2.2)
IQ range	(-0.85; 0.53)	(-0.89; 0.18)
Body mass index z-score at baseline		
N	112	40
Mean (SD)	-0.13 (1.356)	-0.41 (1.406)
Median	0.02	-0.36
Range	(-5.2; 2.7)	(-4.2; 2.3)
IQ range	(-1.13; 0.91)	(-1.28; 0.73)

Key: CD = Crohn's disease; IQ = interquartile
Note: N is the number of subjects with non-missing values for each parameter.
Note: Index date is defined as the date of the first dose of ustekinumab.
Note: Baseline value is defined as the non-missing measurement closest to the index date within the baseline window (ie, from -12 weeks to +2 weeks from the index date).
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

Baseline Disease Characteristics

At baseline, the Crohn’s disease characteristics indicated that the Paediatric Patients (Primary Cohort) were a bio-refractory patient population with moderately to severely active Crohn’s Disease.

The Crohn’s disease characteristics were generally similar to that of the young adult reference cohort with the exception that the primary cohort had a shorter disease duration, 3.99 years (IQR: 2.52,5.79) v 6.2 years (IQR: 3.56, 9.75) and a greater proportion of Young Adults (Reference: Cohort 7) had structuring Crohn's disease

Table *32*.

Table 32: Summary of Baseline Disease Characteristics; Primary Cohort and Cohort 7 Full analysis Set (Study CNTO1275CRD3010)

	Pediatric Patients (Primary Cohort)	Young Adults (Cohort 7)
N	114	51
Age at diagnosis, median (IQR), years	11 (9.0;13.0)	12 (9.0;15.0)
Crohn's disease duration median (IQR), years	3.99 (2.42; 5.79)	6.20 (3.56; 9.75)
Lower GI (ileocolonic) disease	76 (66.7%)	39 (76.5%)
Crohn's disease phenotype at ustekinumab induction		
– Stricturing only	10 (8.8%)	9 (17,6%)
– Penetrating only	10 (8.8%)	10 (2.0%)
sPCDAI score at baseline (median)	40.0	45.0
sPCDAI score at baseline (>40 [severe])	55 (48.2%)	27 (52.9%)
SEMA-CD score, Median (IQR) at baseline (N=38)	8.5 (5.0; 13.0)	6.5 (3.0; 9.0)
Receiving corticosteroids at baseline	68 (59.6%)	33 (64.7%)
Number of prior unique biologics used:	99.1%	
– Prior biologic therapy.	61.5%	96.1%
– Exposed to ≥2 biologics.	26.3%	54.9%
– Failed anti-integrin therapy (vedolizumab)		23.5%

Key: CD = Crohn's disease; IQ = interquartile; GI = gastrointestinal; sPCDAI = short pediatric Crohn's disease activity index; PCDAI = pediatric Crohn's disease activity index; disease; PGA = physician's global assessment

[a] Disease history, medication history for prior exposure to biologics, and prior surgeries are assessed using data from all visits prior to or on the index date.

Note: N is the number of subjects with non-missing values for each parameter.

Note: Index date is defined as the date of the first dose of ustekinumab.

Note: Baseline value is defined as the non-missing measurement closest to the index date within the baseline window (ie, from -12 weeks to +2 weeks from the index date), unless otherwise specified.

Note: Baseline sPCDAI is defined as the highest complete or partial sPCDAI score within the baseline window.

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.

Dosing

The route of the first induction dose for the Paediatric Patients (Primary Cohort) for 108 (94.7%) of 114 patients was IV. A majority of the patients (104 [93.7%] of 111) 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 (Primary Cohort).

A total of 94 (89.5%) of 105 patients in the Paediatric Patients (Primary Cohort) received an initial maintenance dose of ustekinumab of 90 mg q8w. A majority of the patients (96 [91.4%] of 105) 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 50 (49.0 %) of 102 patients in the Paediatric Patients (Primary Cohort) received a final maintenance dose of ustekinumab of 90 mg q8w. Approximately half of the patients (58 [56.9%] of 102) 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. By Week 52, the proportion of patients in the Paediatric Patients (Primary Cohort) receiving 90 mg q8w declined from 89.5% to 49.0%, while the proportion of patients in the Paediatric Patients (Primary Cohort) receiving 90 mg q4w increased from 6.7% to 43.1%. A dose escalation occurred in approximately 40 % of Paediatric Patients (Primary Cohort). In the Young Adults (Reference; Cohort 7), the proportion of participants receiving the q4w dose regimen increased from 5 of 49 (10.2%) for the initial maintenance dose to 9 of 47 (19.1%) for the Week 52 maintenance dose. A dose escalation occurred in a smaller proportion (15%) of Young Adults (Reference; Cohort 7) than the Paediatric Patients (Primary Cohort).

Outcomes and estimation

Primary Endpoint: Patients in Clinical Remission at Week 52

At Week 52, in the Paediatric Patients (Primary Cohort; ≥2 to <18 years and weight ≥40 kg at baseline), 26 (22.8%) of 114 patients were in clinical remission. The 95% CI for the proportion of patients in clinical remission is (16.1%, 31.3%) (Table 33), and the 90% CI for the proportion of patients in clinical remission is (17.0%, 29.9%).

Table 33: Primary Endpoint Analysis (Primary Estimand): Number of Subjects in Clinical Remission at Week 52; Primary Cohort Full Analysis Set (Study CNTO1275CRD3010)

	Total
Analysis set: primary cohort full analysis set	114
Week 52	
N	114
Subjects in clinical remission[a,b,c]	26 (22.8%)
95% CI for proportion of subjects in clinical remission[d]	(16.1% , 31.3%)

Key: CI = confidence interval; sPCDAI = short pediatric Crohn's disease activity index
[a] Clinical remission is defined as sPCDAI ≤ 10.
[b] 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.
[c] After accounting for ICEs, subjects who had missing clinical remission status at Week 52 are considered not to be in clinical remission.
[d] The 95% CI is estimated based on the Wilson method.
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: 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.

There were 45 (39.5%) of 114 patients in the Paediatric Patients (Primary Cohort) who had at least one ICE prior to or on Week 52. There were 10 (8.8%) of 114 patients who had sPCDAI ≤10 and were in clinical remission at Week 52 but were considered treatment failure due to at least one ICE prior to or on Week 52. This includes 4 (3.5%) of 114 patients who discontinued ustekinumab while in remission and were therefore coded as treatment failures (Table 34).

Table 34: Number of Subjects Who Experienced Intercurrent Events; Primary Cohort Full Analysis Set (Study CNTO1275CRD3010)

	Total
Analysis set: primary cohort full analysis set	114
Subjects who had at least one ICE prior to or on Week 52	45 (39.5%)
IBD-related surgery	9 (7.9%)
Discontinuation of ustekinumab	19 (16.7%)
Increase above baseline in corticosteroids or new corticosteroids within 90 days prior to endpoint assessment	21 (18.4%)
Initiation of AZA, 6-MP, or MTX after baseline within 90 days prior to endpoint assessment	9 (7.9%)
Initiation of cyclosporine, tacrolimus, or biologic agents	1 (0.9%)
Subjects who had sPCDAI ≤10 at Week 52 and had at least one ICE prior to or on Week 52	10 (8.8%)
IBD-related surgery	4 (3.5%)
Discontinuation of ustekinumab	4 (3.5%)
Increase above baseline in corticosteroids or new corticosteroids within 90 days prior to endpoint assessment	6 (5.3%)
Initiation of AZA, 6-MP, or MTX after baseline within 90 days prior to endpoint assessment	0
Initiation of cyclosporine, tacrolimus, or biologic agents	1 (0.9%)

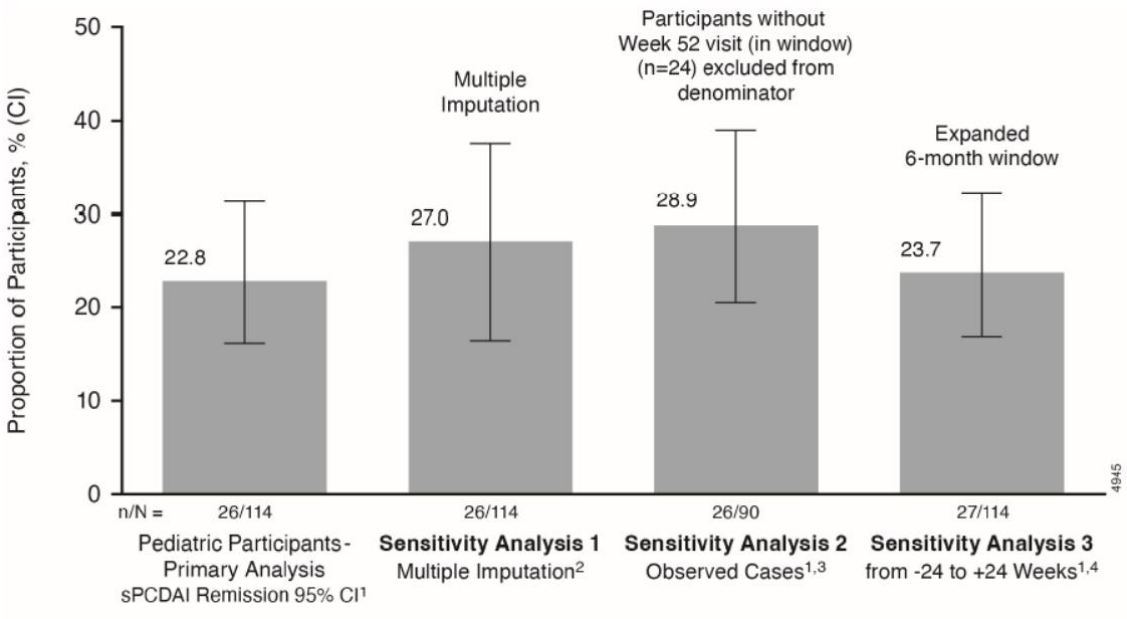
Key: ICE = Intercurrent events.
Note: subjects may have more than one intercurrent event.

The proportion of patients in clinical remission in the Young Adults (Reference; Cohort 7) was 21.6% (95% CI: 12.5%, 34.6%), similar to that of the Paediatric Patients (Primary Cohort), described further below.

Clinical Remission in Paediatric Patients (Primary Cohort) at Week 52

Three sensitivity analyses: (1) multiple imputation, (2) by observed cases, and (3) widening visit window from -24 to +24 weeks (for Week 52 visit) were conducted and demonstrated similar proportions of Paediatric Patients (Primary Cohort) with moderately to severely active Crohn's disease achieving clinical remission at Week 52 (Figure 35). These sensitivity analyses illustrate the robust nature of the data for the Paediatric Patients (Primary Cohort) shown in Table 33.

Figure 35: Clinical Remission at Week 52



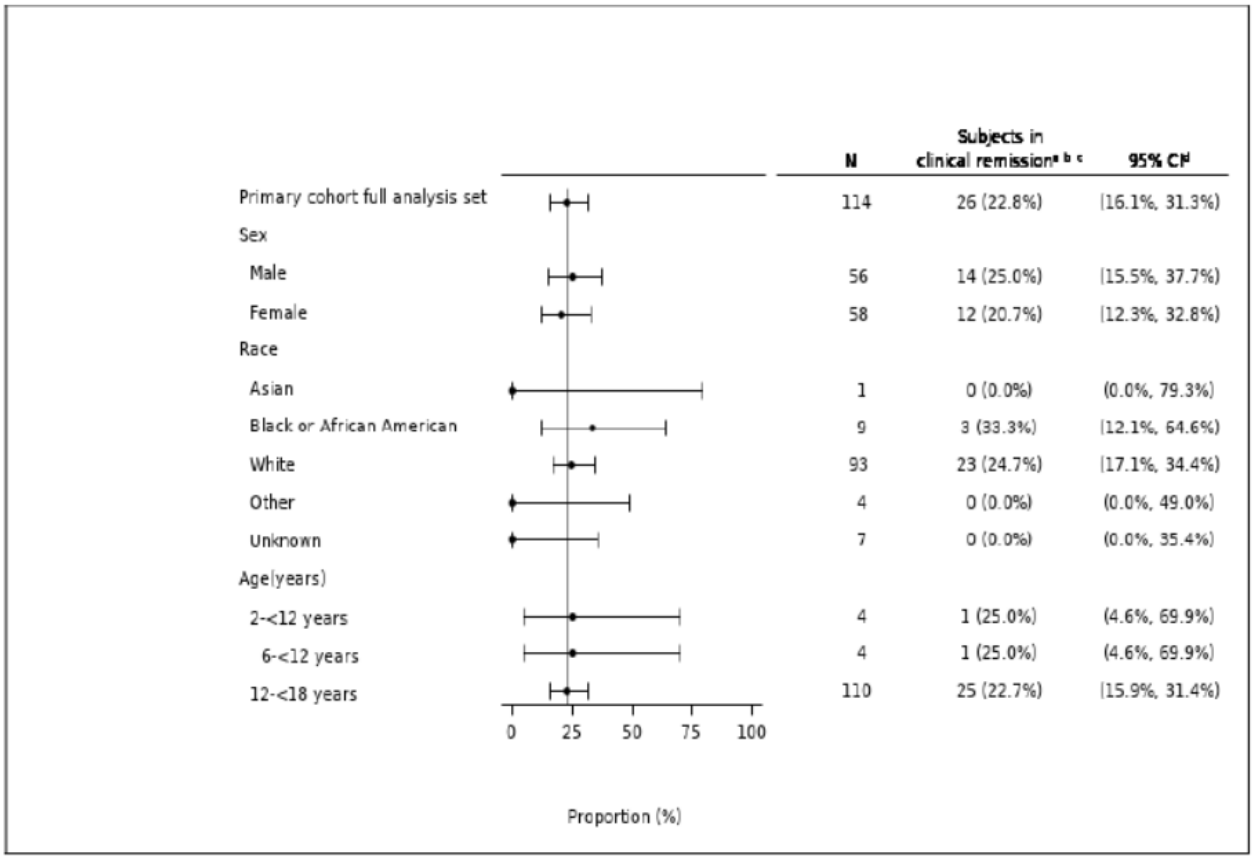
1 The CI is estimated based on the Wilson method.
2 After accounting for ICEs, missing clinical remission status at Week 52 are handled using the multiple imputation approach. The Rubin's combination rules are used to combine results from imputed data to obtain estimates of the proportion of participants in clinical remission and the associated 95% CI.
3 N is the number of participants who initiated ustekinumab. Participants who had missing clinical remission status at Week 52 after accounting for ICEs are excluded.
4 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 -24 to +24 weeks from Week 52).

Subgroup Analyses

Forest plots showing the number of patients in clinical remission by baseline demographics and baseline clinical characteristics for the Paediatric Patients (Primary Cohort) are provided in

Figure *36*. The proportion of treated patients in clinical remission was similar across all races, sexes, and ages; however, the small sizes of the subgroups preclude any conclusions. The proportion of patients in clinical remission were also generally similar across baseline medication groups, and numerically lower in those who had received ≥3 prior biologics.

Figure 36: Primary Endpoint Analysis: Number of Subjects in Clinical Remission at Week 52 by Baseline Demographics and Baseline Clinical Characteristics: Primary Cohort Full Analysis Set (CNTO1275CRD3010)



Totality of Evidence Comparisons

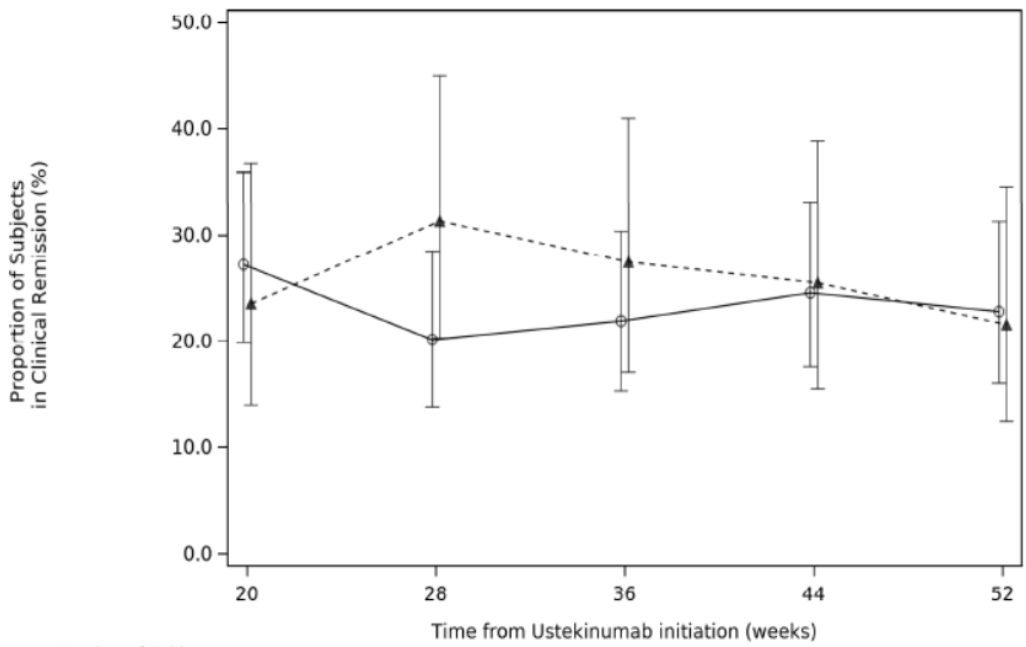
The evaluation of the effectiveness of ustekinumab in a real-world setting is based on the totality of evidence. A meta-analysis of clinical remission proportions was originally suggested to obtain a threshold for comparison based on adult placebo data. However, the original specified selection criteria for the adult studies for the meta-analysis did not yield any viable adult studies to compare with as no adult Crohn's disease study has a placebo-period beyond induction. Therefore, 3 alternative methods below were suggested to be used to assess the effectiveness of ustekinumab of the Paediatric Patients (Primary Cohort).

Totality of Evidence Comparison 1: Young Adults (Reference, Cohort 7)

Comparison 1 evaluates the proportion of patients treated with ustekinumab in clinical remission in the Paediatric Patients (Primary Cohort) to that of the Young Adults (Reference; Cohort 7), a population in which ustekinumab is already approved. At Week 52, the proportion of paediatric patients weighing ≥40 kg at baseline in the Paediatric Patients (Primary Cohort) achieving clinical remission was 26 (22.8% [95% CI: 16.1%, 31.3%]) of 114 patients and was comparable with the proportion of patients (11 [21.6% {95% CI: 12.5%, 34.6%}] of 51) achieving clinical remission in the Young Adults (Reference; Cohort 7) with moderately to severely active Crohn's disease (Figure 38). The 90% CI for the proportion of patients in clinical remission is (13.7%, 32.3%). The sensitivity analysis of number of patients in clinical remission at Week 52 using observed cases showed similar results.

A line plot of the number of patients in clinical remission over time by cohort for the Paediatric Patients (Primary Cohort) and Young Adults (Reference; Cohort 7) demonstrated that the proportion of patients in clinical remission over time were generally similar between the Paediatric Patients (Primary Cohort) and Young Adults (Reference; Cohort 7); **Figure *37***.

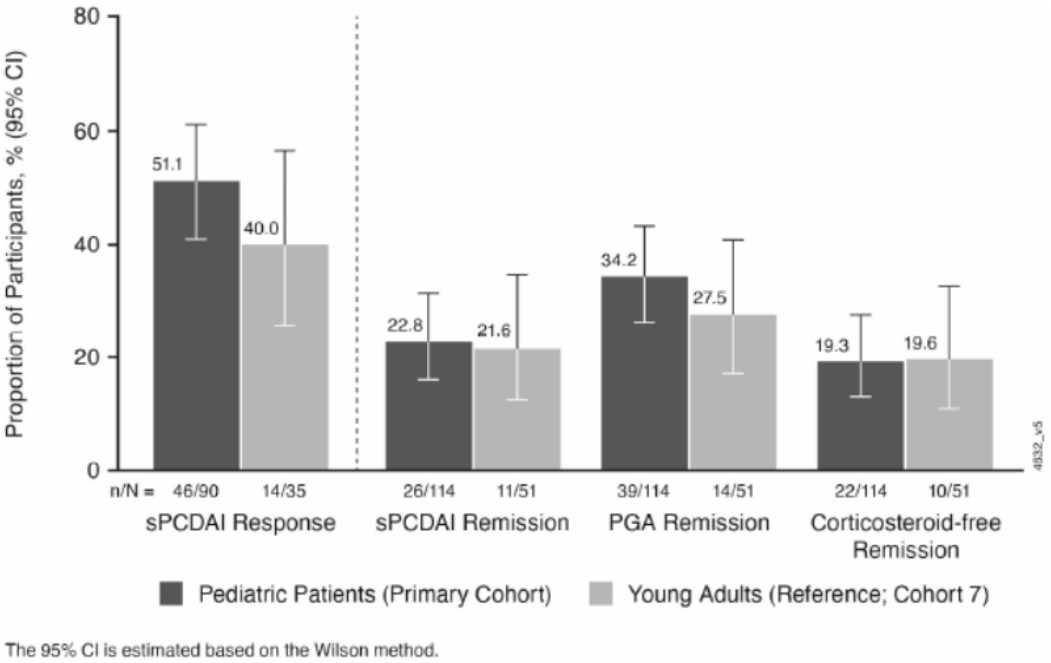
Figure 37: Ad-hoc Analysis: Line Plot of Number of Subjects in Clinical Remission Over Time by Cohort; Primary and Cohort 7 Full Analysis Set (Study CNTO1275CRD3010)



Note: Clinical remission is defined as sPCDAI ≤ 10.
Note: N is Number of subjects who initiated ustekinumab. The window for Week X is defined as [X*7-111, X*7+112].
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 CD 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 the endpoint assessment date, (d) initiation of AZA, 6-MP, or MTX within 90 days prior to endpoint assessment date, or (e) initiation of cyclosporine, tacrolimus, or biologic agents prior to the date of clinical remission assessment or the date of ustekinumab discontinuation.
Note: All patients who initiated treatment and did not discontinue the study at Week X are included for that week. Patients who neither have any ICEs nor have sufficient information on sPCDAI to determine remission status algebraically are considered as non-responders at Week X.
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 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: The 95% CI is estimated based on the Wilson method.

A consistent trend for the effectiveness endpoints between the Paediatric Patients (Primary Cohort) and Young Adults (Reference; Cohort 7) across remission and response rates was observed: sPCDAI clinical remission, PGA clinical remission, corticosteroid-free clinical remission, and clinical response (Figure 38).

Figure 38: Clinical Remission and Response at Week 52 in Participants with Moderately to Severely Active Crohn's Disease in Study CRD3010



The 95% CI is estimated based on the Wilson method.

There were 20 (39.2%) of 51 patients in the Young Adults (Reference: Cohort 7) who had at least one ICE prior to or on Week 52. There were 6 (11.8%) of 51 patients who had sPCDAI ≤10 at Week 52 and had at least one ICE prior to or on Week 52 (Table 35). The most common ICE in patients with a sPCDAI ≤10 at Week 52 (5 [9.8%] of 51 patients) was discontinuation of ustekinumab (Table 35).

Table 35: Number of Subjects Who Experienced Intercurrent Events; Cohort 7 Full Analysis Set (Study CNTO1275CRD3010)

	Total
Analysis set: cohort 7 full analysis set	51
Subjects who had at least one ICE prior to or on Week 52	20 (39.2%)
IBD-related surgery	5 (9.8%)
Discontinuation of ustekinumab	10 (19.6%)
Increase above baseline in corticosteroids or new corticosteroids within 90 days prior to endpoint assessment	5 (9.8%)
Initiation of AZA, 6-MP, or MTX after baseline within 90 days prior to endpoint assessment	8 (15.7%)
Initiation of cyclosporine, tacrolimus, or biologic agents	0
Subjects who had sPCDAI ≤10 at Week 52 and had at least one ICE prior to or on Week 52	6 (11.8%)
IBD-related surgery	2 (3.9%)
Discontinuation of ustekinumab	5 (9.8%)
Increase above baseline in corticosteroids or new corticosteroids within 90 days prior to endpoint assessment	2 (3.9%)
Initiation of AZA, 6-MP, or MTX after baseline within 90 days prior to endpoint assessment	2 (3.9%)
Initiation of cyclosporine, tacrolimus, or biologic agents	0

Key: ICE = Intercurrent events.
Note: subjects may have more than one intercurrent event.

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

Comparison 2 compares the clinical remission proportion in the Paediatric Patients (Primary Cohort) to the proportion of placebo participants in clinical remission observed in the adult ustekinumab Studies CNTO1275CRD3003 (IMUNITI) that includes the maintenance portion of the induction studies CNTO1275CRD3001 (biologic-failure population) and CNTO1275CRD3002 (biologic-naive population). All participants who received placebo at induction were included in the analysis with clinical remission status at Week 52 determined as follows: obtained directly from CNTO1275CRD3003 study for the induction responders who continued on placebo during maintenance or assumed as not achieved at Week 52 for the induction non-responders.

After determining the clinical remission status as mentioned above, only data from CNTO1275CRD3001 (biologic-failure population) were included in the final analysis to obtain the proportion of adult participants on placebo in clinical remission at Week 52 since all but one Paediatric Patient in the Primary Cohort failed treatment with a prior biologic. At Week 52, a larger proportion of Paediatric Patients (Primary Cohort) (moderately to severely active) achieved clinical remission: 26 (22.8% [95% CI: 16.1%, 31.3%]) of 114 patients; Table 33) compared with the proportion of adults with moderately to severely active Crohn's disease on placebo participating in Study CNTO1275CRD3001 (19 [7.7% {95% CI: 5.0%, 11.7%}] of 247 patients) (**Table *36***).

This comparison suggests the effectiveness of ustekinumab in treating paediatrics patients with moderately to severely active Crohn's disease since the lower limit of the 2-sided 95% CI for the proportion of Paediatric Patients (Primary Cohort) in clinical remission at Week 52 (16.1%) is greater than the upper limit of the 2-sided 95% CI for the proportion of adult placebo in clinical remission in Studies CNTO1275CRD3001/CNTO1275CRD3003 (11.7%) (Table 36; Figure 39).

Figure 39: Proportion of Paediatric Patients (Primary Cohort) in Remission Compared with Adult Patients with Crohn's Disease on Placebo

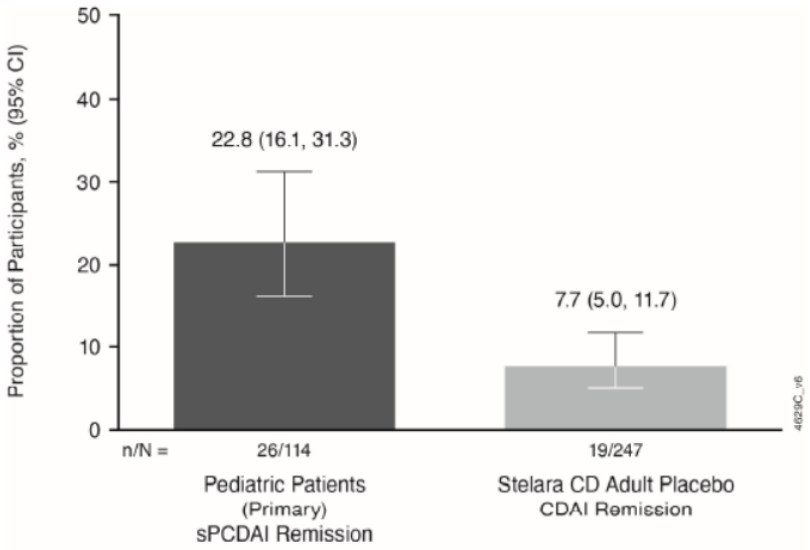


Table 36: Number of Adult Subjects on Placebo in Clinical Remission at Week 52 in CNTO1275CRD3003 study; (Study CNTO1275CRD3010)

	CNTO1275CRD3001 and /3003
N	247
Subjects in clinical remission[a,b]	19 (7.7%)
95% CI for proportion of subjects in clinical remission[c]	(5.0%, 11.7%)
90% CI for proportion of subjects in clinical remission[c]	(5.3%, 11.0%)

Key: CI = confidence interval.
a Clinical remission in CNTO1275CRD3003 is defined as CDAI < 150. 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 be in clinical remission, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission.
b Clinical remission status at week 52 is obtained from the CNTO1275CRD3003 study.
c The 95% CI is estimated based on the Wilson method.
Note: CNTO1275CRD3003 includes the maintenance portion of studies CNTO1275CRD3001 [biologic-failure population] and CNTO1275CRD3002 [biologic-naïve population]. Only subjects from CNTO1275CRD3001 are included in the summary since the observed proportion of patients who were prior biologic failure in the Primary cohort of the current study is greater than 95%.

Totality of Evidence Comparison 3: Data from Meta-analysis

The initial adult placebo inclusion criteria did not identify any eligible, completed, treat-through studies. Consequently, the meta-analysis was conducted using more expansive inclusion criteria for study selection. The broader criteria identified 12 studies with biologic-failure populations. However, all 12 studies had placebo treatment duration of 6 to 12 weeks (Meta-analysis Report). Notably, substantial heterogeneity was shown between studies, with 2 studies exerting significant influence on the overall analysis. Therefore, the meta-analysis was conducted with the full set of 12 studies and using a subset of 10 studies, excluding the 2 outlier studies.

The pooled proportion of patients on placebo in clinical remission at Week 52 using all 12 studies was 13.9% (95% CI: 9.6% to 19.8%) (Figure 40 Panel A, Figure 41). The sensitivity analysis with 10 studies results in a lower estimate of the proportion of patients in clinical remission of 11.2% (95% CI: 8.4% to 14.8%) (Figure 40 Panel B). This comparison revealed that the lower limit of the 2-sided 95% CI for the proportion of Paediatric Patients (Primary Cohort) achieving clinical remission at Week 52 (16.1%) did not surpass the upper limit of the 2-sided 95% CI for the proportion of patients on placebo achieving clinical

remission at Week 52 in the primary meta-analysis (19.8%) but did exceed the upper limit of the 2-sided 95% CI for the sensitivity meta-analysis (14.7%).

Figure 40: Proportion of Paediatric Patients in Remission Compared with Adults

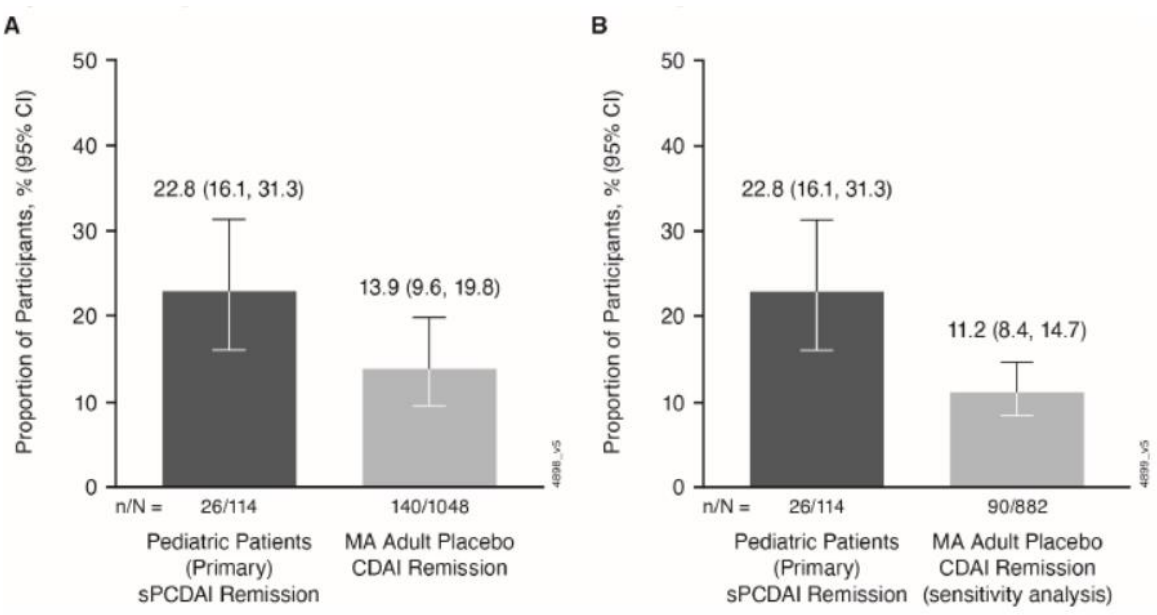
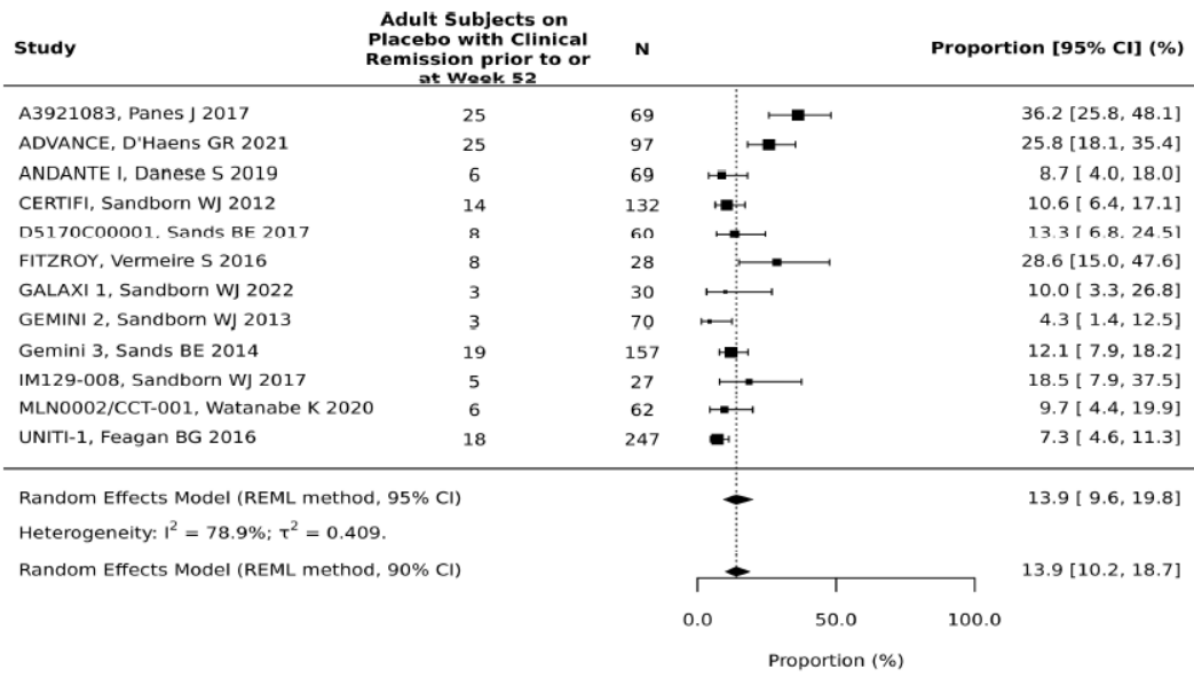
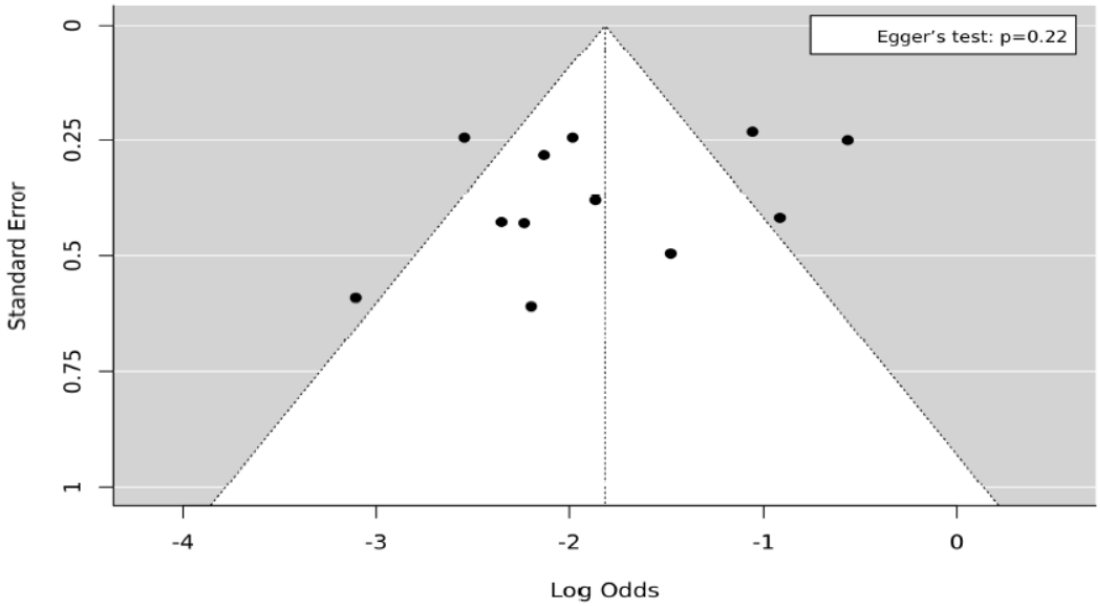


Figure 41: Forest Plot of Number of Adult Subjects on Placebo in Clinical Remission Prior to or at Week 52 by Meta-analysis; (Study CNTO1275CRD3010)



Visual inspection of the funnel plot (Figure 42) 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 and potential bias. Although the Egger's regression test for publication bias is not statistically significant (p-value of 0.22), the inconsistency between the visual inspection of the funnel plot and the Egger's test for the publication bias might be due to a small sample size (only 12 studies included in the meta-analysis).

Figure 42: Funnel Plot of Studies Used in the Meta-Analysis; (Study CNTO1275CRD3010)



Clinical Response

At Week 52, 46 (51.1% [95% CI: 41.0%, 61.2%]) of 90 patients in the Paediatric Patients (Primary Cohort) (observed cases), were in clinical response. At Week 52, the proportion of patients in clinical response were numerically higher in the Paediatric Patients (Primary Cohort) compared with the Young Adult (Reference; Cohort 7); Table 37.

Table 37: *Ad-hoc* Other Endpoint Analysis: Number of Subjects in Clinical Response at Week 52 (Observed Cases); Primary Cohort and Cohort 7 Full Analysis Set (Study CNTO1275CRD3010)

	Pediatric Patients (Primary Cohort)	Young Adults (Reference; Cohort 7)
Analysis set:	114	51
Week 52		
N	90	35
Subjects in clinical response[a,b]	46 (51.1%)	14 (40.0%)
95% CI for proportion of subjects in clinical response[c]	(41.0%, 61.2%)	(25.6%, 56.4%)

Key: CI = confidence interval; sPCDAI = short pediatric Crohn's disease activity index
[a] Clinical response is defined as a reduction from baseline in the sPCDAI ≥ 10.
[b] Subjects who had intercurrent events (ICEs) are considered not to be in clinical response: (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.
[c] The 95% CI is estimated based on the Wilson method.
Note: N is the number of subjects who initiated ustekinumab. Subjects who had missing clinical response status at Week 52 after accounting for ICEs are excluded.
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: 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.
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.

Clinical Remission by Ustekinumab induction by dose bands

The proportion of patients in clinical remission at Week 52 was analysed by ustekinumab dose bands:

- Induction dose band;
- Initial maintenance dose band;
- Final maintenance dose band.

The majority of patients in the Paediatric Patients (Primary Cohort) received the induction dose in the range of 0.5 to <1.65 mg/kg/week, among which 22 (21.2% [95% CI: 14.4%, 30.0%]) of 104 patients were in clinical remission at Week 52. The majority of patients in the Paediatric Patients (Primary Cohort) received the initial maintenance dose in the range of 0.08 to ≤0.28 mg/kg/week, of which 23 (24.0% [95% CI: 16.5%, 33.4%]) of 96 patients were in clinical remission at Week 52. In the final maintenance dose bands, the proportion of patients in clinical remission in the Paediatric Patients (Primary Cohort) was slightly higher in the 0.08 to ≤0.28 dose band (15 [25.9%] of 58; 95% CI: 16.3%, 38.4%) than the >0.28 dose band (8 [18.6%] of 43; 95% CI: 9.7%, 32.6%). Similar results were obtained for cohort 7.

In an *ad-hoc* analysis of clinical remission by final maintenance dose and frequency for the Paediatric Patients (Primary Cohort), the proportion of patients who were in clinical remission at Week 52 (14 [28.0% {95% CI: 17.5%, 41.7%}] of 50) in the 90 mg q8w group was higher (8 [18.2% {95% CI: 9.5%, 32.0%}] of 44) than in the 90 mg q4w group (**Table *38***).

Table 38: *Ad-hoc* Analysis: Number of Subjects in Clinical Remission at Week 52 by Ustekinumab Final Maintenance Dose and Frequency; Primary Cohort Full Analysis Set (Study CNTO1275CRD3010)

	Final Maintenance Dose and Frequency[e]	
	90 mg Q8W	90 mg Q4W
Analysis set: primary cohort full analysis set	50	44
Week 52		
N	50	44
Subjects in clinical remission[a,b,c]	14 (28.0%)	8 (18.2%)
95% CI for proportion of subjects in clinical remission[d]	(17.5% , 41.7%)	(9.5% , 32.0%)

Key: CI = confidence interval; sPCDAI = short pediatric Crohn's disease activity index
[a] Clinical remission is defined as sPCDAI ≤ 10.
[b] 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.
[c] After accounting for ICEs, subjects who had missing clinical remission status at Week 52 are considered not to be in clinical remission.
[d] The 95% CI is estimated based on the Wilson method.
[e] 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: 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: 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.

Of note, although the proportion of patients in clinical remission were numerically lower in those who had a final dosing regimen of q4W compared with those whose final dose was q8w, an *ad-hoc* analysis showed similar discontinuation rates between the q8w and q4w group and may indicate continued benefit from treatment with Ustekinumab (data not shown). A similar pattern is observed in the Young Adults (Reference; Cohort 7).

Corticosteroid-Free Clinical Remission at Week 52

At Week 52, 22 (19.3% [95% CI: 13.1%, 27.5%]) of 114 patients in the Paediatric Patients (Primary Cohort) were in corticosteroid-free clinical remission. Corticosteroid-free clinical remission was similar in the Paediatric Patients (Primary Cohort) and the Young Adults (Reference; Cohort 7) (Table 39).

Table 39: Other Secondary Endpoint Analysis: Number of Subjects in Corticosteroid-Free Clinical Remission at Week 52; Primary Cohort and Cohort 7 Full Analysis Set (Study CNTO1275CRD3010)

	Primary Analysis Cohort	Young Adult Reference Cohort
Analysis set:	114	51
Week 52		
N	114	51
Subjects in clinical response[a,b]	22 (19.3%)	10 (19.6%)
95% CI for proportion of subjects in clinical response[c]	(13.1%, 27.5%)	(11.0%, 32.5%)

Key: CI = confidence interval; sPCDAI = short pediatric Crohn's disease activity index
[a] Corticosteroid-free clinical remission is defined as sPCDAI ≤ 10 without use of corticosteroids at Week 52.
[b] Subjects who had intercurrent events (ICEs) are considered not to be in corticosteroid-free 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.
[c] After accounting for ICEs, subjects who had missing corticosteroid-free clinical remission status at Week 52 are considered not to be in corticosteroid-free clinical remission.
[d] The 95% CI is estimated based on the Wilson method.
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: 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.

At Week 52, 11 (16.2% [95% CI: 9.3%, 26.7%]) of 68 patients (those who received corticosteroids at baseline) in the Paediatric Patients (Primary Cohort) were in corticosteroid-free clinical remission (

Table *40*). Similar results were obtained analysis for the Young Adults (Reference; Cohort 7).

Table 40: *Ad-hoc* Secondary Endpoint Analysis: Number of Subjects in Corticosteroid-Free Clinical Remission at Week 52; Subjects Who Received Corticosteroids at Baseline in Primary Cohort Full Analysis Set (Study CNTO1275CRD3010)

	Total
Analysis set: subjects who received corticosteroids at baseline in primary cohort full analysis set	68
Week 52	
N	68
Subjects in corticosteroid-free clinical remission[a,b,c]	11 (16.2%)
95% CI for proportion of subjects in corticosteroid-free clinical remission[d]	(9.3%, 26.7%)

Key: CI = confidence interval; sPCDAI = short pediatric Crohn's disease activity index
[a] Corticosteroid-free clinical remission is defined as sPCDAI ≤ 10 without use of corticosteroids at Week 52.
[b] Subjects who had intercurrent events (ICEs) are considered not to be in corticosteroid-free 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.
[c] After accounting for ICEs, subjects who had missing corticosteroid-free clinical remission status at Week 52 are considered not to be in corticosteroid-free clinical remission.
[d] The 95% CI is estimated based on the Wilson method.
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: 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.

Clinical Remission as Determined by PGA at Week 52

A numerically higher proportion of Paediatric Patients (Primary Cohort) were in PGA clinical remission (a PGA rating of quiescent at Week 52) compared with the Young Adults (Reference; Cohort 7) at Week 52 (Table 41).

Table 41: Other Secondary Endpoint Analysis: Number of Subjects in Clinical Remission and Response (observed cases) at Week 52 as Determined by PGA; Primary Cohort and Cohort 7 Full Analysis Set (Study CNTO1275CRD3010)

	Pediatric Patients (Primary Cohort)	Young Adults (Reference; Cohort 7)
Analysis set:	114	51
Week 52		
N	114	51
Subjects in clinical remission determined by PGA[a,b,c]	39 (34.2%)	14 (27.5%)
95% CI for proportion of subjects in clinical remission determined by PGA[d]	(26.1%, 43.3%)	(17.1%, 40.9%)

Key: CI = confidence interval, PGA= physician's global assessment
[a] Clinical remission based on PGA is defined as having a PGA rating of quiescent.
[b] Subjects who had intercurrent events (ICEs) are considered not to be in clinical remission based on PGA: (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 or missing reason for discontinuation, (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.
[c] After accounting for ICEs, subjects who had missing clinical remission status based on PGA at Week 52 are considered not to be in clinical remission based on PGA.
[d] The 95% CI is estimated based on the Wilson method.
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: 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.

Growth Parameters

In general, 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 represents a shift from a low z-score range, indicative of underweight/ malnutrition status, to a narrower (but still important) range, suggesting growth recovery and possible catch-up group in some patients.

In general, a positive median change from baseline in BMI z-score was shown, suggestive of an improvement in growth status for the Young Adults (Reference; Cohort 7). 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, along with a Week 52 BMI z-score range >-1 to 1, may reflect a pattern of normal growth among patients in the Young Adults (Reference; Cohort 7).

Endoscopy Assessments

Overall, 77 (67.5%) of 114 patients in the Paediatric Patients (Primary Cohort) had ≥1 endoscopy assessment during the study. Baseline demographics were comparable between patients with and without endoscopy assessments. At baseline the disease characteristic by endoscopy assessment in the Paediatric Patients (Primary Cohort) were as follows:

- Median SEMA-CD was 8.5 (IQR: 5.0; 13.0 [N=38]) in patients with endoscopy assessments
- Median sPCDAI was 40 (IQR: 35.0;50.0 [N=77]) in paediatric patients with and (IQR: 30.0;50.0 [N=37]) without endoscopy assessments

- Patients with endoscopic assessments vs. without endoscopic assessments had:
    - slightly longer median time since Crohn's disease diagnosis (4.24 vs 3.7 years)
    - more ileocolonic disease activity (72.7% vs 54.1%)
    - more perianal disease (39.0% vs 35.1%)
    - more stricturing phenotype (10.4% vs 5.4%)
    - greater use of 2 prior unique biologics (42.9% vs. 35.1%).

The proportion of Paediatric Patients (Primary Cohort) in clinical remission at Week 52 by endoscopic assessments: with endoscopic assessments: 16 (20.8% [95% CI: 13.2%, 31.1%]) of 77; without endoscopic assessment: 10 (27.0% [95% CI: 15.4%, 43.0%]) of 37 (**Table *42***).

Table 42: Other Supportive Analysis: Number of Subjects in Clinical Remission at Week 52 by Endoscopy Assessment Status; Primary Cohort Full Analysis Set (Study CNTO1275CRD3010)

	With Endoscopy Assessment[e]	Without Endoscopy Assessment[f]
Analysis set: primary cohort full analysis set	77	37
Week 52		
N	77	37
Subjects in clinical remission[a,b,c]	16 (20.8%)	10 (27.0%)
95% CI for proportion of subjects in clinical remission[d]	(13.2% , 31.1%)	(15.4% , 43.0%)

Key: CI = confidence interval; sPCDAI = short pediatric Crohn's disease activity index
[a] Clinical remission is defined as sPCDAI ≤ 10.
[b] 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.
[c] After accounting for ICEs, subjects who had missing clinical remission status at Week 52 are considered not to be in clinical remission.
[d] The 95% CI is estimated based on the Wilson method.
[e] Subjects who had at least one endoscopic assessment during the study period (i.e., -12 weeks to + 68 weeks from the index date).
[f] Subjects who did not have any endoscopy during the study period (i.e., -12 weeks to + 68 weeks from the index date).
Note: N is the number of subjects who initiated ustekinumab.
Note: Index date is defined as the date of the first dose of 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: 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.

The proportion of the Young Adults (Reference; Cohort 7) in clinical remission at Week 52 by endoscopic assessments: with endoscopic assessments: 7 (19.4% [95% CI: 9.8%, 35.0%]) of 36 participants; without endoscopic assessment: 4 (26.7% [95% CI: 10.9%, 52.0%]) of 15 participants.

There were only 20 patients evaluable for endoscopic remission at Week 52. At Week 52, 4 (20.0% [95% CI: 8.1%, 41.6%]) of 20 patients who had at least one SEMA-CD score within the Week 52 window and not having resection surgery in the Paediatric Patients (Primary Cohort) were in endoscopic remission (Table 43).

Table 43: Other Secondary Endpoint Analysis: Number of Subjects in Endoscopic Remission at Week 52; Primary Cohort Full Analysis Set (Study CNTO1275CRD3010)

	Total
Analysis set: Primary cohort full analysis set	114
Week 52	
N	20
Subjects in endoscopic remission[a,b,c]	4 (20.0%)
95% CI for proportion of subjects in endoscopic remission[d]	(8.1%, 41.6%)

Key: CI = confidence interval; SEMA-CD = simplified endoscopic mucosal assessment for Crohn's disease.
[a] Endoscopic remission is defined as having the SEMA-CD score of 0 or 1.
[b] Subjects who had intercurrent events (ICEs) are considered not to be in endoscopic 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.
[c] After accounting for ICEs, subjects who had missing endoscopic remission status at Week 52 are considered not to be in endoscopic remission.
[d] The 95% CI is estimated based on the Wilson method.
Note: N is the number of subjects who initiated ustekinumab and are evaluable for endoscopic assessment that is defined as having at least one SEMA-CD score within Week 52 window and not having resection surgery.
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: 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.

An *ad-hoc* analysis, with no treatment failure rules, identified one more patient in endoscopic remission at Week 52, i.e., 5 (25.0% [95% CI: 11.2%, 46.9%]) of 20. One (33.3%) of 3 patients evaluable was in endoscopic remission at Week 52 among patients in the Young Adults (Reference: Cohort 7).

Only 9 patients were evaluable for change in baseline SEMA-CD scores at Week 52. The median (IQR) value for the change from baseline in SEMA-CD scores for the Paediatric Patients (Primary Cohort) (N=9) was -2.00 (-4.00; -2.00) (

Table *44*).

Table 44: Other Secondary Endpoint Analysis: Summary of SEMA-CD Scores and Change From Baseline at Week 52; Primary Cohort Full Analysis Set (Study CNTO1275CRD3010)

	Total
Analysis set: primary cohort full analysis set	114
Baseline	
N	38
Mean (SD)	8.84 (4.624)
Median	8.50
Range	(0.0; 18.0)
IQ range	(5.00; 13.00)
Week 52	
N	22
Mean (SD)	6.09 (3.951)
Median	6.50
Range	(0.0; 12.0)
IQ range	(4.00; 9.00)
Change from baseline	
N	9
Mean (SD)	-3.00 (1.658)
Median	-2.00
Range	(-6.0; -1.0)
IQ range	(-4.00; -2.00)

	Total

Key: IQ = interquartile, SEMA-CD = simplified endoscopic mucosal assessment for Crohn's disease
Note: N 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.
Note: Index date is defined as the date of the first dose of ustekinumab.
Note: Baseline value is defined as the non-missing measurement closest to the index date within the baseline window (ie, from -12 weeks to +2 weeks from the index date).
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: 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.

The small number of patients (n=3) with endoscopy data at Week 52 for the change from baseline in SEMA-CD scores for the Young Adults (Reference; Cohort 7) precludes any statistical analysis and comparisons.

Analysis evaluated clinical remission at Week 52 in patients with active endoscopic disease (defined as SEMA-CD score of ≥2) within the age group of ≥2 and <18 years and weight ≥40 kg at baseline. At Week 52, 16 (25.0% [95% CI: 16.0%, 36.8%]) of 64 patients between the ages of ≥2 to <18 years and weighing ≥40 kg at baseline were in clinical remission. A similar analysis for Young Adults demonstrated 21% of patients in clinical remission.

Clinical Remission as Determined by full PCDAI at Week 52

Full PCDAI was calculated in those subjects who had laboratory evaluations available. Of the 21 patients in the Paediatric Patients (Primary Cohort) who had non-missing PCDAI assessment at Week 52, 5 (23.8% [95% CI: 10.6%, 45.1%]) patients were in full PCDAI clinical remission at Week 52. Despite the small sample size with a full PCDAI score, these results are consistent with that seen with sPCDAI. For patients in cohort 7, 4 of 9, (44.4% (95% CI: 18.9%, 73.3%)) were in full PCDAI clinical remission at Week 52.

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

Comparison of studies CRD3004 and CRD1001

In CRD1001, 10 participants ≥40 kg received 390 mg IV that was equivalent to the IV dosing in CRD3004.

The demographic characteristics across the paediatric studies CRD3004 and CRD1001 were similar overall with the exception of measures of height and weight trending lower in CRD1001. Crohn's disease characteristics at baseline and medication history across studies CRD3004 and CRD1001 were representative of a population of paediatric participants with moderately to severely active Crohn's disease. Notably, a greater proportion of participants in CRD1001 (9 [90%] of 10) had a history of intolerance or failure to biologics than participants in CRD3004 19 [39.6%] of 48.

Summary side by side results for the induction periods are presented below.

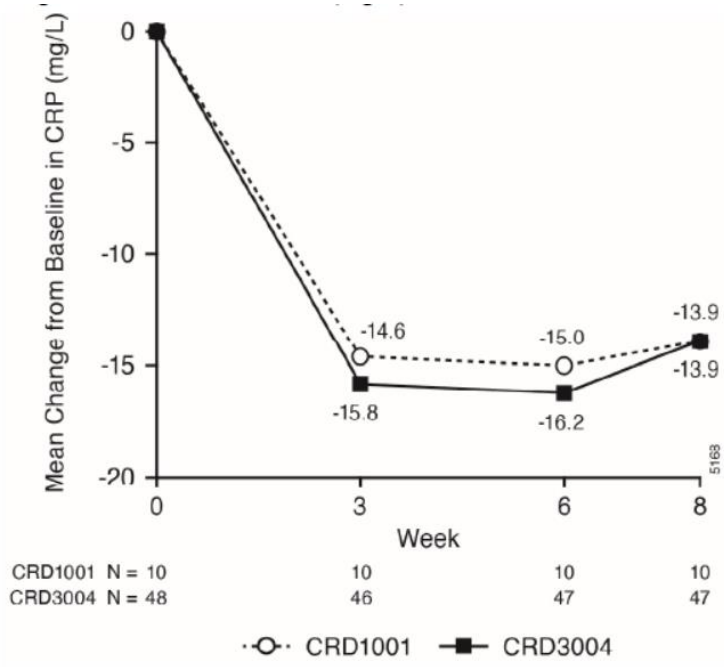
Table 45: Number of Participants with Improvement in Clinical Outcomes Through Week I-8 (Week 8) by Individual Studies Among Participants Weighing at Least 40kg and Receiving 390mg Induction Ustekinumab IV in CRD1001 and Participants Weighing at Least 40kg in CRD3004; Full Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)

	Ustekinumab	
	CRD1001 390 mg IV	CRD3004
Analysis set: Full Analysis Set	10	48
Primary Endpoint		
Clinical Remission at Week I-8		
N	10	48
Participants in clinical remission[a,b1,b2]	3 (30.0%)	25 (52.1%)
95% CI[c]	(10.8%, 60.3%)	(38.3%, 65.5%)
Secondary Endpoints		
Clinical Response at Week I-8		
N	10	48
Participants in clinical response[a,b1,b2]	7 (70.0%)	45 (93.8%)
95% CI [c]	(39.7%, 89.2%)	(83.2%, 97.9%)
PCDAI Scores at Week I-8		
Change from baseline		
N	10	48
Mean (SD)	-27.00 (14.710)	-29.90 (11.392)
Endoscopic Response at Week M-8		
N	8	47
Participants in endoscopic response[a1,a2,b1,b2]	5 (62.5%)	14 (29.8%)
95% CI[c]	(30.6%, 86.3%)	(18.7%, 44.0%)

[a] Clinical remission is defined as a PCDAI score ≤10 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: Participants 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). Participants 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, participants who had missing endpoint data are considered to not have achieved the endpoint.
[b2] For CRD1001, participants 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. Participants 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.

The mean changes from baseline in CRP concentrations at Week I-8 are presented in **Figure *43***.

Figure 43: Mean Change from Baseline in CRP (mg/L)



A total of 48 participants from CRD3004 and 23 participants ≥40 kg from CRD1001 were included in the comparisons for the maintenance portion of the study (after Week I-8).

Summary side by side results for the maintenance phases are presented below.

Table 46: Clinical Overview Table 9 Revised: Number of Participants With Improved Clinical Outcomes Through Week M-44/Week 48 by Individual Studies Among Participants Weighing at Least 40 kg; Full Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)

	Ustekinumab			
	CRD1001	CRD3004		
	q8w	q8w	q12w	Total CRD3004 (q8w and q12w)
Analysis set: Full Analysis Set	23	23	25	48
Clinical Remission at Week M-44/Week 48				
N	23	23	25	48
Participants in clinical remission[a,b1,b2]	9 (39.1%)	10 (43.5%)	15 (60.0%)	25 (52.1%)
95% CI[c]	(22.2%, 59.2%)	(25.6%, 63.2%)	(40.7%, 76.6%)	(38.3%, 65.5%)
Clinical Response at Week M-44/Week 48				
N	23	23	25	48
Participants in clinical response[a,b1,b2]	11 (47.8%)	12 (52.2%)	15 (60.0%)	27 (56.3%)
95% CI[c]	(29.2%, 67.0%)	(33.0%, 70.8%)	(40.7%, 76.6%)	(42.3%, 69.3%)
PCDAI Scores at Week M-44/Week 48				
Change from baseline				
N	23	23	25	61
Mean (SD)	-16.63 (18.319)	-19.02 (19.273)	-23.10 (20.275)	-22.91 (18.898)
Corticosteroid-free Clinical Remission at Week M-44/Week 48				
	23	23	25	48
Participants in corticosteroid-free clinical remission[a1,a2,b1,b2]	9 (39.1%)	10 (43.5%)	15 (60.0%)	25 (52.1%)
95% CI[c]	(22.2%, 59.2%)	(25.6%, 63.2%)	(40.7%, 76.6%)	(38.3%, 65.5%)

[a] Clinical remission is defined as a PCDAI score ≤10 points.
[b1] For CRD3004, intercurrent events (ICEs) include: (1) Participants 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: Participants 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). Participants 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, participants who had missing endpoint data are considered to not have achieved the endpoint.
[b2] For CRD1001, participants 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. Participants 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: All participants in the CRD1001 study with body weight ≥40 kg are included, regardless of the dose received at induction.

Table 47: Clinical Overview Table 10 Revised: Summary of Mean Change from Baseline in Other Endpoints at Week M-44/Week 48 by Individual Studies Among Participants Weighing at Least

40 kg; Full Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)

	Ustekinumab			
	CRD1001	CRD3004		
	q8w	q8w	q12w	Total CRD3004 (q8w and q12w)
Analysis set: Full Analysis Set	23	23	25	48
CRP, Change from baseline (mg/L) [a,b1,b2,c,d]				
N	23	23	25	48
Mean (SD)	-8.38 (17.760)	-10.85 (19.832)	-11.46 (27.969)	-11.17 (24.159)
tin, Change from [a,b1,b2,c,d]				
N	23	21	24	55
Mean (SD)	-963.26 (1813.810)	-398.86 (1181.617)	-660.21 (1358.175)	-843.20 (1603.051)
IMPACT-III Scores Change from baseline [a,b1,b2,c,d]				
N[e]	20	18	18	36
Mean (SD)	17.0 (21.51)	29.8 (36.18)	11.4 (18.66)	20.6 (29.86)

[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) Participants 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: Participants 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. Participants with ICE 6 have their data assumed missing after the ICE 6 occurred.
[b2] For CRD1001, participants 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. Participants who had insufficient data to calculate the PCDAI score at a visit are considered to not have achieved the endpoint..
[c] The endpoint was measured at Week M-44 (Week 52) for the CRD3004 study and at Week 48 for the CRD1001 study.
[d] For CRD1001, participants who entered the long-term extension study were included.
[e] Participants who were at Least 10 Years of Age at Week I-0
Note: All participants in the CRD1001 study with body weight ≥40 kg are included, regardless of the dose received at induction.

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:

- CRD300 (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 TNFα 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.

Baseline Crohn's Disease Characteristics

The clinical disease characteristics at baseline for paediatric and adult populations are representative of populations with moderately to severely active Crohn's disease (**Table *48***).

- The mean (SD) duration of disease was shorter for paediatric CRD3004 study participants 2.6 (2.30) years than for adult study participants (12.69 [9.246] years for CRD3001 and 8.68 [8.436] years for CRD3002).
- The mean (SD) and median CDAI scores at baseline in the paediatric CRD3004 study were greater than in either adult study, indicating a higher severity of disease for the paediatric population. The mean (SD) CDAI scores were 412.58 (167.763), 327.6 (62.02), and 302.2 (58.85) for CRD3004, CRD3001, and CRD3002, respectively. The median CDAI scores were 365.30, 319.0, and 286.0, in CRD3004, CRD3001, and CRD3002, respectively.
- The mean (SD) and median baseline CRP and faecal calprotectin in the paediatric study were numerically higher than for adult studies.

Table 48: Summary of Crohn's Disease Characteristics Between Paediatric and Adult Ustekinumab Studies

Study Type	Pediatric			Adult	
Study	CRD3004			CRD3001	CRD3002
Dose	Total 90 mg, q12w (N=25)	Total 90 mg, q8w (N=23)	Total 90 mg, q12w+q8w (N=48)	Total 6 mg/kg (N=249)	Total 6 mg/kg (N=209)
Crohn's Disease Duration (years)					
Mean (SD)	2.7 (2.65)	2.6 (1.91)	2.6 (2.30)	12.69 (9.246)	8.68 (8.436)
Median	1.9	2.1	2.0	10.97	6.21
CDAI Score					
Mean (SD)	431.21 (212.108)	392.62 (106.482)	412.58 (167.763)	327.6 (62.02)	302.2 (58.85)
Median	364.30	393.50	365.30	319.0	286.0
PCDAI Score					
Mean (SD)	42.00 (9.043)	41.20 (6.024)	41.61 (7.675)	NA	NA
Median	40.00	40.00	40.00	NA	NA
C-reactive Protein, mg/mL					
Mean (SD)	24.40 (29.69)	27.17 (32.39)	25.73 (30.71)	19.50 (25.347)	17.52 (24.139)
Median	10.70	13.10	11.35	9.93	7.82
Abnormal CRP (>3 mg/kg)					
	20 (80.0%)	17 (73.9%)	37 (77.1%)	197 (79.1%)	165 (78.9%)
Fecal Calprotectin, mg/kg					
Mean (SD)	3274.9 (3138.04)	3110.9 (4448.20)	3198.1 (3765.31)	963.03 (1364.250)	784.20 (1080.701)
Median	1971.0	1874.5	1971.0	530.15	523.23
Abnormal Fecal Calprotectin (>250 mg/kg)					
	24 (96.0%)	19 (86.4%)	43 (91.5%)	158 (63.5%)	135 (64.6%)

Concomitant Medications for Crohn's Disease

Paediatric populations in CRD3004 had comparable concomitant Crohn's disease-related medication use for immunomodulators, corticosteroids and aminosalicylates; these were similar to disease-related medication use in the adult study populations from CRD3001, CRD3002, and CRD3003. In CRD3004, a total of 19 (39.6%) of 48 participants had a history of biologic failure. Enrolment criteria for CRD3001 included a history of biofailure. However, participants may have been categorised initially as a biofailure without definitive proof, in which case they were subsequently reclassified as a conventional failure. A total of 224 (90.0%) of 249 participants in the 6 mg/kg treatment group in CRD3001 had a history of biologic failure. In CRD3002, all participants (207 [99.0%] of 209) in the 6 mg/kg treatment group had no demonstrated biofailure.

Efficacy Results - Induction (through Week I-8)

All comparisons are descriptive only without formal statistical testing. Efficacy results for the ustekinumab induction IV groups from the paediatric study CRD3004 at Week I-8 are compared descriptively side-by-side with the 6 mg/kg induction dose utilised in the adult studies CRD3001 and CRD3002. The efficacy results reported for clinical remission and clinical response consist of PCDAI scores for participants from CRD3004 and CDAI scores for participants from CRD3001, CRD3002, and CRD3003.

For this section, the adult data are presented as combined data from CRD3001 and CRD3002 rather than each study individually side by side. This was done to approximate the overall percentage of participants with a history of biologic failure in the paediatric study CRD3004. At Week I-8, induction therapy given to paediatric participants in CRD3004 induced clinical remission in a higher proportion of participants (25 [52.1%] of 48) compared with combined results from CRD3001 and CRD3002 (136 [29.7%] of 458). The corresponding adult placebo intervention clinical remission proportion was 59 (12.9%) of 456. Of note, at Week I-8 the lower bound of the proportion of paediatric participants in clinical remission in CRD3004 exceeded that of the upper-bound of the combined placebo group from the adult studies.

At Week I-8, the proportion of paediatric study CRD3004 participants in clinical response (45 [93.8%] of 48) was higher than in adult participants in CRD3001 and CRD3002 (combined results) (215 [46.9%] of 458). The proportion of adult participants on placebo in CRD3001 and CRD3002 (combined results) was 117 [25.7%] of 456. Of note, the lower bound of the proportion of paediatric participants in clinical response in CRD3004 exceeded that of the upper-bound of the combined placebo group from the adult studies.

The proportions of paediatric study CRD3004 participants in clinical remission at Week I-8 were higher in those with a history of non-biologic (conventional medication) failure at baseline than in participants with history of biologic failures at baseline (62.1% vs. 36.8%). A similar trend was observed in the adult studies with a greater proportion of participants in the CRD3002 (conventional therapy failure) achieving clinical remission (84 [40.2%] of 209) compared with participants in the CRD3001 (anti-TNF failures) (52 [20.9%] of 249). The mean change from baseline in CRP and faecal calprotectin decreased in both the paediatric and adult studies; overall, mean decreases from baseline at Week I-8 were smaller in the adult studies, but the trends were similar.

At Week I-8, the proportions of participants in clinical remission and clinical response in both the biologic failure and non-biologic failure subgroups were numerically higher in the paediatric studies than the corresponding adult studies (Figure 44 and Figure 45).

Figure 44: Comparison of Clinical Remission Across Paediatric and Adult Ustekinumab Studies with Biologic or Non-Biologic Failure at Study Entry

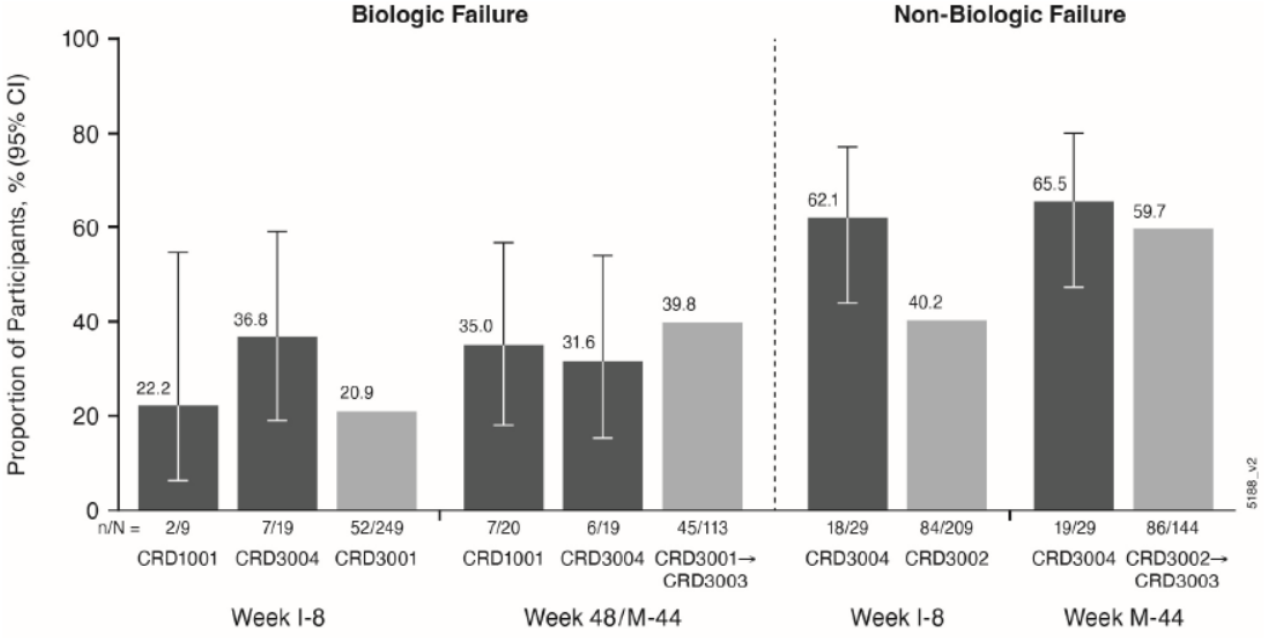
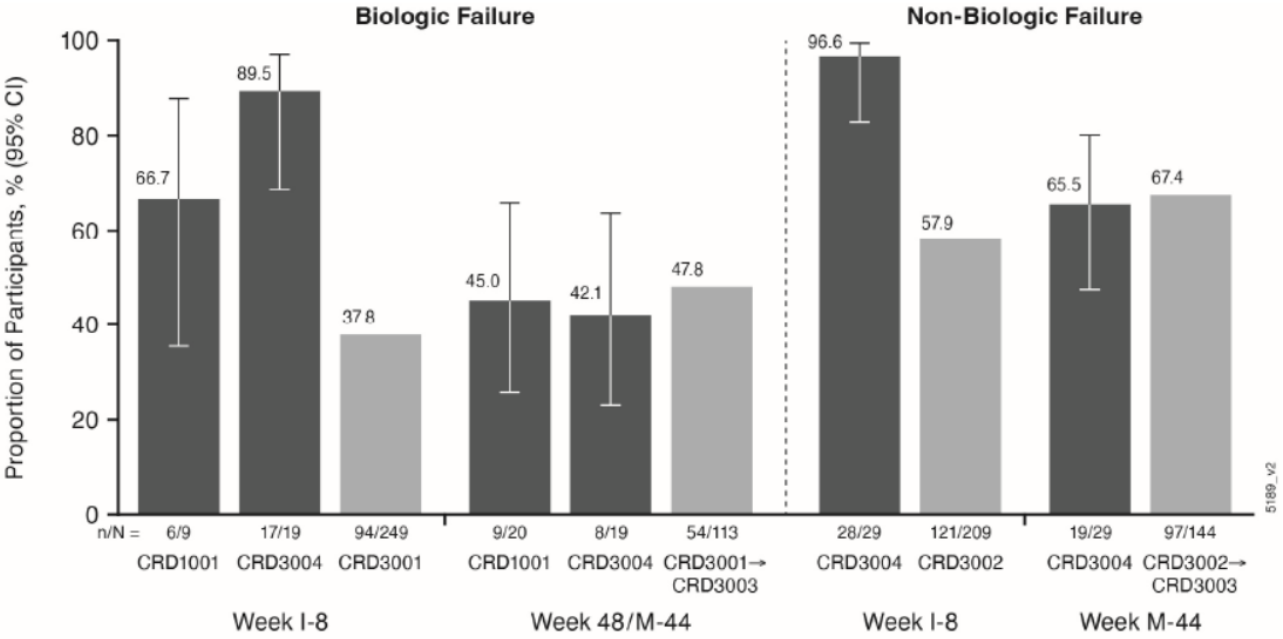


Figure 45: Comparison of Clinical Response Across Paediatric and Adult Ustekinumab Studies with Biologic or Non-Biologic Failure at Study Entry



Maintenance (through Week M-44/48)

Overall, clinical remission, clinical response, and changes in inflammatory biomarkers (CRP and faecal calprotectin) were similar between paediatric and adult studies of ustekinumab at Week M-44/Week 48 (Table 49). The paediatric maintenance efficacy results are reported in all randomised participants (i.e. responders and nonresponders), while adult results are in responders only.

- The proportion of paediatric participants in clinical remission (25 [52.1%] of 48) in CRD3004 was similar to adult participants (131 [51.0%] of 257) in CRD3003 and higher than that of adult participants on placebo in CRD3003 (47 [35.9%] of 131).

- The proportion of participants in clinical response (27 [56.3%] of 48) in CRD3004 was similar to that of adult participants in CRD3003 (151 [58.8%] of 257) and higher than that of adult participants on placebo (58 [44.3%] of 131).
- The proportion of participants in corticosteroid-free clinical remission (25 [52.1%] of 48) was higher than adult participants in CRD3003 (111 [43.2%] of 257) and higher than that of adult participants on placebo (39 [29.8%] of 131).
- Mean changes from baseline for CRP and faecal calprotectin for the paediatric CRD3004 study maintenance treatment groups compare favourably with both treatment groups in the adult CRD3003 study.
- The proportions of paediatric participants and the proportion of adult participants who achieved clinical remission and clinical response were similar in the biologic failure and in the non-biologic failure subgroups, with higher proportions in the non-biologic failure subgroup (Figure 44 and Figure 45).

Table 49: Efficacy Endpoints During Maintenance through Week M-44/Week 48

Study Type	Pediatric			Adult			
Study	CRD3004			CRD3003			
Ustekinumab Dose	90 mg, q8w (N=23)	90 mg, q12w (N=25)	Total 90 mg, q8w+q12w (N=48)	90 mg, q8w (N=128)	90 mg, q12w (N=129)	Total 90 mg, q8w+q12w (N=257)	Placebo (N=131)
N Clinical Remission 95% CI	10/23 (43.5%) (25.6%, 63.2%)	15/25 (60.0%) (40.7%, 76.6%)	25/48 (52.1%) (38.3%, 65.5%)	68/128 (53.1%)	63/129 (48.8%)	131/257 (51.0%)	47/131 (35.9%)
N Clinical Response 95% CI	12/23 (52.2%) (33.0%, 70.8%)	15/25 (60.0%) (40.7%, 76.6%)	27/48 (56.3%) (42.3%, 69.3%)	76/128 (59.4%)	75/129 (58.1%)	151/257 (58.8%)	58/131 (44.3%)
N Corticosteroid-free Clinical Remission 95% CI	10/23 (43.5%) (25.6%, 63.2%)	15/25 (60.0%) (40.7%, 76.6%)	25/48 (52.1%) (38.3%, 65.5%)	60/128 (46.9%)	55/129 (42.6%)	115/257 (44.7%)	39/131 (29.8%)
Mean change in CRP from baseline, mg/L (SD)	-10.85 (19.832)	-11.46 (27.969)	-11.17 (24.159)	4.16 (24.078)	4.41 (17.182)	4.28 (20.863)	8.02 (16.128)
Fecal calprotectin (mean change from baseline, mg/kg) SD	-398.9 (1181.62)	-660.2 (1358.18)	-538.20 (1271.33)	-54.19 (634.347)	31.79 (1161.435)	-10.85 (936.916)	413.47 (1382.975)

Endoscopic Response - Induction

The endoscopic data from the adult studies CRD3001 and CRD3002 were collected as part of a sub study. The sites and participants were not randomly selected, and unintentional selection bias cannot be excluded from this adult sub study. The endoscopic response endpoint in the paediatric study was 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. In the adult study, endoscopic response was an "other endpoint" and defined as a reduction from induction baseline in SES-CD score ≥50%. The primary endpoint in the adult sub study was change from baseline in SES-CD sub score.

At Week M-8, the proportion of paediatric participants who were in endoscopic response in the CRD3004 was (14 [29.8%] of 47) and is numerically greater than the proportions of adult participants at Week 8 in the non-randomised endoscopic sub study (18 [21.7%] of 83) and the placebo group from the combined adult studies (13 [13.4%] of 97) (Table 50).

Table 50: Number of Participants in Endoscopic Response at Week M-8 by Induction Dose in Paediatric and Adult Studies

Study Type	Pediatric	Adult			
Study	CRD3004	CRD3001 and CRD3002			
	CRD3004 (N=47)	CRD3001 (N=66)	CRD3002 (N=89)	Combined CRD3001 and CRD3002 6mg/kg subgroup (N=83)	Combined CRD3001 and CRD3002 Placebo (N=97)
N Endoscopic Response 95% CI	14/47 (29.8%) (18.7%, 44.0%)	9/66 (13.9%)	23/89 (25.8%)	18/83 (21.7%)	13/97 (13.4%)

Note: Endoscopic response is 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.

Note: In the adult study, change from baseline in SES-CD score was used instead of endoscopic response. It is an "other endpoint".

Maintenance (through Week M-44)

At Week M-44, a numerically greater proportion of paediatric participants in CRD3004 than adults in CRD3003 were in endoscopic response (**Table *51***). Notably, endoscopic response in the q8w groups were similar for both paediatric and adult participants.

Table 51: Number of Participants in Endoscopic Response at Week M-44 by Induction Dose in Paediatric and Adult Studies

Study Type	Pediatric			Adult			
Study	CRD3004			CRD3003			
	q8w N=23	q12w N=25	Total q8w+q12w N=48	q8w N=29	q12w N=17	Total q8w+q12w N=46	Placebo N=24
N Endoscopic Response 95% CI	5/22 (22.7%) (10.1%, 43.4%)	7/25 (28.3%) (14.3%, 47.6%)	12/47 (25.5%) (15.3%, 39.5%)	7/29 (24.1%)	1/17 (5.9%)	8/46 (17.4%)	1/24 (4.2%)

Similarity of Response and Remission for Ustekinumab Therapy in Adult onset and Paediatric-onset Crohn's Disease

In order to assess similarity of clinical response to ustekinumab therapy within the Stelara clinical development program in adult- and paediatric-onset Crohn's disease, data from adult Crohn's disease Phase 3 studies were analysed, with data stratified into cohorts of adult-onset (diagnosed ≥18 years) and paediatric-onset (diagnosed <18 years) participants.

Data were analysed from UNITI-1 (N=741; anti-TNFα failure) and UNITI-2 (N=628; conventional therapy failure) studies of adults with moderately to severely active Crohn's disease (Feagan 2016). Baseline clinical characteristics were stratified by age at Crohn's disease diagnosis, paediatric onset (diagnosis <18 years) and adult onset (diagnosis ≥18 years) and presented using descriptive statistics. The proportions of participants in clinical response and clinical remission at induction Week 6 and maintenance Week 44 were summarised, and ORs and 95% CIs computed to evaluate treatment response by age of Crohn's disease onset.

Overall, 254 participants in the adult ustekinumab Crohn's disease program had paediatric-onset Crohn's disease. Participants with paediatric-onset Crohn's disease from UNITI-1 (N=181, 24.4%) and UNITI-2 (N=73, 11.6%) had a mean (SD) age of onset of Crohn's disease of 14.2 (3.0) years and 15.2 (2.1) years, respectively. Participants with adult-onset Crohn's disease from UNITI-1 (N=559, 75.6%) and UNITI-2 (N=554, 88.4%) had a mean (SD) age of onset of Crohn's disease of 29.5 (10.3) years and 32.7 (11.8) years, respectively. At induction baseline, median duration of Crohn's disease was slightly greater in the paediatric-onset group, and clinical characteristics (ileocolonic disease, bowel stricturing, CDAI score, and CRP) were generally worse compared with the adult-onset group.

Across both induction and maintenance, patients with paediatric onset disease and those with adult onset disease had similar response and remission.

The proportions of participants with paediatric-onset and adult-onset Crohn's disease, respectively, treated with ustekinumab in clinical response at Week 6 in each study were similar (UNITI-1, 30.1% and 35.3%; UNITI-2, 56.9% and 53.1%). At IM-UNITI maintenance Week 44, the odds ratios of clinical response and clinical remission were similar among participants with paediatric- and adult-onset IBD, with the CIs of the ORs overlapping for both groups, despite the paediatric-onset participants having longer disease duration, higher CRP, and higher CDAI scores at baseline.

In maintenance, the rates of clinical remission were similar between paediatric-onset and adult-onset disease for both the q8 and q12 maintenance dose.

2.4.4. Discussion on clinical efficacy

Study CRD3004, phase 3

The applicant presents a pivotal ongoing phase 3 study of ustekinumab in paediatric Crohn's disease patients. The primary endpoint of the trial was 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. SEMA-CD is a novel measurement tool that allows clinicians to more simply assess endoscopic mucosal activity. In contrast to the SES-CD, SEMA-CD does not rely exclusively on endoscopy videos but rather can be scored using written endoscopy reports contained in medical records.

The inclusion and exclusion criteria, summarised here but detailed fully in the protocol, should be effective to select moderate to severe CD paediatric patients. 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 are weight based and have been selected based on the phase I PK results using the 'higher induction' dose and popPK modelling. Doses are also in line with the authorised doses for adult patients.

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 generally accepted. The clinical trial has been performed broadly in line with that agreed in the PIP.

All patients (n=48) are included in the primary analysis. 7 patients were discontinued throughout the maintenance phase and substudy.

The baseline characteristics are generally evenly spread between the two treatments groups with the exception of sex, where more than double the number of males were included in the q8w arm compared to females. However, as there is no formal comparison with a comparator or placebo arm in this clinical trial, any baseline differences between the two treatment groups are of low importance.

No patients weighing less than 40kg have been included in the study. The youngest patient was 10 years old. Compliance was 100%, no subject missed an administration of ustekinumab during the study.

As per inclusion criteria, patients must have moderately to severely active Crohn's disease as defined by a baseline PCDAI score >30, however 3 patients were included with PCDAI score of less than 30 in the q12w arm. Following queries the applicant explained 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. The applicant demonstrated that excluding these 3 patients did not have a large impact on results with the primary endpoint analysis changing from 52.1% to 53.3%**.**

The primary analysis was clinical remission (PCDAI score ≤10 points) at week 8. 52% of patients had entered clinical remission. No patient had an intercurrent event and 100% of patients were included in the primary analysis. However, 19% of patients were missing one PCDAI sub score. All missing data was related to missing laboratory values, however PCDAI scores were still calculatable imputing missing Week I-8 laboratory values with values from Week I-0 which represents a conservative approach, as it assumes no improvement in the laboratory values. A higher proportion of males than females experienced a clinical remission at 8 weeks, as did patients with severe CD, and those without a history of failure to treatment with biologics (failed conventional therapy) at baseline. The percentage of patients with a clinical response at week 8 was high at 94%.

Results from the maintenance phase are described thereafter. The numbers of patients who maintained clinical remission throughout the study remained steady over time and were roughly consistent across both dosing frequencies, although there was variation across specific timepoints. Overall, at week M-44, 52% of patients were in clinical remission with the same % in corticosteroid free remission. In comparison, the percentage of patients who experienced a clinical response was not maintained and gradually decreased over the maintenance period with 56% of patients in response at week M-44 (falling from 94% after induction). 25.5% of patients had endoscopic responses at M-44 (by SES-CD score). 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 (44% of patients overall, and 21% of patients in remission).

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 comparable at I-8 at 40%, 33% and 44%; however at the same timepoints clinical response rates were not comparable at 94%, 46% and 96%. With the alternative definition of PCDAI, CDAI and sPCDAI (M-40) questionnaires, clinical remission results at M-44 were 50%, 31% and 52% and clinical responses rates were 56%, 44% and 60%. Following queries 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 sPCDAI is a pragmatic and practical tool for use in the real-world setting. 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.

Based on the submitted data, it is unclear whether paediatric Crohn's disease patients who lose response on ustekinumab maintenance dosing once every 12 weeks may benefit from an increase in the ustekinumab maintenance dosing frequency to once every 8 weeks. However, the MAH has justified that switching paediatric Crohn's disease patients who lose response on ustekinumab maintenance dosing from q12w to q8w treatment was based on extrapolating data from the adult studies. Therefore, it can be accepted based on the PK modelling and the totality of evidence. The recommended dosing is the following (SmPC 4.2):

"The first subcutaneous administration of 90 mg STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1)."

As a biomarker of inflammation CRP values decreased from 25.7mg/L at baseline to 11.5 and 14.6mg/L at the end of the induction (week 8) and maintenance (week 52) periods respectively. By the end of the study, 14% of patients had normalised CRP levels (<3 mg/L). Faecal calprotectin levels decreased from 3904.5 mg/kg at baseline to 1531.5 mg/kg at the end of the induction period, but this was not maintained and rose again to 3453.6 mg/kg by the end of the maintenance phase. 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 15% and 11% of patients has normalised faecal calprotectin (≤250 mg/kg) and lactoferrin (>7.24 µg/g) levels.

At M-44, there was a small increase in the average BMI z-scores for both sexes and posology treatment arms. For PRO QoL questionnaires (IMPACT-III), scores increased from baseline by 20.6 by the end of the study, with a greater increase in scores observed in the q8w arm.

The percentage of patients in endoscopic remission (SES-CD score ≤2 (in participants with a baseline SES-CD score of ≥3)) was 17 and 15%, 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 30 and 25.5% at M-8 and M-44 timepoints. At the same timepoints 33% and 33% of patients who had 1 or more fistulas at baseline achieved complete fistula response however the numbers involved were very limited (1 of 3).

Finally, the applicant presented data from the Exposure Optimisation Substudy (EOS) Analyses, where patients were treated every 4 weeks. Results demonstrated that 16 weeks after entering the sub study, 7/7 (100%) and 4/7 (57%) of subjects were in clinical response and clinical remission.

Further discussion on this phase 3 trial can be found in the section 'Analysis performed across trials'.

Overall data from this phase 3 trial demonstrates positive efficacy to support the use of ustekinumab in paediatric patients ≥40 kg with moderately to severely active Crohn's disease.

Study CRD1001 + LTE, phase 1

The MAH performed a phase I 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.

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). As the proposed extension of indication is limited to patients ≥40kg, the lower weight patients are not so relevant and not the focus of this assessment. 59% (26 subjects) had a body weight ≥40 kg at the start of the trial. For patients ≥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 90 mg maintenance dose which is aligned to the proposed dosing. 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.

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 (4 subjects).

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 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 might be biased, 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 too low to be reliable. A number of subjects had missing PCDAI scores, i.e. 56% and 44% of patients had complete PCDAI scores at week 8 and 48, respectively. The majority of patients were missing one subscore. Given the uncertaintiy on how this may impact the endpoint analysis these data can be considered as supportive only in particular as this was a phase 1 and not the pivotal trial and considering only a subset (n=10) of patients were treated with the relevant posology.

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 23 mg/L at baseline to 16 mg/L at week 8 and 12 mg/L by week 48. By week 8 and 48, 22% and 59% of patients had normalised CRP levels (<3 mg/L). Faecal calprotectin levels decreased from 3915 mg/kg at baseline to 2588 mg/kg at week 8 and to 1505 mg/kg at week 48. Faecal Lactoferrin levels decreased from 252 mg/g at baseline to 235 mg/g at week 8 and to 180 mg/g at week 48. At week 8, 8% and 5% of patients has normalised faecal calprotectin (≤250 mg/kg) and

lactoferrin (>7.24 µg /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 disease-related 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 for any meaningful interpretation.

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 the first part of the study.

Further discussion on this phase 1 trial can be found in the section 'Analysis performed across trials'. Overall data from this phase 1 trial demonstrates positive efficacy to support the use of ustekinumab in paediatric patients ≥40 kg with moderately to severely active Crohn's disease.

Study 3010, RWE observational study

The MAH has submitted a retrospective study examining the effects of ustekinumab on Crohn's disease in 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, while data is captured from outpatient appointments only and not hospitalisations. Nonetheless this database contains a large number of useable patients' data 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 this application, cohort 1 (paediatric patients ≥40kg, severe/moderate CD) and cohort 7 (young adults, severe/moderate CD) are the most relevant. Other cohorts, particularly cohorts with patients <40kg may serve useful should the applicant wish to pursue an indication in younger patients in the future.

Cohort 1 had 114 patients, while cohort 7 had 51 patients. A similar number of patients discontinued in both cohort 1 and 7, 25.4 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 little difference in the average weight between the two groups, with an average weight of 57.6 in cohort 1 (paediatrics ≥40 kgs) and 61.6kg and cohort 7 (young adults) subgroups.

Regarding baseline disease characteristics, cohort 7 patients had a higher median duration of Crohn's disease than cohort 1 (6.2 v 4 years) which is not surprising given the age difference between the two cohorts. Cohort 7 patients also had a higher sPCDAI score at baseline compared to cohort 1 (45 v 40). In both cohorts, the majority of patients had previously used biologics, 99% (cohort 1) v 96% (cohort 7).

Overall, the majority of patients received induction and maintenance doses in line with the approved posology.

The primary analysis demonstrated 23% of paediatric patients ≥40kg were in clinical remission (sPCDAI) 52 weeks after initiation of ustekinumab treatment with 39.5% of patients experiencing at least one intercurrent event and considered treatment failures. Sensitivity analyses were performed on the primary analysis using a multiple imputation method, excluding patients who had missing week 52 remission status and widening the timeframe for the week 52 analysis. Sensitivity results demonstrated remission rates comparable to the primary analysis of 24 to 29%.

Comparable results were obtained for young adults in cohort 7 with 22% of patients in clinical remission 52 weeks after initiation of ustekinumab treatment and with 39% of patients experiencing at least one intercurrent event and considered treatment failures. These results were also steady and comparable over time, for up to 52 weeks.

Two analyses were performed comparing cohort 1 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 ≥40kg 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 1 which does not suggest effectiveness of ustekinumab in treating paediatric patients with Crohn's disease when compared to placebo. When a sensitivity analysis was performed excluding 2 of these studies, results demonstrated there was no overlap in 95% CIs when

compared to cohort 1 which would support effectiveness of Ustekinumab; however this sensitivity analysis was not pre-specified in the protocol or SAP and while the MAH argued that the excluded studies showed divergent clinical remission estimates and a funnel plot suggested asymmetry, the Egger's regression test for publication bias was not statistically significant (p value: 0.22) and the exclusion of these studies was likely subject to prejudice and cannot be relied upon. Following queries, the MAH further discussed why it is not suitable to 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. Furthermore, the clarification on the different scoring systems also highlights the limitations of any comparisons between studies using CDAI (meta-analysis) versus PCDAI (phase 3 paediatric clinical trial). Other outcomes demonstrated that at week 52, the percentage of patients in clinical response and PGA clinical remission was higher in paediatric patients ≥40kg compared to young adults, 51 v 40% (clinical response) and 34 v 27.5% (PGA remission). A similar percentage of patients were in corticosteroid-free clinical remission (19 v 20% for paediatrics ≥40kg v young adults).

In both cohort 1 and 7, fewer patients with endoscopy assessments were in clinical remission than those without endoscopy assessments. This may be connected to the fact that some patients underwent endoscopy assessment because they weren't doing well or needed an intervention. Of the patients with endoscopy assessments, only a subset of these were evaluable for endoscopy remission at week 52, these results demonstrated 20 and 33% of patients in cohort 1 and cohort 7 were in endoscopic remission. Within the same cohorts, but for patients with active CD, 25 and 21% of patients experienced clinical remission at week 52.

Of the patients who could be assessed by full PCDAI at Week 52, 24 and 44% of patients in cohort 1 and cohort 7 experienced clinical remission. For cohort 1, 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.

44 patients switched to a q4w dosing frequency and the applicant provided some limited efficacy data, for this group. The rate of clinical efficacy was 18% in the q4w group compared to 28% in the q8w group. This data is in addition to the 10 patients who switched to q4w in the pivotal phase 3 trial. There were proposed updates to the product information where the MAH recommended or referred to dosing every 4 weeks for patients who lose clinical response and have low ustekinumab exposure, however the applicant has since agreed to delete reference to q4w dosing. This proposed dosing frequency is not approved in adult patients and is currently not supported.

Overall, the results of this observational study should be interpreted with caution due to some limitations. In addition to the general limitations applicable to all observational studies, there are also some limitations relevant to this specific study. Not all patients received dosing in line with the approved SmPC dose, there was a wide timeframe in which time-specific outcomes were measured, some 'baseline' measurements were taken after administration of ustekinumab, and the adult population studied is limited to young adults aged 18 to 26 rather than a wider range of adult ages.

However, there are also many 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, however, this observational real-world evidence can be considered supportive to the clinical trial data for the paediatric extrapolation of ustekinumab in adults in CD. However, some concerns remain when the paediatric data is compared to adult placebo data (see also uncertainties section).

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 10 patients (≥40kg, 390 IV dose) are included. As previously discussed, 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) and clinical response (>20% difference), 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 applicant's comment that these differing results may be partly explained by a much higher percentage of biologic failure participants in CRD1001 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 posologies. In addition, for clinical remission, clinical response 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=10), and lack of formal statistical analyses limits interpretation. In contrast a lower percentage of patients experienced endoscopic response at week 16 (M-8) in the phase 3 trial compared to the phase 1 trial. CRP levels reduced by a comparable level in both trials at week 8.

For the maintenance phase, data from all patients from the phase 3 trial are presented but for comparative purposes the q8w group (n=23) is most relevant. For the phase 1 trial data from all patients ≥40kg are included. The main time point also differs across the two studies, M-44 (52 weeks in total) v week 48.

For a more accurate comparison, some data were presented again, calculating results based on the number of patients included at baseline for CRD1001 (as was presented for CRD3004). Overall, 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 and CRP levels and a higher change from baseline in faecal calprotectin levels in the phase 1 trial compared to the phase 3 trial at week 48/M-44.

In summary, 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 ≥40kg with moderate to severe Crohn's disease.

Comparison of studies CRD3004 and adult studies

Results are presented side by side between the paediatric trial and the pivotal adult trials (induction studies (UNITI-1 and UNITI-2) and a maintenance study (IM-UNITI)). 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, with higher CDAI scores, CRP 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, 2.6 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 and clinical response was higher in the paediatric patients (52% and 94%) when compared with adult patients (30% and 47% (the 2 induction studies combined)). CIs 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, 40% of patients had a history of biologic failure, compared to 90.0% in CRD3001 and 1% CRD3002. Similar trends with higher results in the paediatric study than the corresponding adult studies were observed when looking at clinical remission and response rates between biologic failure and non-biologic failure subgroups.

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 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 CRP and faecal calprotectin levels with greater reduction in the paediatric study than the corresponding adult studies.

For the maintenance phase the main time point differs across the studies, M-44 (52 weeks in total - paediatrics) v week 48 (adults). However, the results demonstrated that levels of clinical remission, clinical response and corticosteroid-free clinical remission are 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 applicant was asked to compare CDAI results in paediatric patients to adult studies. As requested, the applicant has provided details on the comparison of CDAI maintenance outcomes for a more relevant comparison across the paediatric and adult studies. CDAI maintenance remission and response rates were lower in paediatric participants (Study CRD3004) than those observed in the Adult IM-UNITI study (Study CRD3003). However, the applicant adequately discussed why these results may not be reliable including 40% of paediatric patients with missing CDAI data, the small number of paediatric patients involved, a limited number of non-responders included in the paediatric study (none in the adult study), a higher rate of induction response and a higher baseline CDAI score in the paediatric study compared to the adult study. The applicant also performed a sensitivity analysis to estimate clinical remission and clinical response rates in paediatric participants with non-missing CDAI data at baseline. Results demonstrated similar clinical response rates between paediatric and adult studies. There was still a difference in clinical remission rates between paediatric and adult studies, however the difference was narrowed, and 95% CI overlapped. Overall, the sensitivity analysis and associated discussions can be considered supportive.

While there are differences across the trials limiting interpretation, results from the phase 3 trial in paediatric patients ≥40kg 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.

Finally, the applicant also presented a position paper demonstrating similarity of response and remission for ustekinumab therapy regardless of whether the disease was adult onset, or paediatric onset. Similar results were also obtained when looking at other agents (infliximab, guselkumab) in Crohn's disease.

2.4.5. Conclusions on the clinical efficacy

Overall, the clinical trials and RWE support the extrapolation of ustekinumab from adults to paediatric patients ≥40kg with moderately to severely active Crohn's disease.

2.5. Clinical safety

Introduction

Patient exposure

The primary evidence of safety of ustekinumab in paediatric patients with Crohn's disease comes from the pivotal Phase 3 CRD3004 study (UNITI Jr.) and phase 1 PK Study (CRD1001, UNISTAR). Both studies examined induction and maintenance study intervention in paediatric patients with moderately to severely active Crohn's disease. In both studies the induction dose was administered at week 0. At week 8 the maintenance period began.

Safety data for CRD3004 was collected up to 44-weeks for the EMA randomised analysis set of participants with body weight ≥40 kg.

Safety data for CRD1001 was collected up to 16-weeks (primary analysis) and final safety assessment at week 28. Safety assessment also continued until the last participant completed the last subject study visit at Week 236 from optional LTE. For the purposes of the safety analysis, all data collected after the participant received their first SC maintenance dose of ustekinumab at the Week 8 visit through Week 48 (±10 days) is considered occurring during the maintenance. All other data beyond Week 48 are reported during the LTE period of study CRD1001, see additional safety data below.

Safety data from both the pivotal Phase 3 Study (CRD3004) and phase 1 PK Study (CRD1001) were pooled for the safety analyses to provide integrated evidence for induction (I-0 to M-0, 8 weeks) and maintenance (M-0 to M-44, a total of 44 weeks for CRD3004 and from week 8 to week 48, a total of 40 weeks for CRD1001).

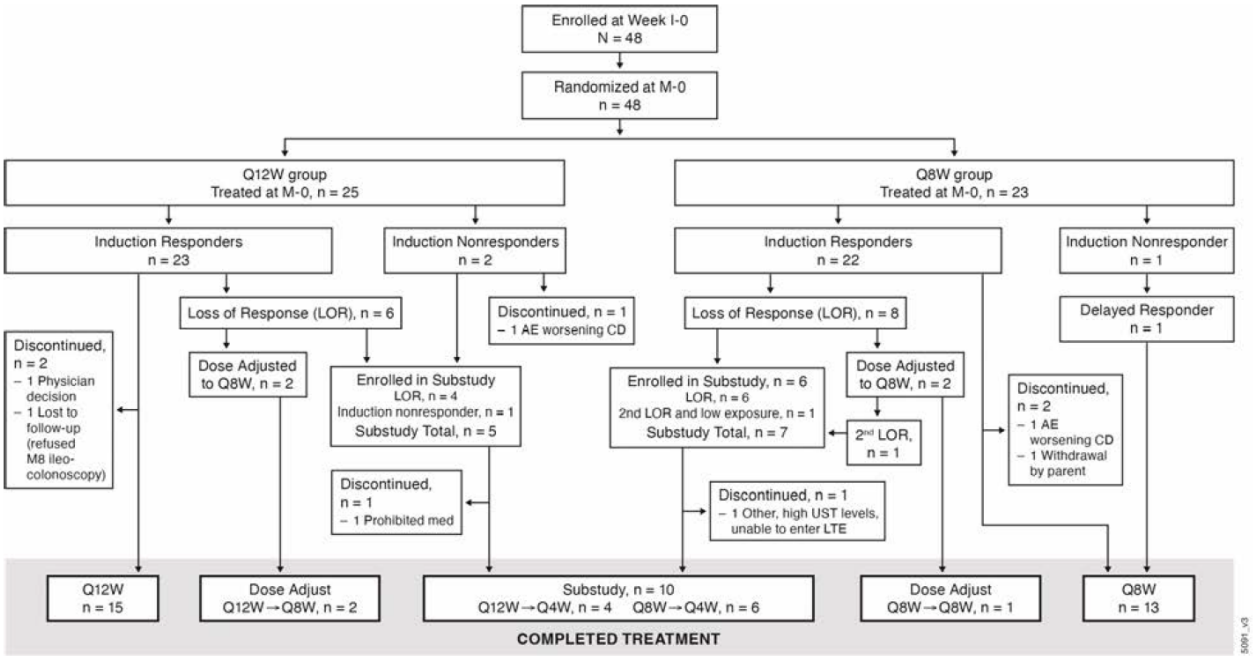
CRD3004 interim analysis

The study population is defined as EMA Randomised Analysis Set for Participants with Body Weight ≥40 kg (ERAS): All participants who had body weight ≥40 kg at Week I-0 and Week M-0, received at least 1 administration of study intervention during maintenance, and completed Week M-44 visit or terminated the main study prior to Week M-44 at the interim DBL, including participants who entered the sub study.

For the population of interest for this extension of indication (paediatric participants with moderately to severely active Crohns disease weighing ≥40 kg), 48 participants were enrolled. Participant disposition is outlined in **Figure *46***.

The mean cumulative total dose of ustekinumab 90mg q8w was 540mg, with a median total duration of exposure of 48.1 weeks, (n=23). The mean cumulative total dose of ustekinumab 90mg q12w was 360mg, with a median total duration of exposure of 44 weeks, (n=25). The average duration of follow-up was 8.3 weeks through Week I-8 and 37.4 weeks from Week M-0 through Week M-44.

Figure 46: Disposition of Randomised Participants



CRD1001

All randomised subjects who received at least 1 administration of ustekinumab are included in the safety analysis set. A total of 44 subjects were randomised and treated with ustekinumab: 23 in the low-induction dose group (ustekinumab 3mg/kg IV or 130 mg IV), and 21 in the high-induction dose group (ustekinumab 9 mg/kg IV or 390 mg IV).

For the population of interest for this extension of indication (≥40 kg), 23 participants were enrolled and included in safety data. The mean cumulative total dose was 540mg, with a median total duration of exposure of 46.7weeks of ustekinumab 90mg q8w.

Pooled

The safety analysis set (SAS) included all participants in the final analysis set (FAS) for each study (CRD3004 and CRD1001) who received at least 1 administration of ustekinumab and who had a body weight of ≥40 kg at Week 0 and Week 8. The pooled safety data includes the induction period and the maintenance period.

The combined number of participants from CRD3004 and CRD1001 is 71 for the population of interest for this extension of indication (≥40 kg). The combined number of participants in the SAS of ustekinumab Q8W is 46 from CRD3004 and CRD1001. The number of participants in the SAS of ustekinumab Q12W is 25.

The average duration of follow up from week 0 through week M-44/week 48 was 43.3weeks. The average number of exposures was 6.8 administrations.

Demographic characteristics of the 71 paediatric clinical study participants in the pooled SAS are as follows:

- Most participants were white (63 [91.3%] of 69 participants) and not Hispanic or Latino (68 [95.8%] of 71 participants).
- 35 (49.3%) of 71 participants were female.
- Median age was 15 years [range 10-17]. Most participants (67 [94.4%] of 71 participants) were aged ≥12 to <18 years. 4 participants were aged ≥6 to <12 years. None were aged <6years.

- Median body weight was 51 kg (IQ range: 45.1 kg to 61.7 kg; mean [SD] BMI z-score of 0.03 [1.028]). All participants were ≥40kg. The majority of participants (45 [63.4%]) were ≥40 to ≤ 55kg.
- Measures of height and weight trended lower in CRD1001.

Clinical disease characteristics at baseline were representative of a paediatric population with moderately to severely active Crohn's disease. A majority (52 [73.2%]) of the 71 participants from both studies were taking at least 1 Crohns disease-related concomitant medication at baseline. 39 [54.9%] of the 71 participants had a history of biologic failure; 19 (39.6%) of 48 participants in CRD3004, and 20 (87.0%) of 23 participants in CRD1001.

Adverse events

Induction period

Approximately two-thirds (66.2%) of the total participants in both studies reported at least 1 AE during the induction period; 16 (69.6%) participants in CRD1001 and 31 (64.6%) participants in CRD3004. Two participants experienced severe AEs; myalgia and nephrolithiasis. 4 participants experienced SAEs; 3 in CRD1001 and 1 in CRD3004. The majority of AEs were considered not related to study intervention.

Infections were the most commonly reported AE, occurring in approximately one-third (33.8%) of the total participants. However, there were no serious infections and few of the non-serious infections (5.6%) required oral and/or parenteral antibiotics for treatment.

The SOCs with the highest proportion of overall participants with AEs were Infections and infestations (23 [32.4%] participants) and Gastrointestinal disorders (15 [21.1%] participants). The most frequently reported PTs (≥5% of the total participants) were anaemia (11 [15.5%] participants), upper respiratory tract infection (9 [12.7%] participants), headache (9 [12.7%] participants), nasopharyngitis (4 [5.6%] participants), and anal fistula (4 [5.6%] participants).

During the induction period, 3 (4.2%) participants from CRD3004 had AEs that were considered "reasonably related" by the investigator (nausea, headache, and psoriasis).

Table 52: Overall Summary of TEAEs During the Induction Period Among Participants Weighing at Least 40 kg; SAS (Studies CRD3004 and CRD1001)

	Ustekinumab IV		
	CRD1001	CRD3004	Total
Analysis set: SAS	23	48	71
Average duration of follow-up (weeks)	8.0	8.3	8.2
Average exposure (number of administrations)	1.0	1.0	1.0
Participants with 1 or more:			
AEs	16 (69.6%)	31 (64.6%)	47 (66.2%)
SAEs	3 (13.0%)	1 (2.1%)	4 (5.6%)
AEs leading to death	0	0	0
AEs leading to discontinuation of study intervention	1 (4.3%)	0	1 (1.4%)
AEs reasonably related to study intervention[a]	0	3 (6.3%)	3 (4.2%)
AEs of severe intensity	1 (4.3%)	1 (2.1%)	2 (2.8%)
Infections	8 (34.8%)	16 (33.3%)	24 (33.8%)
Serious infections	0	0	0
Infection requiring oral and/or parenteral antimicrobial treatment	2 (8.7%)	2 (4.2%)	4 (5.6%)
Malignancy	0	0	0
Active TB infections	0	0	0
Opportunistic infections	0	0	0
AEs temporally associated with the infusion of study intervention at Week I-0 (Week 0)[b]	1 (4.3%)	1 (2.1%)	2 (2.8%)

[a] An AE that was assessed by the investigator as related to study intervention or if the relationship to study intervention was missing.
[b] These are AEs that occurred during or within 1 hour after the IV infusion of study intervention.
Note: Participants are counted only once for any given event type, regardless of the number of times they actually experienced the event.

Maintenance Period

Nearly all (91.5%) participants from both studies reported an AE during the maintenance period. A total of 7 (9.9%) participants had at least 1 AE of severe intensity; 2 participants in CRD3004 q12w and 5 participants in CRD1001. There were 9 PTs severe AEs reported; Crohn's disease (n=2), large intestinal stenosis, small intestinal obstruction, abscess intestinal, chronic recurrent multifocal osteomyelitis, suicide attempt, eczema and seborrhoeic dermatitis. 14 participants (19.7%) experienced SAEs. None of the AEs were considered related to study intervention. 5 participants (7%) had AEs leading to discontinuation of study intervention.

Overall, there were 17 participants (23.9%) who required antimicrobial treatment for an infection. Infections requiring oral and/or parenteral antimicrobial treatment were higher in the combined q8w treatment group (32.6%) than in the q12w treatment group (8%). Infections requiring oral and/or parenteral antimicrobial treatment were lower in CRD3004 group vs CRD1001; 18.8% vs 34.8% respectively.

Table 53: Overall Summary of TEAEs During the Maintenance Period Among Participants Weighing at Least 40 kg; SAS (Studies CRD3004 and CRD1001)

	Ustekinumab					
		q8w		q12w	Total	Total
	CRD1001	CRD3004	Combined	CRD3004	CRD3004	
Analysis set: SAS	23	23	46	25	48	71
Average duration of follow-up (weeks)	30.7	39.4	35.1	35.5	37.4	35.2
Average exposure (number of administrations)	4.5	6.8	5.7	6.3	6.5	5.9
Participants with 1 or more:						
AEs	21 (91.3%)	21 (91.3%)	42 (91.3%)	23 (92.0%)	44 (91.7%)	65 (91.5%)
SAEs	6 (26.1%)	4 (17.4%)	10 (21.7%)	4 (16.0%)	8 (16.7%)	14 (19.7%)
AEs leading to death	0	0	0	0	0	0
AEs leading to discontinuation of study intervention	3 (13.0%)	1 (4.3%)	4 (8.7%)	1 (4.0%)	2 (4.2%)	5 (7.0%)
AEs reasonably related to study intervention[a]	0	0	0	0	0	0
AEs of severe intensity	5 (21.7%)	0	5 (10.9%)	2 (8.0%)	2 (4.2%)	7 (9.9%)
Infections	14 (60.9%)	16 (69.6%)	30 (65.2%)	17 (68.0%)	33 (68.8%)	47 (66.2%)
Serious infections	1 (4.3%)	0	1 (2.2%)	0	0	1 (1.4%)
Infection requiring oral and/or parenteral antimicrobial treatment	8 (34.8%)	7 (30.4%)	15 (32.6%)	2 (8.0%)	9 (18.8%)	17 (23.9%)
Malignancy	0	0	0	0	0	0
Active TB infections	0	0	0	0	0	0
Opportunistic infections	0	0	0	0	0	0
Injection-site reaction[b]	0	0	0	0	0	0

[a] An AE that was assessed by the investigator as related to study intervention or if the relationship to study intervention was 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: Participants are counted only once for any given event type, regardless of the number of times they actually experienced the event.

Note: Data from the time of substudy onward in CRD3004 are not included and are summarized separately.

The SOCs with the highest proportion of total participants were Gastrointestinal disorders (48 participants [67.6%]), Infections and infestations (42 participants [59.2%]) and General disorders and administration site conditions (16 [22.5%] participants). This was generally consistent across all subgroups, study and maintenance interval.

The proportion of AEs of SOC 'Gastrointestinal disorders' were similar across studies and treatment groups. The most frequently reported Gastrointestinal PTs in the total group were Crohn's disease (25 [35.2%] of 71 participants), diarrhoea (7 [9.9%] participants), abdominal pain (5 [7.0%] participants), anal fistula, constipation, or vomiting (4 [5.6%] participants each), and anal fissure, large intestinal stenosis, or nausea (3 [4.2%] participants each). Other PTs were reported with a frequency of <3%.

The most frequently reported Infections and infestations PTs in the total group were upper respiratory tract infection (20 [28.2%] participants), nasopharyngitis (10 [14.1%] participants), and COVID-19 (7 [9.9%] participants). The proportions of participants who had a reported event of upper respiratory tract infection and nasopharyngitis were similar between treatment groups; COVID-19 was reported only in the CRD3004 study. Other PTs were reported with an overall frequency of <3%.

The most frequently reported General disorders and administration site conditions PTs in the total group was Pyrexia (8 [11.3%] participants) and Asthenia (3 [4.2%] participants). Other PTs were reported with a frequency of <3%. The frequency of General disorders and administration site conditions was slightly higher in CRD1001 (34.8%) compared to CRD3004 q8w (13%) and q12w (20%). This was driven by the frequency of pyrexia being slightly higher in CRD1001 (17.4%, 4 participants) compared to CRD3004 (4 [4.36%] of 48 participants [1 in the q8w treatment group and 3 in the q12w treatment group]).

Other AEs that occurred in ≥5% of participants included the PTs anaemia (8 [11.3%] of 71 participants), arthralgia (7 (9.9%) participants), headache (8 [11.3%] participants), and mood altered (4 [5.6%] participants). Anaemia was reported more frequently in CRD3004 than CRD1001 (7 [14.6%] of 48 participants [4 in the q8w treatment group and 3 in the q12w treatment group] versus 1 [4.3%] of 23 participants, respectively). Headache was reported more frequently in combined q8w (7 [15.2%] participants) than q12w (1 (4%) participant).

Other AEs that occurred in ≥10% of participants included the PTs anaemia (SOC Blood and lymphatic system disorders) and headache (Nervous system disorders; 8 [11.3%] of 71 participants each). Anaemia was reported more frequently in CRD3004 than CRD1001 (7 [14.6%] of 48 participants [4 in the q8w treatment group and 3 in the q12w treatment group] versus 1 [4.3%] of 23 participants, respectively).

During the maintenance period, no participant had AEs that were considered "reasonably related" by the investigator.

Serious adverse event/deaths/other significant events

AESI were considered as serious infections, malignancy, opportunistic infections, active TB infections, anaphylaxis or delayed hypersensitivity (serum sickness-like) reactions or injection-site reactions.

Induction period

There were no AEs leading to death, serious infections, malignancy, opportunistic infections, active TB infections, anaphylaxis or delayed hypersensitivity (serum sickness-like) reactions or injection-site reactions.

4 participants (5.6%) experienced at least 1 SAEs; 3 in CRD1001 and 1 in CRD3004. Events from CRD1001 included vision blurred (SOC Eye disorders), intestinal obstruction (SOC Gastrointestinal disorders), myalgia (SOC Musculoskeletal and connective tissue disorders), and events from CRD3004 included nephrolithiasis (SOC Renal and urinary disorders). None were considered related to study investigation.

Two (2.8%) of 71 total participants had a reported AE temporally associated with infusion (defined as an AE, except for laboratory abnormalities, which occurred during or within 1 hour after the infusion of study intervention) at Week I-0 (Week 0). The PTs were pyrexia (SOC General disorders and administration site conditions) and headache (SOC Nervous system disorders). No AEs temporally associated with infusion resulted in discontinuation of study intervention and none were serious.

Maintenance period

There were no AEs leading to death. No malignancy, active TB, opportunistic infection, anaphylaxis or delayed hypersensitivity (serum sickness-like) reactions, or injection-site reaction occurred.

A total of 14 (19.7%) participants had at least 1 SAE (8 participants in CRD3004 and 6 participants in CRD1001). The proportion of participants who had at least 1 SAE were similar in the CRD3004 q8w (17.4%) and q12w treatment groups (16%), but higher in the CRD1001 study (26.1%).

The SOC with the highest proportion of participants SAEs remained Gastrointestinal disorders (10 [14.1%] of 71 participants); 4 participants in CRD3004 and 6 participants in CRD1001. The most frequently reported PT was Crohn's disease (5 [7.0%] of the total participants; 2 participants in the q12w treatment group in CRD3004, and 3 participants in CRD1001). One SAE was a suicide attempt in a CRD3004 participant with a prior diagnosis of untreated depression. Most of the remaining SAEs were singular events, anal fistula, anal ulcer, diarrhoea haemorrhagic, large intestinal stenosis, and small intestinal obstruction. None were considered reasonably related to study investigation.

There was 1 serious infection in CRD1001 study: intestinal abscess. This was considered not related to study intervention and event resolved with sequelae.

Incidence rates

Throughout the reporting period, the incidence rate of SAEs per 100 person-years in the q8w and q12w treatment groups from CRD3004 was 19.10 and 23.89 per 100 person-years, respectively. The incidence rate of SAEs per 100 person-years from CRD1001 was 99.65 per 100 person-years. Of note, 2 participants accounted for 11 of the total 17 SAEs in CRD1001, and this contributed to the higher observed SAE rate (i.e., without the 2 participants' 11 SAEs, the incidence rate would be 37.47 per 100 person-years). The SOC with the highest rate of SAEs per 100 person-years was Gastrointestinal disorders (22.06 per 100 person-years). The PT with the highest rate of SAEs per 100 person-years was Crohn's disease (10.18 per 100 person-years).

The incidence rate of infections per 100 person-years in the q8w and q12w treatment groups from CRD3004 was 224.40 and 138.57 per 100 person-years, respectively. None were serious or required hospitalisation. In CRD1001, the incidence rate of infections per 100 person-years was 187.58 infections per 100 person-years. Across both treatment groups, the rate of infections was 181.50 infections per 100 person-years combined. The PTs with the highest number per 100 person-years included upper respiratory tract infection (52.60 per 100 person-years), and nasopharyngitis (25.45 per 100 person-years). In CRD1001, the incidence rate of serious infections was 5.86 per 100 person-years. The incidence rate of serious infections in CRD3004 was 0.00 per 100 person-years.

Laboratory findings

Haematology laboratory parameters

During the induction period, no Grade 4 abnormalities were observed, and only 1 (1.5%) of 65 participants had Grade 3 decreased lymphocyte counts. Grade 2 or higher abnormalities of anaemia (6 [9.2%] of 65 participants) and decreased lymphocyte counts (8 [12.3%] of 65 participants) were observed through the induction period. The remaining haematology laboratory parameter abnormalities were Grade 1 in severity.

During the maintenance period, no Grade 4 abnormalities were observed. Three (4.3%) of 70 participants had Grade 3 decreased lymphocyte counts. Grade 2 or higher abnormalities of anaemia (8 [11.3%] of 71 participants), decreased lymphocyte counts (11 [15.7%] of 70 participants), and decreased neutrophil counts (1 [1.4%] of 70 participants [CRD1001]) were observed through the maintenance period. The remaining haematology laboratory parameter abnormalities were Grade 1 in severity. The proportion of participants who had markedly abnormal values was low and consistent between the q8w and q12w treatment groups, with the exception that a numerically higher proportion of participants from CRD1001 had Grade 2 anaemia than the q8w treatment group from CRD3004 (4 [17.4%] of 23 participants versus 1 [4.3%] of 23 participants, respectively).

A large proportion of all participants (72%) had ≥1 grade anaemia. Haematology parameter-related abnormalities that have been reported as AEs of anaemia were reported in 17 (23.9%) of 71 participants;

7 (28%) of q12w participants compared to 10 (21.7%) q8w combined participants. These AEs were not considered serious by the investigator, and none resulted in discontinuation of study intervention.

Clinical chemistry parameters

During the induction period, no Grade 3 or 4 clinical chemistry parameter abnormalities were observed, and chemistry parameter abnormalities of Grade 2 occurred in only 2 [2.9%] of 69 participants; hypokalaemia and increased creatinine. During the induction period, all participants had ALT, AST, and total bilirubin values within normal range at baseline, with the exception of 1 participant who had abnormalities (>1×ULN) at baseline. There were no observations of AST or ALT values >5×ULN or total bilirubin values >2×ULN (>42 µmoL/L). Four participants had AST/ALT/bilirubin abnormalities through induction: 1 participant in the CRD3004 q12w treatment group (ALT >1 and ≤3×ULN), 1 participant in the CRD3004 q12w treatment group (AST >1 and ≤3×ULN), 2 participants in the CRD1001 group (total bilirubin >1 and ≤2×ULN). No participants met the criteria of possible Hy's law.

During the maintenance period, few Grade 2 clinical chemistry parameter abnormalities of increased blood bilirubin, increased creatinine, hypernatremia, and hypoalbuminemia were observed, mostly occurring in the q8w treatment group. One (1.4%) of 71 participants in the q8w treatment group had Grade 3 increased AST at Week M-24 (AST: 252 U/L). AST levels were within normal range at the Week M-32 visit. No participants in the q12w treatment group had Grade 3 abnormal post-baseline clinical chemistry values. No Grade 4 abnormalities were observed in either treatment group. No participants met the criteria of possible Hy's law.

Several clinical chemistry parameter-related abnormalities have been reported as AEs (PTs blood alkaline phosphatase increased, blood bilirubin increased, CRP increased, hepatic enzyme increased, liver function test increased, hypoalbuminemia, and hypoproteinaemia). These occurred in only 1 (1.4%) of 71 participants each. None of these AEs resulted in discontinuation of study intervention and were not considered serious by the investigator, except for the event of hepatic enzyme increased (the event resolved and was considered not related to study intervention).

Vital signs and physical findings were monitored by the investigator in both CRD3004 and CRD1001. To date, there have been no clinically meaningful changes from baseline in vital signs or physical examination findings. Vital sign-related AEs were reported and analysed as standard AEs.

Growth

In CRD3004, at Week I-8, there was an increase from baseline in BMI z-scores mean (SD): females, 0.19 (0.241); males, 0.10 (0.321). At Week M-44, there was a small increase from baseline mean BMI z-scores, among males and females and across the q12w and q8w treatment group. At Week M-44, the combined mean (SD) BMI z-score in females was 0.39 (0.860) and was 0.12 (1.226) in males, within the normal growth range (BMI z-score >-1).

In CRD1001 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.

Safety in special populations

Biologic failure status

During the induction phase, the overall proportion of participants with AEs in the prior biologic failure subgroup was 71.8% and 59.4% in the non-biologic failure subgroup. The proportion of participants with SAEs, AEs of severe intensity, reasonably related AEs, AEs leading to discontinuation of study

intervention, infections requiring oral and/or parenteral antimicrobial treatment, and AEs temporally associated with the infusion of study intervention were low in both subgroups.

During the maintenance phase, the proportion of participants with AEs in the prior biologic failure subgroup was 94.9% and 87.5% in the non-biologic failure subgroup. The proportions of participants with SAEs (28.2% of participants) in the prior biologic failure subgroup were numerically higher than in the nonbiologic failure subgroup (9.4% of participants). The proportions of participants with infections requiring oral and/or parenteral antimicrobial treatment in the prior biologic failure subgroup (35.9% of participants) were numerically higher than the nonbiologic failure subgroup (9.4% of participants). AEs leading to discontinuation of study intervention occurred only in participants who had prior biologic failure (5 [12.8%] participants). AEs of severe intensity occurred in a higher frequency of participants who had prior biologic failure (6 [15.4%] participants) than non-biologic failure participants (1 [3.1%] participant).

Age

The age range of the enrolled participants was 10 to 17 years. Due to the low number of participants ≥2 to <12 years of age (n=4) compared with participants ≥12 to <18 years of age (n=67), no meaningful comparisons can be made between the 2 age groups.

Sex

When evaluated according to the participant's sex in the induction and maintenance periods, there were no notable safety differences between the subgroups.

Pregnancy and lactation

No pregnancies were reported.

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, 1 (2.1%) of 48 participants was positive for antibodies to ustekinumab through Week I-8. The participant positive for antibodies was also positive for NAbs. Among 46 participants who received ustekinumab during both induction and maintenance, 1 participant (2.2%) was positive for antibodies to ustekinumab through Week M-44. This participant was also positive for NAbs.

For study CRD1001, no subject was positive for antibodies to ustekinumab through Week 16 in this study.

Discontinuation due to adverse events

AEs leading to discontinuation of study intervention during the induction period occurred in no participants in CRD3004 and only 1 participant in CRD1001; PT Crohn's disease.

5 participants (7%) had AEs leading to discontinuation of study intervention during the maintenance period; 2 participants (4.2%) in CRD3004 and 3 participants (13%) in CRD1001. All 6 events leading to discontinuation of study intervention were coded to the SOC Gastrointestinal disorders. The most common AE by PT was Crohn's disease (4 [5.6%] of the total population; 2 participants in CRD3004 and 2 participants in CRD1001). Other AEs included singular events of intestinal obstruction and small intestinal obstruction in CRD1001.

Additional clinical data

Study CRD3004 Exposure Optimisation Sub study

Participants who had a confirmed LOR and had low steady-state trough ustekinumab concentrations (low exposure) were eligible to participate in the optional EOS and received a modified dosing regimen of 90 mg SC q4w. The planned duration of the study intervention was 16 weeks in optional EOS.

A total of 12 (25%) of 48 participants in the main study enrolled in the EOS. These participants have also been included in EROS and pooled safety analysis above. Five participants in the q12w arm and 7 participants in the q8w arm entered the EOS. Among the 12 participants who were treated, 2 (16.7%) discontinued the EOS treatment; 1 due to initiation of prohibited medication and 1 due to 'other' high ustekinumab exposure levels. The average duration of follow-up was 22.9 weeks, with an average exposure of 5.6 administrations.

9 (75%) of 12 participants reported 1 or more AEs. 1 (8.3%) of 12 participants reported an SAE. 1 (8.3%) of 12 participants reported an AE of severe intensity. 6 (50%) of 12 participants reported infection. 1 (8.3%) of 12 participants reported serious infections: gastroenteritis with aeromonas. There were no AEs judged by the investigators to be related to study intervention, no malignancies, no opportunistic infections, no cases of TB, no deaths, and no injection-site reactions.

The most frequent AEs reported in the sub study participants were in the Gastrointestinal disorders SOC (6 [50%] of 12 participants; Crohn's disease was the most commonly reported PT in 3 [25%] participants), followed by the Infections and infestations SOC (5 [41.7%] participants, with upper respiratory tract infection reported in 2 [16.7%] participants).

Long-term Extension From Study CRD1001

Study CRD1001 allowed paediatric participants from the randomised, double-blind period who were receiving benefit from ustekinumab maintenance therapy (through Week 16) to continue receiving ustekinumab. Data from week 16 to 48 has been reported in the pooled safety analysis above. All data from Week 48 onwards are reported during the LTE period. The LTE period was up to Week 268 (approximately 4 years).

Of the 40 subjects who completed participation through Week 16, 34 subjects participated in the LTE: 18 subjects from the low dose group and 16 subjects from the high dose group. However, this includes both subjects with body weight <40 kg and ≥40 kg; 16 subjects and 18 subjects respectively.

In summary, for the overall population as presented a total of 26/34 (76.5%) subjects terminated study participation from Week 16 through the final safety follow-up visit. Only 8 participants completed the LTE period. Through the final safety follow-up visit, 5/34 (14.7%) subjects discontinued study agent because of 1 or more AEs. All AEs resulting in study intervention discontinuation were gastrointestinal disorders, with the PT Crohn's disease (worsening Crohn's disease) being most frequently reported.

Through the final safety follow-up visit, 94.1% of subjects reported 1 or more AEs. 32.4% subjects reported 1 or more SAEs. The majority of SAEs were in the SOC Gastrointestinal disorders (29.4%). Among the SAEs, PT Crohn's disease (worsening Crohn's disease) was most frequently reported (6 [17.6%] of 34 participants). The remaining SAEs were singular events commonly related to Crohn's disease (PTs anal ulcer, large intestinal stenosis, malnutrition, vomiting) or other singular events (PTs constipation, pancreatitis [due to azathioprine], appendicitis, syncope, and pyrexia). No malignancies or deaths were reported. No serious infections or opportunistic infections (including tuberculosis) were reported. 82.4% of subjects reported 1 or more infections. The PTs Upper respiratory tract infection and Nasopharyngitis were most frequently reported. No deaths, serious infections, or neoplasms (malignant) were reported through the final safety follow-up visit. No injection site reactions were reported. There were no reports of possible anaphylactic or delayed hypersensitivity reactions. Of the 34 subjects with appropriate samples who were treated with ustekinumab during the LTE period, 1/34 (2.9%) subject was positive for antibodies to ustekinumab through the final safety visit with a peak titre of 1:100. The subject was positive for NAb.

Post marketing experience

The proposed indication for paediatric CD is further supported by pharmacovigilance data, data from the ImproveCareNow (ICN) registry and data from safety data from other approved indications for ustekinumab in paediatric & adult populations.

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 for IBD as part of routine clinical care. C0168Z02 also captures safety data from participants who were treated with other therapies, including ustekinumab, with or without prior exposure to advanced therapies.

119 paediatric patients (<18 years of age) weighing at least 40 kg have been included in this safety analysis. This relates to 287.1 patient-years of ustekinumab exposure, 244.4 patient-years during the follow-up period, and 42.8 patient-years during the long-term follow-up portion (transition period) of the study. The median duration of exposure to ustekinumab was 29 months (range 1;80). More than half of the patients (54.6%) received ustekinumab for at least 24 months and another 23 (19.3%) received ustekinumab for 12-23 months. The ustekinumab-treated population in DEVELOP were children with refractory disease. Nearly all patients (116 [97.5%] of 119 patients) received an IBD-targeted biologic prior to ustekinumab treatment in the study, with 51 (42.9%) patients receiving 2 prior biologics and approximately one-fourth (29 [24.4%]) of patients receiving 3 or more. Median age of ustekinumab exposure was 16 years.

During the registry, the 119 patients experienced AEs at a rate of 177.62 AEs per 100 patient-years of exposure. The most common AEs were Crohn's disease (30 events), abdominal pain (17 events), diarrhoea (17 events), *Clostridium difficile* infection (14 events), and haematochezia and pyrexia (each, 11 events). None of the 119 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 21 reported SAEs of Crohn's disease, and 2 events each of malnutrition, anal abscess, anal fistula, abdominal pain, abdominal abscess, and UC. All other SAEs were reported once.

The rate of patients experiencing at least one serious infection was 4.53 per 100 patient-years of exposure (13 patients). The rate of serious infections was 5.57 per 100 patient-years of exposure (16 events). Most of the serious infections were reported only once, except for abdominal abscess and anal abscess, each reported twice. There were no reported cases of TB or colonic dysplasia. There was 1 case of new autoimmune disease: cholangitis sclerosing. There were 2 cases of opportunistic infection; candida infection and cytomegalovirus infection, neither of which were serious. There was one malignancy; malignant carcinoid tumour tip of appendix, which was considered unlikely related. One patient had an infusion reaction, an event reported with the PT of Crohn's disease.

Of the 119 patients exposed to ustekinumab, 30 patients discontinued ustekinumab administration during the study, of which 7 patients discontinued due to an AE; 1 due to ongoing severe Crohn's disease flare resulting in a colectomy and stoma placement and subsequent intra-abdominal abscess, 4 due to a Crohn's disease flare, 1 due to high calprotectin, and 1 due to ileus. The median time to discontinuation was 12 months.

Real World Evidence

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, limited safety data were collected.

114 patients who weighed ≥40 kg were included in the paediatric patients Primary Cohort. 51 patients aged 18 to 26 years of age who weighed ≥ 40 kg were included in the Young Adults Cohort. 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

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.

- < 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.)).

Pediatric PsO Studies			
PSO3006 (CADMUS) Phase 3, multicenter, randomized, double-blind, placebo-controlled study 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% 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 placebo: n=37 half-standard dose: n=37 standard dose*: n=36 *standard dose: ≤60 kg: 0.75 mg/kg >60 to 100 kg: 45 mg >100 kg: 90 mg
Study Number/ Description/Status	**Study Population and Primary Endpoint**	**Treatment Period**	**Number of Participants Enrolled/Treated Participants**
			<60 kg: 51 ≥60 kg: 59 Safety data set: 110 total participants 73 ustekinumab-treated participants were included in the SCS safety analyses
PSO3013 (CADMUS Jr) Phase 3, open-label study of SC administered ustekinumab 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% 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 LTE study: Week 56 through Week 264	Main study: 44 participants (28 participants in the LTE study) <60 kg: 40 ≥60 kg: 4 Safety data set: 44 participants (28 participants in the LTE study) All 44 participants were included in the SCS safety analyses

In the comparison analysis set, more participants in studies CRD3004 & CRD1001 experienced AEs compared to PSO3006 or PS03013, see table below. 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 many of the SAEs in the paediatric Crohn's disease studies were related to Crohn's disease.

Table 54: Overall Summary of TEAEs Among Paediatric Participants Weighing at Least 40 kg in Studies CRD1001 and CRD3004 and Paediatric in PsO Studies PSO3006 and PSO3013

	CRD3004+ CRD1001 (Total)[a]	PSO3006 (Combined)[b]	PSO3013[c]
Analysis set: randomized participants (total N)	71	73	44
Average duration of follow-up (weeks)	43.3	56.61	53.15
Average exposure (number of ustekinumab administrations)	6.8	4.9	4.77
Participants with 1 or more:			
AEs	66 (93.0%)	62 (84.9%)	34 (77.3%)
SAEs	16 (22.5%)	6 (8.2%)	3 (6.8%)
AEs leading to death	0	1 (1.4%)	0
AEs leading to discontinuation of study intervention	6 (8.5%)	2 (2.7%)	0
Serious infections	1 (1.4%)	2 (2.7%)	1 (2.3%)
AESIs			
Malignancy	0	0	0
Active TB infections	0	0	0
Opportunistic infections	0	0	0
Injection-site reactions	0	1 (1.4%)	6 (13.6%)

[a] Includes data from randomized participants from the induction and maintenance periods.
[b] Participants through the end of the reporting period (Week 60).
[c] Randomized participants through the end of the reporting period (Week 56).
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Data from the time of substudy onward in CRD3004 are not included and are summarized separately.

'Gastrointestinal disorders' was the SOC in which the highest proportions of participants reported SAEs in CRD3004 and CRD1001. With the exception of Crohn's disease, no PT was reported as an SAE in more than 1 ustekinumab-treated participant in either the induction or maintenance periods in CRD3004 and CRD1001. In PSO3006 and PSO3013, no participant reported more than a single SAE, and no SAE was reported by more than 1 participant; ear infection and pyelonephritis, injury, leukopenia, dermatitis contact and psoriasis, infectious mononucleosis, eyelid injury, and attention deficit/hyperactivity disorder. In CRD3004 and CRD1001, all 6 events leading to discontinuation of study intervention were coded to the SOC Gastrointestinal disorders (most common AE by PT was Crohn's disease). In PSO3006, the AEs leading to discontinuation of study intervention were fatal injury, worsening of psoriasis, peripheral oedema, and angiopathy. The most commonly reported infections by PT in all studies included nasopharyngitis (which occurred in a higher proportion of participants in the paediatric PsO studies than CRD3004 and CRD1001), and upper respiratory tract infection.

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 is to monitor long term safety and any potential effect on growth and development in paediatric patients.

At data cut off (9 January 2023) for 5th Interval Safety Registry Report, 103 paediatric patients with PsO have been included in this safety analysis; 70 participants-initiated treatment, with a 45 mg dose of

ustekinumab, while 33 patients received a weight-adjusted first dose. The median first dose received per administration was 45 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 13 years (IQ range: 11.0 to 14.0).

At the data cutoff, 61 patients experienced any AE (59.2%). The majority of AE were mild in severity. A total of 4 (3.9%) patients reported at least 1 AE leading to discontinuation of ustekinumab. No deaths were reported during the study.

33 patients (32%) had any AE related to ustekinumab. The most frequently reported related AEs included PTs within SOCs Infections and infestations (17 patients [16.5%]) followed by General disorders and administration site conditions (15 patients [14.6%]) and Respiratory, thoracic and mediastinal disorders (12 patients [11.7%]). Nasopharyngitis was the most frequently reported related AE (9 patients [8.7%]), followed by fatigue, pyrexia, oropharyngeal pain and headache (all of which were reported in 7 patients [6.8%] each).

11 (10.7%) 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 in 4 patients: 1 patient reporting appendicitis, 2 patients with worsening of psoriasis, and 1 patient with primary sclerosing cholangitis. No patient reported a malignancy.

Safety Data for CD Indications for Stelara in adults

Ustekinumab is licenced for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with lost response to, or, were intolerant to either conventional therapy or a TNFα antagonist. This is initiated with a single intravenous dose based on body weight; < 55 kg: 260mg, >55kg to ≤85kg: 390mg, >85kg: 520mg.

The first subcutaneous administration of 90 mg STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks, is recommended. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment.

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).

Induction

The proportion of paediatric participants who had at least 1 AE was similar to adults. The proportion of paediatric participants who had at least 1 reported SAE was similar to adults in the induction studies however the proportion was higher in the paediatric CRD1001 study (13%) than in the adult induction studies. The proportions of participants with discontinuations due to AEs, serious infections, AESIs (malignancies, opportunistic infections, and active TB infections), and infusion reactions were low and similar between the paediatric and adult studies.

Table 55: Overall Summary of TEAEs Among Paediatric Participants Weighing at Least 40 kg During the Induction Period in Studies CRD3004 and CRD1001 and Adult Participants in Induction Studies CRD3001 and CRD3002

	Ustekinumab IV				
	Pediatrics (<18 Years)[a]			Adults (≥18 Years)[b]	
	CRD1001	CRD3004	CRD3004+ CRD1001 (Total)	CRD3001	CRD3002
Analysis set: randomized participants (total N)	23	48	71	495	419
Average duration of follow-up (weeks)	8.0	8.3	8.2	7.84	7.88
Average exposure (number of ustekinumab administrations)	1.0	1.0	1.0	1.0	1.0
Participants with 1 or more:					
AEs	16 (69.6%)	31 (64.6%)	47 (66.2%)	323 (65.3%)	221 (52.7%)
SAEs	3 (13.0%)	1 (2.1%)	4 (5.6%)	30 (6.1%)	16 (3.8%)
AEs leading to death	0	0	0	0	0
AEs leading to discontinuation of study intervention	1 (4.3%)	0	1 (1.4%)	10 (2.0%)	5 (1.2%)
Serious infections	0	0	0	10 (2.0%)	4 (1.0%)
AESIs					
Malignancy	0	0	0	0	0
Active TB infections	0	0	0	0	0
Opportunistic infections	0	0	0	1 (0.2%)	0
AEs temporally associated with the infusion of study intervention[c]	1 (4.3%)	1 (2.1%)	2 (2.8%)	20 (4.0%)	8 (1.9%)

[a] Includes data from randomized participants from the induction period of CRD3004 and CRD1001.
[b] Randomized participants through Week 8, excluding those enrolled prior to study re-start.
[c] These are AEs that occurred during or within 1 hour after the intravenous infusion of study intervention, with the exception of laboratory abnormalities.
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Data from the time of substudy onward in CRD3004 are not included and are summarized separately.

The SOCs with the highest proportions of AEs through the induction periods in the paediatric studies (CRD3004 and CRD1001) and the adult studies (CRD3001 and CRD3002) were infections and infestations and Gastrointestinal disorders. The most frequently reported PTs (occurring in >10% of participants), in the paediatric studies, were upper respiratory tract infection, and anaemia. A numerically higher proportion of participants in the paediatric population had a reported event of upper respiratory tract infection (14.6% of participants in CRD3004 and 8.7% of participants in CRD1001) than the adult population (4.4% and 2.6% in CRD3001 and CRD3002, respectively). A numerically higher proportion of paediatric participants in CRD3004 (14.6%) and CRD1001 (17.4%) reported an AE of anaemia, than in adults (1% [CRD3001], 1.4% [CRD3002]). Headache was the most commonly reported AE PT (≥5% of participants) in both the paediatric and adult studies. Nasopharyngitis occurred in similar proportions between the paediatric and adult studies. Anal fistula was commonly reported in the paediatric study CRD1001 (13.0%). The same AE PT was reported in 2.1% of participants in CRD3004 and 0.4% and 0.2% of participants in the adult studies (CRD3001 and CRD3002, respectively).

Maintenance

The proportion of paediatric participants who had at least 1 AE was similar to adults. The proportion of paediatric participants who had at least 1 reported SAEs were numerically higher (16.7% of participants in CRD3004 and 26.1% of participants in CRD1001) than in the adult maintenance study CRD3003 (11.0% of participants). The SOC with the highest proportions of SAEs that occurred in the paediatric and adult populations were Gastrointestinal disorders with the most common PTs were either Crohn's disease or Crohn's disease-related SAEs. The proportions of participants with discontinuations due to AEs, serious infections, AESIs (malignancies, opportunistic infections, and active TB infections), and injection-site reactions were low and similar between the paediatric and adult studies.

The adult SAE rate on maintenance ustekinumab therapy through Week 44 from CRD3003 was 19.81 SAEs per 100 person-years in the combined treatment group. The adult infection rate on maintenance ustekinumab therapy through Week 44 in CRD3003 was 129.32 infections per 100 person-years in the combined treatment group. The incidence rate of serious infections in adults on ustekinumab maintenance therapy through Week 44 in the adult maintenance study (CRD3003) in the q8w treatment group was 3.38 per 100 person-years.

Table 56: Overall Summary of TEAEs Among Paediatric Participants Weighing at Least 40 kg in the Maintenance Period in Studies CRD3004 and CRD1001 and Adult Participants in the Maintenance Study CRD3003

	Ustekinumab SC			
	Pediatrics (<18 Years)[a]			Adults (≥18 Years)[b]
	CRD1001	CRD3004	CRD3004+ CRD1001 (Total)	CRD3003
Analysis set: randomized participants (total N)	23	48	71	263
Average duration of follow-up (weeks)	30.7	37.4	35.2	35.9
Average exposure (number of ustekinumab administrations)	4.5	6.5	5.9	-
Participants with 1 or more:				
AEs	21 (91.3%)	44 (91.7%)	65 (91.5%)	213 (81.0%)
SAEs	6 (26.1%)	8 (16.7%)	14 (19.7%)	29 (11.0%)
AEs leading to death	0	0	0	0
AEs leading to discontinuation of study intervention	3 (13.0%)	2 (4.2%)	5 (7.0%)	14 (5.3%)
Serious infections	1 (4.3%)	0	1 (1.4%)	10 (3.8%)[c]
AESIs				
Malignancy	0	0	0	1 (0.4%)[d]
Active TB infections	0	0	0	0[e]
Opportunistic infections	0	0	0	0[f]
Injection-site reactions[g]	0	0	0	12 (4.6%)

[a] Includes data from randomized participants from the maintenance period.
[b] Participants randomized from CRD3001 and CRD3002. Includes data through Week 44 or up to the time of dose adjustment.
[c] Infection as assessed by the investigator.
[d] 1 participant with basal cell carcinoma was also reported in the placebo group.
[e] Through Week 44 of this study, there was 1 event of presumed active primary TB reported in a participant who was randomized to ustekinumab 130 mg IV as induction treatment and then received placebo maintenance treatment.
[f] In the nonrandomized population, there was 1 opportunistic infection: a nonserious event of esophageal candidiasis.
[g] In CRD3004 and CRD1001, 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. In CRD3003, injection-site reaction is defined as any AE at an injection site that was identified as an injection-site reaction by the investigator on the CRF.
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Data from the time of substudy onward in CRD3004 are not included and are summarized separately.

The SOCs with the highest proportions of AEs through the maintenance reporting periods in the paediatric studies (CRD3004 and CRD1001), and the adult maintenance study were Gastrointestinal disorders and Infections and infestations. The proportion of participants who had a reported event of Crohn's disease was numerically higher in the paediatric Crohn's disease studies (CRD3004 and CRD1001) than the adult maintenance study; 37.5% in CRD3004, 30.4% in CRD1001, and 12.2% in CRD3003. The proportion of participants who had a reported event of upper respiratory tract infection was numerically higher in the paediatric Crohn's disease studies (CRD3004 and CRD1001) than the adult maintenance study; 27.1% in CRD3004, 30.4% in CRD1001, and 8.4% in CRD3003. The proportion of participants who had a reported event of anaemia was numerically higher in the paediatric Crohn's disease studies (CRD3004 and CRD1001) than the adult maintenance study; 11.3% compared to 3%. The PTs diarrhoea (13.0%),

pyrexia (17.4%), and headache (17.4%) occurred in a numerically higher proportion of participants in CRD1001 than the adult study CRD3003 (6.1%, 7.2%, and 11.8%, respectively). Other commonly reported PTs occurring in ≥5% of the paediatric participants from CRD3004 and <5% of adult participants in CRD3003 included anal fistula (SOC Gastrointestinal disorders), vomiting (SOC Gastrointestinal disorders), and anaemia (Blood and lymphatic system disorders). COVID-19 (SOC Infections and infestations) occurred only in the CRD3004 study. The PT constipation (SOC Gastrointestinal disorders) occurred in ≥5% of the paediatric participants from CRD1001 and <5% of participants in CRD3004 and CRD3003.

2.5.1. Discussion on clinical safety

With this variation, the MAH seeks to add a new indication for the treatment of paediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease. The proposed induction and maintenance posology for paediatric CD is the same as that for adult patients with CD. This application is supported by data from 2 clinical studies: Phase 3 open label Study CRD3004 (UNITI Jr.) and phase 1 PK Study CRD1001 (UNISTAR). Study CRD1001 has been considered fulfilled by PIP compliance check adopted on 28 February 2020 (EMEA-C1-000311- PIP04-13-M01). Study CRD3004 has been considered fulfilled for patients weighing 40 kg and above by the most recent PIP compliance check EMEA-C2-000311-PIP04-13-M06 dated 31 May 2024. Compliance still needs to be checked for patients weighing <40kg. CRD3004 is still ongoing for patients weighing <40kg.

The applicant confirmed that the submitted CSR is based on an interim DBL (data cut-off date of 1 December 2023). It included all randomised participants in this cohort (n=48) with body weight ≥40 kg who completed the Induction Week I-8 and Maintenance Week M-44 visit (or terminated the study participation prior to Week M-44). It also included any additional data collected after Week M-44 visit up until the DBL.

The applicant confirmed that not all participants with body weight ≥40 kg have completed the final safety visit. A final DBL is planned and the remaining data will be submitted following completion of this variation, including all data collected during safety-follow-up and/or optional substudy visits that were not previously included in the present CSR.

The mean duration of ustekinumab exposure for the 23 subjects receiving ustekinumab 90mg q8w included in study CRD3004 was 48.1weeks. The mean duration of ustekinumab exposure for the 25 subjects receiving ustekinumab 90mg q12w included in study CRD3004 was 44 weeks. The mean duration of ustekinumab exposure for the 23 subjects included in study CRD1001 was 46.7 weeks. The mean duration of exposure of the pooled safety analysis set was 43.3 weeks.

The median age of the studied patients in the pooled analysis set was 15 years (range 10-17). The majority (~90%) was older than 12 years, and only 4 of the patients were below 12 years of age. The median body weight was 51kg (IQ range: 45.1 kg to 61.7 kg). The majority of participants (45 [63.4%]) were ≥40 to ≤55kg.

Both studies had an 8-week induction period followed by a maintenance period. Safety data for CRD3004 was collected up to 52-weeks for the EMA randomised analysis set of participants with body weight ≥40 kg, n=48. Study CRD1001 collected data up to week 236 (safety follow-up), however for the purposes of the safety analysis data up to Week 48 were only included in the safety analysis for this proposed indication >40kg.

Safety data related to patients exposed to ustekinumab for more than 1 year is lacking. This has been reflected in the RMP where "Long-term safety in paediatric patients with moderately to severely active Crohn's disease" has been added as missing information. A Phase 3 LTE basket study ISD3001 (UNITED)

forms part of the RMP as a category 3 additional pharmacovigilance activity to address this missing information.

Induction phase

Two different induction regimens were studied.

- CRD1001: 130mg or 390mg
- CRD3004: Induction was weight tiered which is the similar to the adult dosing regimen (≥40 kg to ≤55kg: 260mg, >55kg to ≤85kg: 390mg, >85kg: 520mg).

During the induction phase, a total of 66.2% of the patients reported any AEs. The frequency of AEs was similar across studies (59.6% CRD1001 and 64.6% CRD3004). Only 1 patient (1.4%) experienced adverse events leading to discontinuation of the study drug.

Most TEAEs reported were mild to moderate in severity. The SOCs with the most frequently reported TEAEs were infections and infestations (32.4%) and gastrointestinal disorders (21.1%). The most frequently reported PTs (≥5% of the total participants) were anaemia, upper respiratory tract infection, headache, nasopharyngitis, and anal fistula. Anaemia & anal fistula probably reflects disease activity rather than a consequence of the treatment. The other 3 AEs are known side effects reported as "common" in the SmPC. 3 (4.2%) participants had AEs that were considered "reasonably related" by the investigator (nausea, headache, and psoriasis). All are known side effects, reported in the SmPC.

4 participants (5.6%) experienced at least 1 SAEs; 3 in CRD1001 and 1 in CRD3004. None were considered related to study investigation. Two (2.8%) of 71 total participants had a reported AE temporally associated with infusion: pyrexia and headache. This is consistent with the known safety profile of ustekinumab.

There were no AESI in induction period. There were no deaths.

Maintenance phase

Two different maintenance regimens were studied (from week 8 and onwards): 90mg q12w or 90mg q8w.

During the maintenance phase, nearly all (91.5%) participants from both studies reported an AE during the maintenance period, this was matched across studies and posology frequencies. Few were considered of severe intensity.

The SOCs with the most frequently reported TEAEs were gastrointestinal disorders (67.6%) and infections and infestations (59.2%). Crohn's disease and Upper respiratory tract infection were most commonly observed adverse events.

The proportion of subjects who experienced AEs was slightly higher in the combined q8w group than in the q12w group for the following PTs: Chron's disease, weight decrease and headache. These likely reflect underlying disease activity. Headache is a known side effect reported in the SmPC.

There was similar number of AEs of serious infection in both groups however more participants in combined q8w group had an infection requiring antimicrobial treatment than q12w group, (32.6% vs 8%), but the absolute number of cases was low with only 1 serious infection in CRD1001; intestinal abscess. This was considered not related to study intervention and event resolved with sequelae. There were no other AESI.

A total of 14 (19.7%) participants had at least 1 SAE. SAEs were slightly more frequent for the q8w group (10 (21.7%) participants), than for the q12w group (4 (16%) participants). 10 of these SAEs were

related to SOC Gastrointestinal disorders. These reflect disease activity rather than a consequence of the treatment. None were considered reasonably related to study investigation.

There were no deaths and only 5 participants (7%) had AEs leading to discontinuation of study intervention.

In summary, the observed adverse events are expected given the known safety profile of Ustekinumab, and there seemed to be no significant dose-relation in the frequency or severity of adverse events.

No distinct trends were observed in the safety profile for ustekinumab across laboratory findings. Although over 50% of all participants had Grade 1 or Grade 2 values, this is not uncommon for the paediatric disease under study. The rate of ADAs was low.

No distinct trends were observed in the safety profile for ustekinumab across subgroups based on age, and sex. Safety data in the youngest patients is very limited. The aim range of the pooled cohort was 10 to 17 years with only 4 participants aged <12 years. This is related to the weight restriction of ≥40kg which usually represents ~50th centile of a 12-year-old.

In the overall summary of TEAEs From Week I-0 (Week 0) Through Week M-44/Week 48, those with prior biological failure had a numerically higher frequency of SAEs, AEs leading to discontinuation of study intervention, AEs of severe intensity, infections and infections requiring oral and/or parenteral antimicrobial treatment, compared to the non-biologic failure subgroup. The MAH further discussed this difference between biological failure status with no expected implications on ustekinumab safety in those with prior biological failure and the product information.

Study CRD3004 Exposure Optimisation Sub study

Study CRD3004 also includes an Exposure Optimisation Sub study (EOS), which was an optional open-label exposure optimisation sub study of minimum 16 weeks duration, with dose interval adjustment to q4w. Participants who had a confirmed LOR and had low steady-state trough ustekinumab concentrations (low exposure) were eligible to participate in the optional EOS and received a modified dosing regimen of 90 mg SC q4w.

This population who received ustekinumab q4w is small (n=12) with limited safety data. These participants have also been included in EROS and pooled safety analysis. The reported AEs are similar to the pooled safety group; however, the numbers are limited to draw any conclusions from this data.

Long-term Extension From Study CRD1001

Study CRD1001 allowed paediatric participants from the randomised, double-blind period who were receiving benefit from ustekinumab maintenance therapy (through Week 16) to continue receiving ustekinumab. Data from week 16 to 48 has been reported in the pooled safety analysis above. All data from Week 48 onwards are reported during the LTE period. The LTE period was up to Week 268 (approximately 4 years). 34 subjects participated in the LTE. This includes both subjects with body weight <40 kg and ≥40 kg; 16 subjects and 18 subjects respectively. This population is small with limited safety data. Of note, the CRD1001 Long-term Extension Clinical Study report does not analyse AEs in terms of body weight ≥40 kg which relates to this proposed new indication. A summary for the whole population is provided. No new significant concerns have been identified; however the numbers are too limited to draw any conclusions from this data.

As mentioned above, "Long-term safety in paediatric patients with moderately to severely active Crohn's disease" has been included in RMP as missing information.

The proposed updates to SmPC section 4.8 suggest a longer safety follow up for CRD1001 of 240 weeks. The pooled safety assessment only supports safety up to 48 weeks for CRD1001. Initially, the LTE period from study CRD1001 has not provided a breakdown of safety for the 18 subjects who weighed ≥40 kg

who participated in the LTE. The applicant was asked to amend the PI. The applicant provided additional safety data and analysis of AEs in terms of body weight ≥40 kg from Week 0 through the end of the LTE reporting period which is reflected in the updated PI.

Post marketing experience

The applicant has summarised post-marketing data from several sources to support the proposed indication. These include pharmacovigilance data and data from the ImproveCareNow (ICN) registry. The limitations with these data must be acknowledged. There were no deaths or TB cases. There was one case of malignancy which was considered unlikely related.

Data is also presented from other approved indications for ustekinumab in paediatric & adult populations. No significant safety concerns have been raised. This data can be considered supportive.

2.5.2. Conclusions on clinical safety

Although the exposure of ustekinumab to paediatric patients with CD is limited, there is no new safety signal identified in the paediatric clinical development program submitted. The safety profile in the paediatric population was generally comparable with that seen in the adult population and known safety profile of ustekinumab and no other new adverse events or safety issues were identified. Ustekinumab has a well characterised safety profile in several authorised indications, including adult CD and paediatric plaque psoriasis (from 6 years).

The current submission mainly includes safety information up to 1-year, long-term safety in paediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease is considered as new missing information as added to RMP.

No additional adverse effects are proposed for the production information. A summary paragraph of safety data sources of paediatric patients weighing at least 40 kg with Crohn's disease has been proposed for SmPC section 4.8 and included in section 5.1.

2.5.3. 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.

2.6. Risk management plan

The MAH submitted an updated RMP version 31.2 dated 03 February 2025 with this application.

The PRAC considered that the risk management plan version 31.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 31.2 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	None
Important potential risks	Serious infections (including mycobacterial and salmonella infections)

Summary of safety concerns

	Malignancy Cardiovascular events Serious depression including suicidality Venous thromboembolism
Missing information	Long-term safety in paediatric psoriasis patients 6 years and older Long-term impact on growth and development in paediatric psoriasis patients 6 years and older Long-term safety in adult patients with moderately to severely active Crohn's disease Long-term safety in adult patients with moderately to severely active ulcerative colitis Long-term safety in paediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease

Pharmacovigilance plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
CNTO1275ISD3001 (UNITED) LTE: A Phase 3, multicentre, open-label, basket, long-term extension study of ustekinumab in paediatric clinical study participants (2 to <18 years of age) Ongoing	To collect long-term safety data in paediatric patients 2 to <18 years of age who receive SC ustekinumab for at least 1year after participating in a primary paediatric ustekinumab trial (CNTO1275CRD1001, CNTO1275PUC3001, CNTO1275CRD3004, and CNTO1275JPA3001)	Long-term safety in paediatric patients 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

Risk minimisation measures

Safety concern	**Routine risk minimisation activities** *Please provide the following information, as applicable:*
Long-term safety in paediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.

2.7. Changes to the Product Information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPCs for 130 mg concentrate for solution for injection, 45mg solution for injection vial and 45 mg & 90 mg solution for injection PFS presentations are being updated to include treatment of paediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease. Section 4.2 of SmPC for 45 mg and 90 mg pre-filled pens is also updated. In addition, editorial changes were introduced in the PI to align wording with other products indicated in Crohn's disease. The Package Leaflet (PL) has been updated accordingly.

2.7.1. 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:

The Applicant would like to make reference to the consultation with target patient groups carried out on the PL of the SC presentation of Stelara 45 mg solution for *injection* which was performed at the time of the initial marketing authorisation application procedure (approved on 16 January 2009) as well as the user consultation testing which was performed at the time of the procedure to add the paediatric psoriasis (12 to less than 18 years of age) indication (approved on 22 June 2015). The applicant considers that it is justified not to perform additional testing based on the following elements:

- 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.
- The PLs for the Stelara IV and SC presentations included in the application are based upon the currently approved Stelara IV and SC PL. User testing in compliance with the above-mentioned legislative requirements was performed on the Stelara SC PL at the time of the initial marketing authorisation application procedure, which was approved on 16 January 2009.
- Additional user consultation testing was performed in July 2015, as part of the procedure to extend the psoriasis indication to include children from 12 to less than 18 years of age (procedure EMEA/H/C/00958/II/0042). In general, readability of the currently approved Stelara

SC PL in the adult and adolescent patient groups fulfilled the EU requirements for user testing.

- The Applicant believes that the contents of the proposed Stelara IV and SC PLs have not significantly changed compared to the currently approved Stelara IV and SC PL. For both the SC and IV PLs, the changes are related to the addition of the new indication paediatric Crohn's disease (patients ≥40kg) and have an impact on section 1 "What Stelara is and what it is used for", section 2 "What you need to know before you use Stelara" and section 3 "How to use Stelara". Very limited wording is changed. No changes to the instruction for use (IFU) are proposed.
- The applicant does not consider that patients in the paediatric Crohn's disease (patients ≥40kg) population are substantially different from those in the Adult Crohn's disease, Ulcerative Colitis, Psoriasis, Psoriatic Arthritis and most importantly the paediatric Psoriasis populations.

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 clinical development program for ustekinumab in 'Paediatric Crohn's disease' consists of 2 Paediatric Crohn's disease clinical studies:

o Phase 3 open label Study CRD3004 (UNITI Jr.) - 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

o Phase 1 PK Study CRD1001 (UNISTAR) - a Phase 1, randomised, double-blind PK study of IV ustekinumab induction followed by SC ustekinumab maintenance in paediatric participants with Moderately to Severely Active Crohn's Disease.

For more details see section 2.4.

3.2. Favourable effects

Efficacy

In the pivotal phase 3 trial CRD3004, 52% and 52% 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 generally consistent across both dosing frequencies. 94% and 56% of patients experienced a clinical response at week 8 and week 52. 46 and 52% of patients were in corticosteroid free remission at week 8 and week 52. 25.5% 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 and posology treatment arms by the end of the study.

Comparable efficacy results were also observed in the phase 1 trial CRD1001. Induction results demonstrated a higher percentage of patients in clinical remission (>20% difference) and clinical response (>20% difference), and a larger reduction in PCDAI scores and faecal calprotectin levels in the phase 3 trial compared to the phase 1 trial at week 8 which the applicant attributes to a higher percentage of biologic failure participants in CRD1001. CRP levels reduced by a comparable level in both trials at week 8. Maintenance results demonstrated a higher but comparable percentage of patients in clinical remission, clinical response and corticosteroid-free clinical remission, and a larger reduction in PCDAI scores, faecal calprotectin levels and a higher increase from baseline in QoL scores in the phase 1 trial compared to the phase 3 trial at week 48/M-44. 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 and clinical response was higher in the paediatric patients (52% and 94%) when compared with adult patients (30% and 50% (the 2 induction studies combined)). Similar trends with higher results in the paediatric study than the corresponding adult studies were observed when looking at clinical remission and response rates between biologic failure and non-biologic failure subgroups. Similar trends were also observed when looking at reductions from baseline in CRP and faecal calprotectin levels with greater reductions in the paediatric study than the corresponding adult studies. For the maintenance phase, results demonstrate that levels of clinical remission, clinical response and corticosteroid-free clinical remission are comparable across the paediatric and adult studies. For CRP and faecal calprotectin levels, there are greater reductions in paediatric patients compared to adult studies.

The main advantage of the RWE observational study is 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. In this study, 23% of paediatric patients were in clinical remission (sPCDAI) at week 52 comparable with 22% of young adults. These results were also steady and comparable over time, for up to 52 weeks. 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 ≥40kg compared to young adults, 51 v 40% (clinical response) and 34 v 27.5% (PGA remission). A similar percentage of patients were in corticosteroid-free clinical remission (19 v 20% for paediatrics ≥40kg v young adults).

Overall data from the phase 3 trial demonstrates positive efficacy to support the use of ustekinumab in paediatric patients ≥40 kg 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 ≥40 kg 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, neither study included a placebo or comparator group preventing direct within study comparisons. 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, PCDAI <10, CDAI and sPCDAI), induction clinical response rates varied from 46% to 94% warranting cautious interpretation of comparisons between the paediatric and adult studies which used different scoring systems for many of the endpoints.

For the phase 1 LTE study CRD1001, the induction dosing was not aligned with the proposed dosing in the SmPC or with that from the phase 3 trial and the number of patients who 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, there are a number of differences limiting interpretation of comparisons between the trials. These differences include different inclusion/exclusion criteria, missing data rules and intercurrent or treatment failure rules. Other differences included 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 for the phase 1 trial only a subset of 10 patients have been treated with a relevant dose (≥40kg, 390 IV dose). The main maintenance time point also differs across the two studies, M-44/52 weeks for the phase 3 trial versus week 48 for the phase 1 trial.

When comparing the pivotal phase 3 paediatric trial to adult data, differences exist in the design of these studies requiring critical 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. Other differences apart from the populations include the timing of the main maintenance endpoint (M-44/52 for the paediatric trial versus week 48 for the adult trials), the duration of disease at study entry and the percentage of patients that had a history of biologic failure.

Results from the RWE demonstrated lower levels of efficacy compared to the clinical trials, the RWE study used another different scoring system (sPCDAI) compared to the main scoring system used in the clinical trials limiting comparisons. As with any registry study, this registry has limitations including limited data capture as data is captured from outpatient appointments only and not hospitalisations. Not all patients

received dosing in line with the licenced SmPC dose, there was a wide timeframe in which time-specific outcomes were measured, some 'baseline' measurements were taken after administration of ustekinumab, and the adult population studied is limited to young adults aged 18 to 26 rather than a wider range of adult ages. While a meta-analysis was performed to compare RWE to placebo rates from 12 published studies, the heterogeneity and variations in study design in the adult meta-analysis and the difference in populations pose a challenge to interpretability and the generalisability of the results.

Notwithstanding the methodological aspects mentioned above the extrapolation of the ustekinumab efficacy to paediatric patients with moderately to severely active Crohn's disease weighing 40 kg or more has been confirmed by the pivotal trial and supportive data.

3.4. Unfavourable effects

During the induction phase, a total of 66.2% of the patients reported any AEs; 69.6% among CRD1001 and 64.6% among CRD3004 induction. The SOCs with the most frequently reported TEAEs were infections and infestations (32.4%) and gastrointestinal disorders (21.1%). Upper respiratory tract infection, headache, and anaemia were most commonly observed adverse events. Serious AEs were reported in 13% of the patients in CRD1001 and 2% of the patients in the CRD3004.

During the maintenance phase, a total of 91.5% of the patients reported adverse events (92% in the q12w group and 91.3% in the combined q8w group). The SOCs with the most frequently reported TEAEs were gastrointestinal disorders (67.6%) and infections and infestations (59.2%). Crohn's disease and Upper respiratory tract infection were most commonly observed adverse events. Serious AEs were reported in 21.7% of the patients in combined q8w group and 16% of the patients in the q12w group.

In the combined dataset (overall summary of TEAEs from Week I-0 (Week 0) Through Week M-44/Week 48 Among Subjects Weighing at Least 40kg; Safety Analysis Set), a total of 66/71 patients (93%) experienced adverse events. The most commonly occurring side effects were Crohn's disease, and upper respiratory tract infection. A total of 16/71 patients (22.5%) experienced serious adverse events, with gastrointestinal disorder being most frequent.

There were no malignancies or deaths in the studies.

3.5. Uncertainties and limitations about unfavourable effects

The main limitations of both the paediatric clinical trials include the small sample size, and neither study included a placebo or comparator group preventing direct within study comparisons.

The safety data has been pooled from studies CRD3004 and CRD1001. Differences exist between studies regarding induction dose, maintenance interval q8w vs q12w as well as the main maintenance time point, M-44/52 weeks for the phase 3 trial versus week 48 for the phase 1 trial.

For the phase 1 LTE study CRD1001, the induction dosing was not aligned with the proposed dosing in the proposed SmPC or with that from the phase 3 trial. For the phase 1 trial all induction participants have been included in safety assessment however only a subset of 10 patients have been treated with a relevant induction dose (≥40kg, 390 IV dose).

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.

Safety data in the youngest patients is very limited. The aim range of the pooled cohort was 10 to 17 years with only 4 participants aged <12years. This is related to the indication's weight restriction of ≥ 40kg which usually represents ~50th centile of a 12-year-old.

Safety data related to exposed to ustekinumab for more than 1 year is lacking. Other important uncertainties pertain to adverse events occurring with a low frequency and long latency, because of the small study size and relatively short follow-up time. Therefore, long-term data will be collected post-approval in the Study UNITED LTE which is a part of the revised pharmacovigilance plan.

3.6. Effects Table

Table 57: Effects Table for Stelara paediatric CD

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Clinical remission Week 8 Week 52	≤10 points PCDAI (Max 100 points)	n/N (%)	25/48 (52.1%) 25/48 (52.1%)	-		Phase 3 trial CRD3004
Clinical response Week 8 Week 52	≥12.5 points PCDAI (and total score not more than 30) (Max 100 points)	n/N (%)	45/48 (93.8%) 27/48 (56.3%)	-		Phase 3 trial CRD3004
Endoscopic response Week 16 Week 52	A reduction in the SES-CD score of ⩾50% OR SES-CD score ⩽ 2, in participants with a baseline SES-CD score of ⩾3.	n/N (%)	14/47 (29.8%) 12/47 (25.5%)	-		Phase 3 trial CRD3004
CRP Week 8 Week 52	Inflammatory marker, mean change from baseline	mg/L (SD)	-13.89 (22.825) -11.17 (24.159)	-		Phase 3 trial CRD3004
Faecal calprotectin Week 8 Week 52	Inflammatory marker, mean change from baseline	mg/kg (SD)	-2228 (6008) -538.20 (1271.33)	-		Phase 3 trial CRD3004
Unfavourable Effects						
AE	Adverse event	N (%)	66/71 (93%)		No active control	CRD1001/CRD3004, overall TEAE summary TSFAE01c
SAE	Serious adverse event	N (%)	16/71 (22.5%)		No active control	CRD1001/CRD3004, overall TEAE

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
						summary TSFAE01c
Infections		N (%)	52/71 (73.2%)		No active control	CRD1001/CRD3004, overall TEAE summary TSFAE01c
Serious infections		N (%)	1/71 (1.4%)		No active control	CRD1001/CRD3004, overall TEAE summary TSFAE01c
Malignancies		N	0			CRD1001/CRD3004, overall TEAE summary TSFAE01c
Deaths		N	0			CRD1001/CRD3004, overall TEAE summary TSFAE01c

Notes: TSFAE01c: Overall Summary of Treatment-emergent Adverse Events From Week I-0 (Week 0) Through Week M-44/Week 48 Among Subjects Weighing at Least 40kg; Safety Analysis Set (Studies CNTO1275CRD1001 and CNTO1275CRD3004)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy effects of ustekinumab in paediatric patients are favourable and are broadly 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. The lack of a placebo or comparator group also prohibited formal statistical analyses and as such results are mainly presented by descriptive statistics.

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 could be considered supportive with limitations acknowledged for this new indication. There is however need for long-term safety data to be collected post-approval.

3.7.2. Balance of benefits and risks

The safety profile observed in the studies is consistent with the known safety profile of ustekinumab and no new safety signals were observed. Results across the phase 1 and 3 demonstrated positive efficacy to support the use of ustekinumab in paediatric patients ≥40 kg with moderately to severely active Crohn's disease for up to 1 year of treatment. Results observed are comparable to ustekinumab in the adult pivotal trials, particularly in the maintenance phase. A further long-term follow up is a part of the revised pharmacovigilance plan.

On balance and taking the totality of evidence, the benefit-risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall B/R of ustekinumab in this procedure is positive. The new indication in paediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease is supported.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderately to severely active Crohn's disease in paediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy, based on final results from study CNTO1275CRD3004. This is a Phase 3 Study of the Efficacy, Safety, and Pharmacokinetics of Ustekinumab as Open label Intravenous Induction Treatment Followed by Randomized Double blind Subcutaneous Ustekinumab Maintenance in Pediatric Participants with Moderately to Severely Active Crohn's Disease. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, editorial changes were introduced in the PI to align wording with other products indicated in Crohn's disease. The Package Leaflet is updated in accordance. Version 31.2 of the RMP has also been updated.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric

Investigation Plan P/0341/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMEA/H/C/000958/II/0108

Attachments

1. SmPC, Package Leaflet (changes highlighted).