25 June 2026
EMADOC-1700519818-3138505
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stelara

International non-proprietary name: ustekinumab

Procedure No. EMA/VR/0000316205

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

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
BSA	body surface area
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CSR	clinical study report
CTD	Common Technical Document
DBL	database lock
EOS	Exposure Optimisation Substudy
E-R	exposure-response
FAS	Full Analysis Set
FASCR	Full Clinical Responder Analysis Set
FASRES	All Responder Analysis Set
GCP	Good Clinical Practice
GI	gastrointestinal
GS	Geboes Score
HRQoL	health-related quality of life
IASCR	Immunogenicity Clinical Responder Analysis Set
IASRES	Immunogenicity All Responder Analysis Set
IBD	inflammatory bowel disease
ICE	intercurrent current event
IL	interleukin
IMPACT-III	A Quality of Life Questionnaire for Children with Inflammatory Bowel Disease
IQ	interquartile
IQR	interquartile range
IV	intravenous
IWRS	interactive web response system

LOR	loss of response
LTE	long-term extension
MAR	missing at random
MPD	major protocol deviation
NA	not applicable
Nab	neutralizing antibody
PGA	Physician Global Assessment
PIP	pediatric investigation plan
PK	pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PKASCR	Pharmacokinetic Clinical Responder Analysis Set
PKASRES	Pharmacokinetic All Responder Analysis Set
PRO	participant-reported outcome
PUCAI	Pediatric Ulcerative Colitis Activity Index
q#w	every # weeks
QoL	quality of life
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SASCR	Safety Clinical Responder Analysis Set
SASR	Safety Randomised Analysis Set
SC	subcutaneous
SD	standard deviation
SSAS	Substudy Analysis Set
UC	ulcerative colitis
UCCOD	Ulcerative Colitis Clinical Outcomes Database
Week I-#	Induction Week #
Week M-#	Maintenance Week #

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 NV submitted to the European Medicines Agency on 28 November 2025 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of ulcerative colitis in paediatric patients from the age of 2 years and older for STELARA, based on results from study CNTO1275PUC3001; 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 Pediatric Participants (2 to <18 Years of Age) with Moderately to Severely Active Ulcerative Colitis. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 32.2 of the RMP has also been submitted.

The variation requested 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(s) EMA/PE/0000232680 on the agreement of a paediatric investigation plan (PIP) for Treatment of ulcerative colitis.

At the time of submission of the application, the PIP EMA/PE/0000232680 had been completed.

The PDCO issued on 14 November 2025 a positive opinion on compliance for PIP EMA/PE/0000294320.

All studies/measures contained in the PIP were checked for compliance:

Agreed studies/measures (study identifier)	**Description**
Study 2 - CNTO1275PUC3001	Pivotal study
Study 3 M&S study	Population PK model
Study 4 M&S study	Exposure response model
Study 5 Extrapolation plan	Data to Support Extrapolation Strategy for Pediatric Patients (2 to<18 years of Age) With Moderately to Severely Active Ulcerative Colitis

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

The MAH did not seek scientific advice at the CHMP.

1.2 Steps taken for the assessment of the product

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

Rapporteur: Ruth Kieran Co-Rapporteur: Thalia Maria Thirstrup

Timetable	Actual dates
Submission date	28 November 2025
Start of procedure:	27 December 2025
CHMP Rapporteur's preliminary assessment report circulated on:	22 February 2026
CHMP CoRapporteur's preliminary assessment report circulated on:	04 March 2026
Joint Rapporteur's updated assessment report circulated on:	05 March 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 March 2026
MAH's responses submitted to the CHMP on:	21 April 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	06 May 2026
PRAC RMP advice and assessment overview adopted by PRAC	07 May 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	13 May 2026
MAH's responses submitted to the CHMP on:	28 May 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	18 June 2026
CHMP opinion:	25 June 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Therapeutic indication

The claimed therapeutic indication in this procedure is:

Paediatric ulcerative colitis

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

Induction Posology as proposed by the MAH

Paediatric ulcerative colitis (2 years and older)

Patients weighing at least 40 kg

STELARA treatment is to be initiated with a single intravenous dose based on body weight.

Patients weighing less than 40 kg

Treatment is to be initiated with a single intravenous (IV) dose of 250 mg/m², based on the patient's body surface area (BSA).

Maintenance Posology as proposed by the MAH

Paediatric ulcerative colitis (2 years and older)

Patients weighing at least 40 kg

In paediatric patients with ulcerative colitis weighing at least 40 kg, the recommended maintenance dose is a subcutaneous 90 mg dose.

Patients weighing less than 40 kg

In paediatric patients with ulcerative colitis weighing less than 40 kg the subcutaneous dose of 60 mg/m^2 is administered based on the patient's BSA.

The first subcutaneous administration of 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.

Patients experiencing inadequate or loss of response and low serum ustekinumab trough levels may benefit from transitioning to an every 4 week treatment regimen.

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after dose adjustment.

Disease or condition

Ulcerative colitis (UC) is an inflammatory disorder that involves the surface mucosa, crypt epithelium, and submucosa of the colon. Clinically, patients with UC suffer from diarrhoea, rectal bleeding, weight loss, abdominal pain, and fever, and may also display prominent extra intestinal manifestations, most commonly arthritis.

Epidemiology

UC is a debilitating disease with high morbidity for which approved pharmacologic treatments for children are still quite limited. While the peak occurrence of paediatric UC is in late adolescence, all ages can be affected, and 4% of paediatric IBD patients are diagnosed in early (age <5 years) childhood. Children aged 2 to 6 years account for approximately 10% of paediatric UC.

Unmet medical need

Currently, there are 2 approved biologic agents for paediatric patients with UC and both of these are anti-TNF agents; infliximab and adalimumab. While infliximab and adalimumab are generally safe and well tolerated in the paediatric UC population, less than half of paediatric UC patients achieve sustained clinical remission on infliximab or adalimumab. Adults have many options for access to advanced therapies for the treatment of UC. Ustekinumab is one of the many biologic therapies approved for the treatment of UC in adults (STELARA SmPC 2025). While adalimumab is approved from age 5 years and infliximab is approved from age 6 years.

Additionally, in a population-based study of paediatric onset IBD, approximately 70% of UC patients experienced TNF failure within 5 years. Without effective pharmacologic treatment, the only alternative is colectomy, which is associated with notable morbidity. As such, there is a need for additional safe and efficacious treatment options for paediatric patients with moderately to severely active UC.

Clinical presentation, diagnosis

Ulcerative colitis is defined in the same way in adults and children down to 2 years of age, with some rare phenotypic differences in disease presentation (higher incidence of pancolitis, macroscopic rectal sparing, lack of typical architectural distortion in biopsies at diagnosis, caecal patch of inflammation, upper GI tract involvement, and occurrence of fissuring ulcerations at presentation). The diagnostic evaluation involves gathering evidence to differentiate UC from CD and excluding other confounding conditions such as infections. A physician suspects the diagnosis of IBD based upon history, physical exam, and laboratory findings (bloody diarrhoea, urgency to have a bowel movement, abdominal pain, anaemia, elevated inflammatory markers, and weight loss). There are various modalities to evaluate the disease and support a diagnosis, including upper endoscopy and colonoscopy with biopsies and radiographic studies such as magnetic resonance imaging and ultrasound; the European Society for Paediatric Gastroenterology, Hepatology and Nutrition has published diagnostic guidance (Levine 2014). The most reliable feature to diagnose UC is continuous mucosal inflammation of the colon, starting from the rectum, without small bowel involvement, and without granulomas on biopsy.

Management

The mainstay of therapy for mild to moderate UC is 5-aminosalicylic (5-ASA) agents. These agents are effective at inducing and maintaining remission in UC. Many patients with moderate to severe active UC benefit from topical, oral or parenteral glucocorticosteroids. Remission, however, cannot be maintained with steroids. Azathioprine (AZA) or mercaptopurine (MP) has been employed as glucocorticoid-sparing

agents in patients unable to be weaned from glucocorticoids. Anti-tumour necrosis factor α (TNF) agents and integrin inhibitors are indicated for the treatment of UC patient's refractory to standard treatment. Surgery with colectomy is curative but can be associated with significant morbidity and is thus reserved for acute severe (fulminant) colitis or resistant cases and in some cases as cancer treatment or prevention. Intestinal continuity can be restored by construction of an ileo-anal pouch.

In both the adult and paediatric UC patient populations, the overall goal of treatment is to induce remission in acute, active disease and to maintain disease remission over time. Treatment of paediatric UC generally follows the same treatment paradigms that are used to treat adult UC.

2.1.2. About the product

STELARA (ustekinumab) is a fully human immunoglobulin G1 kappa monoclonal antibody that 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 Th1- and IL-23 Th17-mediated cellular responses.

Ustekinumab is approved for the treatment of adults with moderately to severely active UC. Although the clinical benefit of ustekinumab has been established in adults with moderately to severely active UC, it remains to be established in paediatric participants.

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

- Paediatric (6 years and older) and adult patients with moderate to severe PsO
- Adult patients with active PsA
- Paediatric (from 2 years of age) and adult patients with moderately to severely active Crohn's Disease
- Adult patients with moderately to severely active UC

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

2.1.3. The development programme/Compliance with CHMP scientific advice

Scientific advice was not sought for paediatric Ulcerative Colitis. The MAH has provided an updated paediatric investigation plan that has been accepted by the EMA on the 21st of March 2025. This outlines the changes to specific PIP deferrals (Study 1 – 5) which aims to now be completed by January 2026 (see Information on paediatric requirements).

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 or other paediatric] population." Paediatric extrapolation can extend what is known about the reference population (eg, efficacy, safety, and PK) to the target population (paediatric subset) based on an assessment of the relevant similarities of disease and response to therapy of the 2 populations. Paediatric extrapolation is a well-accepted approach that was also used to facilitate approval of the other available biologics for paediatric UC (i.e., adalimumab and infliximab), although the extrapolation concept is evolving as new data are generated. The ICH guideline E11A stresses that rather than relying on rigid categories of

extrapolation (e.g., full, partial, or none), it is essential to acknowledge that a continuum of similarity and dissimilarity in disease characteristics, drug pharmacology, and treatment response may exist between the populations.

The MAH provided a detailed comparison of adult and paediatric UC populations in their Extrapolation Concept and Plan. In the MAHs current extrapolation concept, the reference population is adults (18 years of age or older) with moderately to severely active UC. The target population is paediatric participants (2 to <18 years of age) with moderately to severely active UC.

2.1.4. General comments on compliance with GCP

R&D Quality - Quality Assurance (RDQ-QA) performed audits for the UNIFI Jr clinical trial to evaluate compliance with internal Standard Operating Procedures (SOPs), International Council for Harmonisation (ICH), Food and Drug Administration (FDA), Good Clinical Practice (GCP) guidelines and local regulatory requirements applicable at the time of the clinical trial.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

Ustekinumab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no Environmental Risk Assessment for ustekinumab is required.

2.2.2. Conclusion on the non-clinical aspects

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

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

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

2.3. Clinical aspects

2.3.1. Introduction

The clinical development program for ustekinumab in paediatric UC was designed to evaluate the efficacy and safety in the treatment of paediatric participants with moderately to severely active UC.

The paediatric UC clinical development program consists of the following studies:

- One paediatric Phase 3 clinical study, CNTO1275PUC3001 (UNIFI Jr)
- A paediatric LTE basket study, CNTO1275ISD3001 (UNITED)
- Supportive data from 1 adult Phase 3 UC study, CNTO1275UCO3001 (UNIFI)

Additional supportive paediatric safety data consists of the following studies:

- Supportive safety data from a Phase 3 paediatric CD study CNTO1275CRD3004 (UNITI Jr)
- Additional paediatric safety data for plaque PsO from CNTO1275PSO3006 (CADMUS) and CNTO1275PSO3013 (CADMUS Jr), and the PASS CNTO1275PSO4056 (STELLAR Teens)
- Supportive ustekinumab safety data from C0168Z02 (DEVELOP), which is a REMICADE (infliximab) PASS that includes ustekinumab-treated paediatric patients with UC

GCP

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

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

Table 1: Tabular Listing of Clinical Studies – Efficacy Assessment

Efficacy and Safety Controlled Clinical Studies						
CNTO1275PUC3001 UNIFI Jr 2019-004224-38 17 March 2021/ 05 June 2025 Completed	BEL, DEU, HUN, ISR, JPN, POL, GBR, USA 32	Phase 3 Multicenter, open-label induction period with a single IV ustekinumab induction dose followed by a maintenance period with a randomized, double blind, parallel-group, 2-arm study design. Pediatric participants 2 to <18 years old with moderately to severely active UC. **Global Objectives:** • To evaluate the efficacy of ustekinumab dosing in inducing clinical remission in pediatric participants with moderately to severely active UC • To evaluate the safety profile of ustekinumab in pediatric participants with moderately to severely active UC. • To evaluate ustekinumab exposure (PK). **US-specific Objectives** • To evaluate the efficacy of ustekinumab dosing in maintaining clinical remission in pediatric participants with moderately to severely active UC. • To evaluate the safety profile of ustekinumab in pediatric participants with moderately to severely active UC. To evaluate ustekinumab exposure (PK)	Planned: ~100 Enrolled: 112 Randomized: 109 (Maintenance Phase)	Ustekinumab IV: 5 mg/mL LIV single use, sterile solution in 30 mL vials. Ustekinumab SC: • body weight <40 kg, 90 mg/mL LIV single use sterile solution in 2 mL vials. • body weight ≥40 kg, 90 mg in 1 mL solution in a PFS-U Placebo: the same appearance as the respective ustekinumab administrations. **Induction period (Week I-0 through Week I-8):** All participants received a single open-label IV administration of ustekinumab at Week I-0. Participants with body weight <40 kg: 250 mg/m^2 IV Participants with body weight ≥40 kg to ≤55 kg: 260 mg IV Participants with body weight >55 kg to ≤85 kg: 390 mg IV Participants with body weight >85 kg; 520 mg IV **Maintenance period (Week M-0 through Week M-40)** All participants who complete the Week I-8/M-0 visit were randomized in a blinded fashion to a 1:1 ratio stratified by response status at Week I-8 (induction responders and induction nonresponders) and weight (<40 kg, ≥40 kg) to receive 1 of 2 SC dose regimens: **Ustekinumab SC q8w:** 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight. at Weeks M-0, M-8, M-16, M-24, M-32, and M-40 and matching placebo at Weeks M-12 and M-36 to maintain the blind. **Ustekinumab SC q12w:** 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight. at Weeks M-0, M-12, M-24, and M-36 and matching placebo at Weeks M-8, M-16, M-32, and M-40 to maintain the blind.	Week I-0: 112 Maintenance Phase: 109 q12w: 55 q8w: 54	Full CSR 23 September 2025 EDMS-ERI-1476752 CSR Addendum 16 October 2025 EDMS-RIM-1743260 Module 5.3.5.1

CNTO1275ISD3001 UNITED 2020-004457-76 18 November 2024 (CD report data cutoff)/ Ongoing 28 April 2025 (UC report data cutoff)/ongoing	-	Phase 3 Multicenter, open-label, basket, long-term extension study of SC ustekinumab in subjects who have participated in a pediatric ustekinumab study. Pediatric participants 2 to <18 years old with moderately to severely active Crohn's disease or moderately to severely active UC or moderate or severe jPsA. Evaluate the long-term safety data of ustekinumab in subjects from one of the following primary studies: CNTO1275CRD3004, CNTO1275PUC3001, or CNTO1275JPA3001.	Enrolled: CD: 68 UC: 66	CNTO1275CRD3004: Dose: 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight Frequency: Previously blinded: q8w Previously unblinded: q4w[1] or q8w CNTO1275PUC3001: Dose: 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight Frequency: Previously blinded: q8w Previously unblinded: q4w[1] or q8w CNTO1275JPA3001: Dose: Body weight <60 kg: 0.75 mg/kg Body weight ≥60 kg but ≤100 kg: 45 mg Body weight >100 kg: 90 mg Frequency: q12w	Qualify for CD q4w= 18 q8w= 48 Qualify for UC q4w=10 q8w=55	CD Safety Report 30 May 2025 EDMS-RIM-1634592 UC Safety Report 26 August 2025 EDMS-RIM-1699631 Module 5.3.5.1

2.3.2. Pharmacokinetics

Bioanalytical Methods

Methodologies and validations of the bioanalytical methods used to determine serum ustekinumab concentrations, as well as ADAs and NAbs to ustekinumab, have previously been submitted. The following updates are included in this summary:

- Validation addenda documenting incurred sample reproducibility and parallelism.

Pharmacokinetics

The clinical programme for ustekinumab in paediatric patients with ulcerative colitis (UC) comprised a single open-label paediatric study (CNTO1275PUC3001). As conducting a double-blind, randomised, placebo-controlled trial in this population was not feasible, the benefit–risk of ustekinumab in the proposed paediatric age group (2 to <18 years) is supported by extrapolating efficacy and safety data from adults with UC, using exposure matching to bridge between populations. As such, a key objective of this submission was to demonstrate that the proposed paediatric doses would provide systemic exposures to ustekinumab that are comparable to those observed in adults receiving the approved adult doses.

Study CNT01275PUC3001: Phase 3 study in paediatric participants with UC

Methods

This was an open-label, Phase 3 study of the efficacy, safety and PK of ustekinumab IV induction treatment followed by SC maintenance treatment in paediatric participants (2 to <18 years of age) with moderately to severely active UC. The paediatric dose regimen was designed to achieve systemic exposures comparable to adults with UC receiving the approved adult ustekinumab dose regimen.

Ustekinumab dose regimen:

Induction period (8 weeks): Single IV dose at Week I-0:

- 250 mg/m^2 for participants with body weight <40 kg

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

Maintenance period (44 weeks): Participants randomised to receive 1 of 2 SC dose regimens, stratified by induction response status at Week I-8 (responders/nonresponders) and weight (<40 kg, ≥40 kg):

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

Exposure Optimisation Substudy (EOS) (at least 16 weeks)

Participants who did not achieve response by Week M-8 or had loss of response (LOR) and had low ustekinumab exposure (i.e. an 8-week, steady-state trough <1.4 µg/mL) could enter the EOS where the maintenance dose regimen was adjusted to q4w dosing. The defined low level of exposure was selected to align with the 8-week trough level in adult Phase 3 studies at which adults were less likely to be in response.

Results

A total of 112 participants, with a median body weight of 46.9 kg (range: 13.6 to 80.0 kg) and a median age of 14.0 years (range: 3 to 17 years), were enrolled and 109 were randomised into the maintenance period. Only 3 participants were aged <6 years and 2 participants weighed <20 kg.

Serum ustekinumab concentrations during induction period

After a single IV administration of the approximately 250 mg/m^2 BSA-based dose or approximately 6 mg/kg tiered fixed dose of ustekinumab, the median (mean) peak serum ustekinumab concentration was 110.91 (115.27) µg/mL. At Week 8, the time of the main efficacy assessment, the median (mean) serum ustekinumab concentration was 3.84 (5.02) µg/mL.

Serum ustekinumab concentrations during maintenance period

Steady-state ustekinumab concentrations were reached approximately 8 or 12 weeks after paediatric participants commenced q8w or q12w maintenance dosing, respectively. There was no apparent accumulation in ustekinumab concentrations over time when given SC q8w or q12w.

In the q8w treatment group, median pre-dose ustekinumab concentrations (at Weeks M-8, M-16, M-24, and M-32) were consistent through Week M-44, ranging from 2.51 µg/mL to 3.51 µg/mL. In the q12w treatment group, median pre-dose ustekinumab concentrations (at Weeks M-12, M-24, and M-36) were also consistent through Week M-44, ranging from 0.54 µg/mL to 0.62 µg/mL.

At Week 44 (ie, 4 weeks and 8 weeks from the previous dose for the q8w treatment group and the q12w treatment group, respectively), when key maintenance efficacy endpoints were assessed, median (mean) serum ustekinumab concentrations were 8.18 (7.60) µg/mL in the q8w treatment group and 1.77 (2.44) µg/mL in the q12w treatment group.

Exposure Optimisation Substudy (EOS)

22 participants entered the EOS (4 participants were induction nonresponders and 18 had LOR in maintenance). The median (range) age and body weight of EOS participants were 14 (4-17) years and 46.4 (14.2-78) kg, respectively.

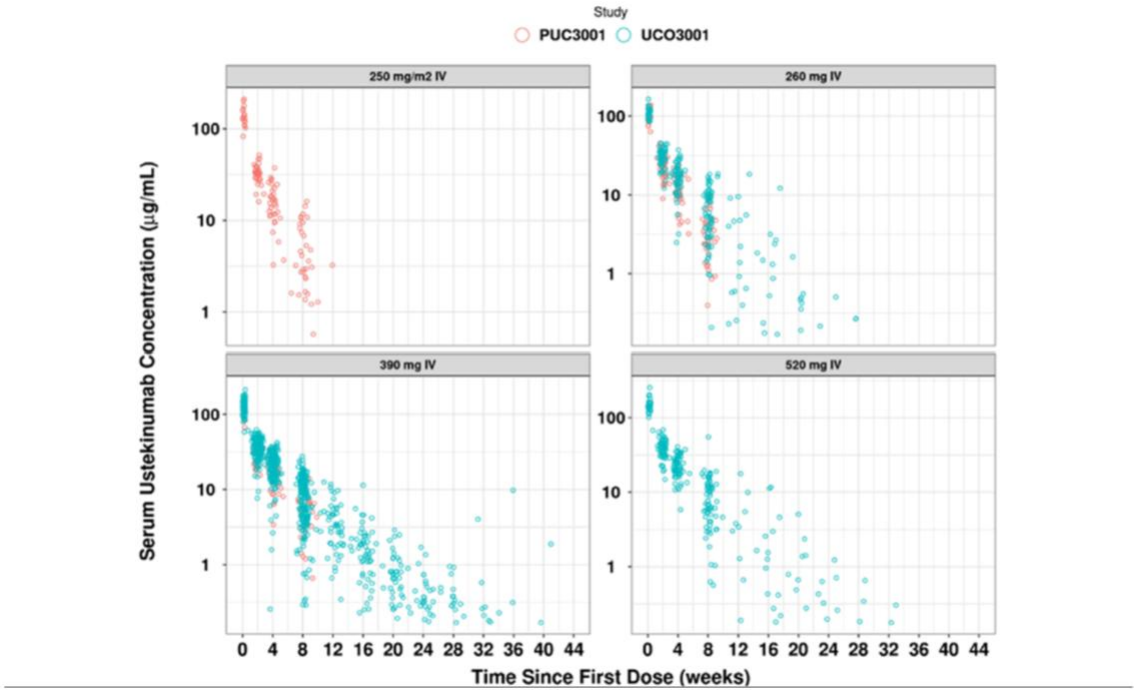
Before administration of the first dose of ustekinumab q4w at Substudy Week 0, the median (mean) ustekinumab concentration was 0.38 (0.97) µg/mL in the combined treatment group (0.0 [0.76] µg/mL in the q12w→q4w treatment group and 1.60 [1.22] in the q8w→q4w treatment group).

Following administration of the q4w dose regimen, ustekinumab concentrations increased but were within the range of the concentrations observed in adults with UC in Study CNTO1275UCO3001. Steady-state trough concentrations ranged from 0.86 to 7.18 µg/mL at Substudy Week 12. Steady-state trough concentrations in adult UC participants who received 90 mg SC q8w ranged between 0.00 and 14.7 µg/mL.

Comparison of ustekinumab concentrations between paediatric and adult UC participants

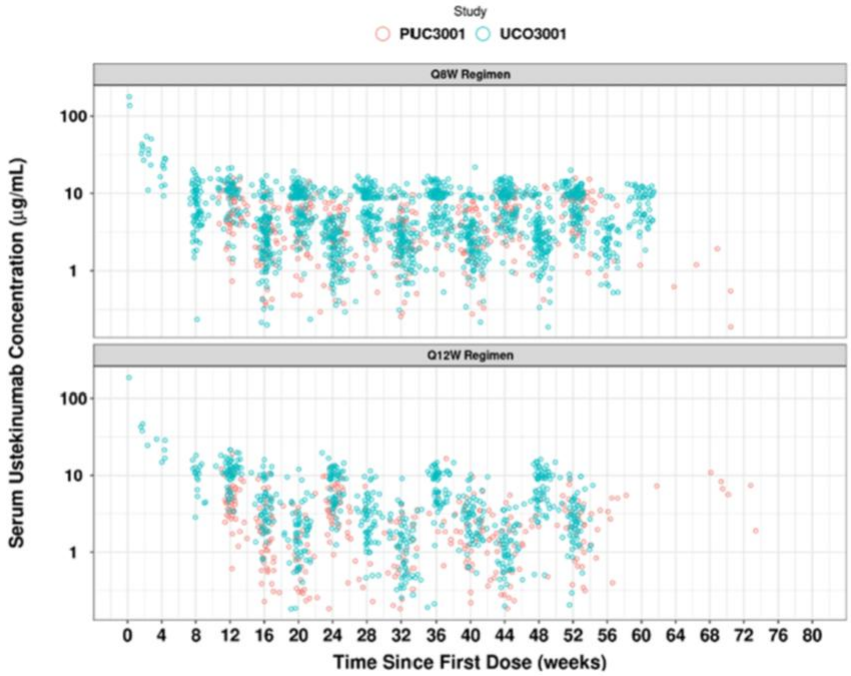
Overall, following the ustekinumab induction dose regimens, ustekinumab concentrations in paediatric participants fell within the range of concentrations observed in adult participants with UC (Figure 1). Median (mean) peak ustekinumab concentrations 1-hour post-infusion at Week I-0 were comparable between the overall paediatric and adult participants with UC (110.9 [115.3] µg/mL versus 127.0 [129.1] µg/mL, respectively). Conversely, the median (mean) ustekinumab concentration at Week I-8 was numerically lower in the overall paediatric participants (3.84 [5.02] µg/mL) compared with adult participants (8.59 [8.86] µg/mL) with UC.

Figure 1: Scatterplot of Ustekinumab Serum Concentrations Versus Time in Pediatric Participants From CNTO1275PUC3001 and in Adult Participants From CNTO1275UCO3001 Following 250 mg/m2 (Body Weight <40 kg) or ~6 mg/kg (Body Weight ≥40 kg) IV Induction



The average steady-state serum ustekinumab concentrations in the overall paediatric UC population were generally comparable to those observed in the adult UC population who received q12w or q8w ustekinumab maintenance dosage (Figure 2 and Table 2).

Figure 2: Scatterplot of Ustekinumab Serum Concentrations Versus Time in Pediatric Participants From CNTO1275PUC3001 and in Adult Participants From CNTO1275UCO3001 With 250 mg/m2 (Body Weight <40 kg) or ~6 mg/kg (Body Weight ≥40 kg) IV Induction Treatment Followed by 60 mg/m2 (Body Weight <40 kg) or 90 mg (Body Weight ≥40 kg) q8w and q12w Maintenance Treatment



Abbreviations: IV=intravenous; PUC3001=CNTO1275PUC3001; qXw=every X weeks; UCO3001=CNTO1275UCO3001.
Note: Adult participants who received placebo in the induction phase and who received placebo in maintenance phase then adjusted to q8w were not included in the comparison.

Table 2: Summary of Pediatric by Baseline Body Weight vs Adult Average Steady State Trough Serum Ustekinumab Concentrations (micrograms/mL); PK Clinical Responder Analysis Set (Studies CNTO1275PUC3001 and CNTO1275UCO3001)

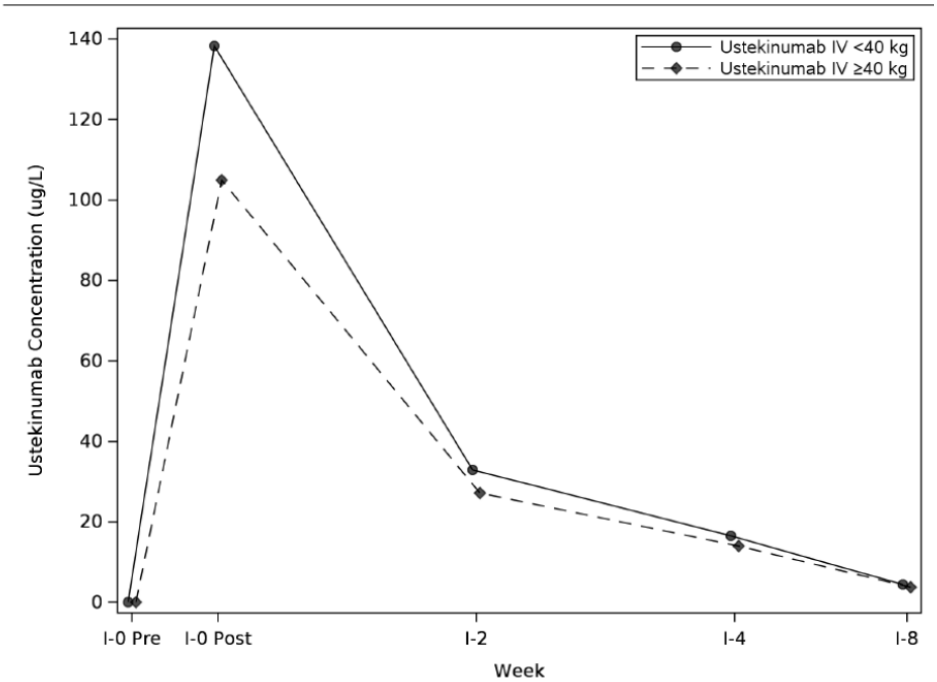
	Ustekinumab					
	Pediatric PUC3001					
	< 40 kg		≥ 40 kg		Adult UCO3001	
	q12w	q8w	q12w	q8w	q12w	q8w
Analysis set: PK Clinical Responder Analysis Set	12	15	28	24	67	70
Average steady state trough concentration						
N	8	14	22	20	64	61
Mean (SD)	1.276 (1.2364)	3.923 (2.6543)	1.049 (1.0582)	3.672 (1.9782)	1.417 (1.1167)	3.553 (2.4691)
Median	0.971	3.641	0.609	3.396	1.193	2.832
Range	(0.00; 3.62)	(0.27; 8.41)	(0.00; 4.51)	(1.45; 7.50)	(0.00; 6.29)	(0.22; 10.61)
IQ range	(0.279; 2.044)	(2.634; 5.551)	(0.393; 1.456)	(1.782; 5.620)	(0.666; 1.788)	(1.928; 3.933)

Key: SD=standard deviation, IQ=interquartile.
Note: Concentrations below the lowest quantifiable concentration (0.1688 µg/mL) were treated as zero in calculating the summary statistics.
Note: Data from the time of dose adjustment or substudy onward are not included and are summarized separately.
Note: For CNTO1275PUC3001, in case of q8w, trough serum ustekinumab concentrations at Week M-24 and Week M-32 are averaged; in case of q12w, trough serum ustekinumab concentrations at Week M-24 and Week M-36 are averaged. For CNTO1275UCO3001, in case of q8w, trough serum ustekinumab concentrations at Week M-24, Week M-32 and Week M-40 are averaged; in case of q12w, trough serum ustekinumab concentrations at Week M-24 and Week M-36 are averaged.
Note: Study CNTO1275PUC3001 included all subjects who were randomized into the maintenance period of the study (Week M-0) and were in clinical response as determined by the IWRS to ustekinumab induction therapy at Week I-8 and had received at least 1 administration of ustekinumab during maintenance and had at least one post Week M-0 blood sample collection in maintenance. Study CNTO1275UCO3001 included all subjects who were randomized to ustekinumab 6 mg/kg at Week I-0 and were in clinical response to ustekinumab induction as determined by the IWRS and were randomized to ustekinumab 90 mg SC q8w or ustekinumab 90 mg SC q12w, and had received at least 1 administration of ustekinumab during maintenance and had at least one post Week M-0 blood sample collection in maintenance.

Serum Ustekinumab Concentrations by Baseline Weight

During induction, serum ustekinumab concentrations through Week I-8 were generally comparable between participants with body weight <40 kg and those ≥40 kg (Figure 3). At 1-hour post-infusion, median (mean) concentrations were slightly higher among participants with body weight <30 kg (138.2 [141.8] µg/mL) and participants at ≥30 to <40 kg (138.2 [138.0] µg/mL), compared with those ≥40 kg (104.9 [104.5] µg/mL). Conversely, at Week I-8, median (mean) serum ustekinumab concentrations were 5.45 (6.84) µg/mL, 4.10 (5.43) µg/mL, and 3.76 (4.59) µg/mL among participants with body weight <30 kg, ≥30 to <40 kg, and ≥40 kg, respectively.

Figure 3: Line Plot of Median Serum Ustekinumab Concentrations (micrograms/mL) Through Week I-8 (Linear Scale) by Baseline Body Weight; PK Analysis Set (Study CNTO1275PUC3001)



In the respective maintenance dose treatment groups, the average steady-state trough concentrations were comparable between the <40 kg and ≥40 kg subgroups, and comparable with adult participants in CNTO1275UCO3001 (Table 3).

Table 3: Summary of Pediatric by Baseline Body Weight vs Adult Average Steady State Trough Serum Ustekinumab Concentrations (micrograms/mL); PK Clinical Responder Analysis Set (Studies CNTO1275PUC3001 and CNTO1275UCO3001)

	Ustekinumab					
	Pediatric PUC3001					
	< 40 kg		≥ 40 kg		Adult UCO3001	
	q12w	q8w	q12w	q8w	q12w	q8w
Analysis set: PK Clinical Responder Analysis Set	12	15	28	24	67	70
Average steady state trough concentration						
N	8	14	22	20	64	61
Mean (SD)	1.276 (1.2364)	3.923 (2.6543)	1.049 (1.0582)	3.672 (1.9782)	1.417 (1.1167)	3.553 (2.4691)
Median	0.971	3.641	0.609	3.396	1.193	2.832
Range	(0.00; 3.62)	(0.27; 8.41)	(0.00; 4.51)	(1.45; 7.50)	(0.00; 6.29)	(0.22; 10.61)
IQ range	(0.279; 2.044)	(2.634; 5.551)	(0.393; 1.456)	(1.782; 5.620)	(0.666; 1.788)	(1.928; 3.933)

Key: SD=standard deviation, IQ=interquartile.
Note: Concentrations below the lowest quantifiable concentration (0.1688 µg/mL) will be treated as zero in calculating the summary statistics.
Note: Data from the time of dose adjustment or substudy onward are not included and are summarized separately.
Note: For CNTO1275PUC3001, in case of q8w, trough serum ustekinumab concentrations at Week M-24 and Week M-32 are averaged; in case of q12w, trough serum ustekinumab concentrations at Week M-24 and Week M-36 are averaged. For CNTO1275UCO3001, in case of q8w, trough serum ustekinumab concentrations at Week M-24, Week M-32 and Week M-40 are averaged; in case of q12w, trough serum ustekinumab concentrations at Week M-24 and Week M-36 are averaged.
Note: Study CNTO1275PUC3001, include all subjects who were randomized into the maintenance period of the study (Week M-0) and were in clinical response as determined by the IWRS to ustekinumab induction therapy at Week I-8 and have received at least 1 administration of ustekinumab during maintenance, and have at least one post Week M-0 blood sample collection in maintenance. Study CNTO1275UCO3001, include all subjects who were randomized to ustekinumab 6 mg/kg at Week I-0 and were in clinical response to ustekinumab induction as determined by the IWRS and were randomized to ustekinumab 90 mg SC q8w or ustekinumab 90 mg SC q12w, and have received at least 1 administration of ustekinumab during maintenance, and have at least one post Week M-0 blood sample collection in maintenance.

Population PK Analysis

The main objectives of the PopPK analysis were to characterise the PK of ustekinumab in paediatric participants with UC, to assess the PK similarity between paediatric and adult participants with UC, and to perform model-based simulations to support the proposed ustekinumab posology for paediatric patients with UC.

Methods

A previously developed adult PopPK model of ustekinumab following IV and SC administration in adult participants with UC (PopPK Report CNTO1275 2018) was updated by fixing allometric exponents to standard values (0.75 for CL and Q, and 1 for V2 and V3). The updated adult model failed to describe the paediatric data adequately in an external validation. Therefore, a separate paediatric PopPK model with the data from the paediatric UC study (CNTO1275PUC3001) alone was developed.

The paediatric data were re-fitted using the same structural model as the adult PopPK model. Structural parameters and covariate effects, other than the fixed allometric scaling exponents, were re-estimated. The model was simplified by fixing additive error to the value in the adult model. BSV on parameters ka and F1 was also fixed to the adult values considering the limited sample size and sparse PK sampling in the paediatric study.

Simulations were performed with the final paediatric and updated adult PopPK models. Body weight for the virtual paediatric population was generated by sampling with replacement from the National Health and Nutrition Examination Survey database (CDC 2025). Body weight for the virtual adult population was generated by sampling with replacement from the adult UC study (ie, CNTO1275UCO3001). Other covariates were set to the reference values in the model. A total of 1,000 simulated PK profiles were generated in adult and paediatric participants for each weight group (<40 kg, ≥40 to ≤55 kg, >55 to ≤85

kg, and >85 kg) based on the approved dose regimens in adults and the paediatric dose regimens in CNTO1275PUC3001.

Results

The final paediatric PopPK analysis dataset included a total of 1,232 serum ustekinumab concentrations from 111 paediatric participants. Descriptive statistics of baseline continuous and categorical covariates are presented in Table 4 and Table 5, respectively.

Table 4: Demographic and Baseline Characteristics of Combined Pediatric and Adult Data (Continuous Covariates)

	CNTO1275PUC3001 (N=111)	CNTO1275UCO3001 (N=822)
Age (years)		
Mean (SD)	13.2 (3.10)	41.5 (13.6)
Median [Min, Max]	14.0 [3.00, 17.0]	41.0 [18.0, 84.0]
Baseline Weight (kg)		
Mean (SD)	47.0 (14.7)	73.1 (17.7)
Median [Min, Max]	47.0 [13.6, 80.0]	71.2 [36.5, 177]
Baseline Albumin (g/L)		
Mean (SD)	42.6 (3.74)	41.2 (4.02)
Median [Min, Max]	43.0 [29.0, 51.0]	41.0 [23.0, 55.0]
Baseline CRP (mg/dL)		
Mean (SD)	0.674 (1.35)	10.8 (18.0)
Median [Min, Max]	0.170 [0.0100, 8.16]	4.64 [0.100, 183]

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

Table 5: Demographic and Baseline Characteristics of Combined Pediatric and Adult Data (Categorical Covariates)

	CNTO1275PUC3001 (N=111)	CNTO1275UCO3001 (N=822)
Sex		
Male	51 (45.9%)	498 (60.6%)
Female	60 (54.1%)	324 (39.4%)
Race/Ethnicity		
Caucasian	93 (83.8%)	619 (75.3%)
Black	2 (1.8%)	8 (1.0%)
Asian	13 (11.7%)	127 (15.5%)
Others	0 (0%)	0 (0%)
Missing	3 (2.7%)	68 (8.3%)
Biologics Failure Status		
Failed	44 (39.6%)	431 (52.4%)
Not failed	67 (60.4%)	391 (47.6%)
TNF Therapy failure status		
Failed	40 (36.0%)	426 (51.8%)
Not failed	71 (64.0%)	396 (48.2%)
Immunogenicity to Ustekinumab		
Positive	2 (1.8%)	45 (5.5%)
Negative	1.09 (98.2%)	777 (94.5%)

Abbreviations: N=number of participants; PUC3001=CNTO1275PUC3001; TNF=tumor necrosis factor; UCO3001=CNTO1275UCO3001.

Final Paediatric PopPK Model

The observed PK profiles of ustekinumab following IV and SC administration to paediatric participants with UC ranging from 13.6 to 80.0 kg were adequately described by a 2-compartment model with first-order absorption and linear elimination.

The parameters of the final model for paediatric participants are summarised in Table 6. Model parameters were adequately estimated with RSE <20% for the structural model parameters and <30% for most of the covariate relationship parameters. The typical population values of CL, Q, V2, and V3 in paediatric participants with a median body weight of 71.2 kg were 0.29 L/day, 0.19 L/day, 4.32 L, and 2.52 L, respectively. The typical values of ka and SC F1 were 0.076 day-1 and 75%, respectively.

Table 6: Parameter Estimates of Ustekinumab for the Final Pediatric PopPK Model in Pediatric Participants With Moderately to Severely Active UC

Parameter, Unit	Estimate[a]	RSE (%)	Shrinkage (%)
CL (L/day)[b]	0.292	4.7%	-
BWT on CL	0.75 Fix	-	-
BALB on CL	-1.27	25.8%	-
Sex on CL	1.14	5.5%	-
IRPD on CL	1.16	36.4%	-
V2 (L)[c]	4.32	3.2%	-
BWT on V2	1 Fix	-	-
Q (L/day)[d]	0.185	14.3%	-
BWT on Q	0.75 Fix	-	-
V3 (L)[e]	2.52	12.3%	-
BWT on V3	1 Fix	-	-
ka (day^{-1})	0.0757	8.0%	-
F1	0.75	5.5%	-
IIV of CL (%CV)	27.5%	10.3%	4%
Correlation between IIV of CL and V2	0.141	-	-
IIV of V2 (%CV)	7.7%	54.4%	56%
Correlation between IIV of CL and V3	-0.504	-	-
IIV of V3 (%CV)	58.2%	9%	12%
Correlation between IIV of V2 and V3	0.256	-	-
IIV of ka (%CV)	55.8% Fix	-	23%
IIV of F1 (%CV)	16.8% Fix	-	29%
Correlation between IIV of ka and F1	-0.636 Fix	-	-
ADD ERR (µg/mL)	0.0883 Fix	16%	-
PROP ERR (CV%)	22.5%	1.4%	-

Abbreviations: ADD ERR=additive error term; BALB=baseline albumin (g/dL); BWT=baseline body weight (kg); CL=clearance; CV=coefficient of variation; exp=exponential; F1=subcutaneous bioavailability; IIV=inter-individual variability calculated as $\sqrt{\exp(variance) - 1} \times 100\%$ except for F1 (logit scale parameter), which is calculated as variance$^{1/2}$*(1-THETA.F1)*100%; IRPD=immune response status dynamic; ka=first-order absorption rate constant; PK=pharmacokinetic(s); PopPK=population pharmacokinetic(s); PROP ERR=proportional error term; Q=intercompartmental flow; RSE=relative standard error; UC=Ulcerative Colitis; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

Note: Median weight of the adult participants from CNTO1275UCO3001 used in the updated adult PopPK model is 71.2 kg.

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

[b] $\text{CL (L/day)} = 0.292 \times \left(\frac{\text{BWT}}{71.2}\right)^{0.75} \times \left(\frac{\text{BALB}}{4.1}\right)^{-1.27} \times 1.14^{\text{SEX}} \times 1.16^{\text{IRPD}}$

[c] $\text{V2 (L)} = 4.32 \times \left(\frac{\text{BWT}}{71.2}\right)^{1.0}$

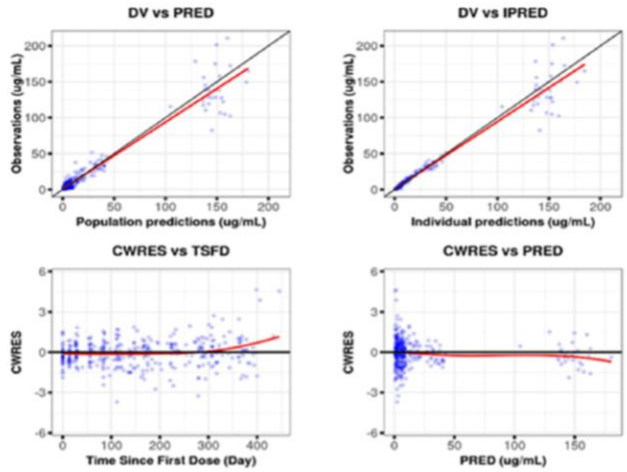
[d] $\text{Q (L/day)} = 0.185 \times \left(\frac{\text{BWT}}{71.2}\right)^{0.75}$

[e] $\text{V3 (L/day)} = 2.52 \times \left(\frac{\text{BWT}}{71.2}\right)^{1.0}$

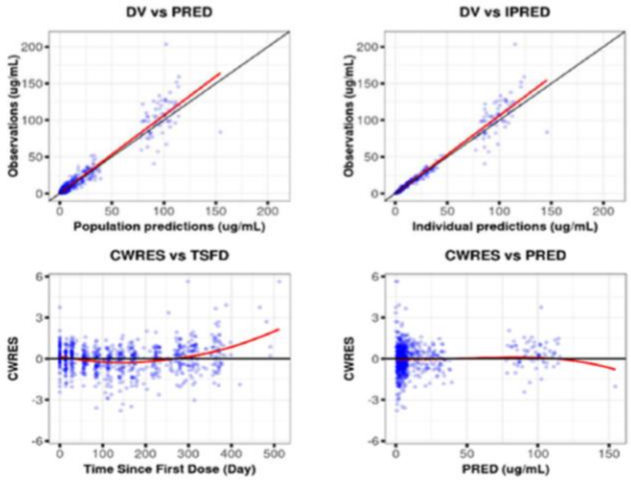
Figure 4 shows the overall GOF plots stratified by body weight cutoff of 40 kg for the final paediatric PopPK model. The population and individual predictions are well aligned with observations and the CWRES were generally centered around zero with homogeneous variation relative to the population predictions and time.

Figure 4: Overall GOF Plots Using the Final Pediatric Model for the Pediatric Dataset of CNTO1275PUC3001 Stratified by Weight Cutoff of 40 kg

Body Weight <40 kg



Body Weight ≥40 kg

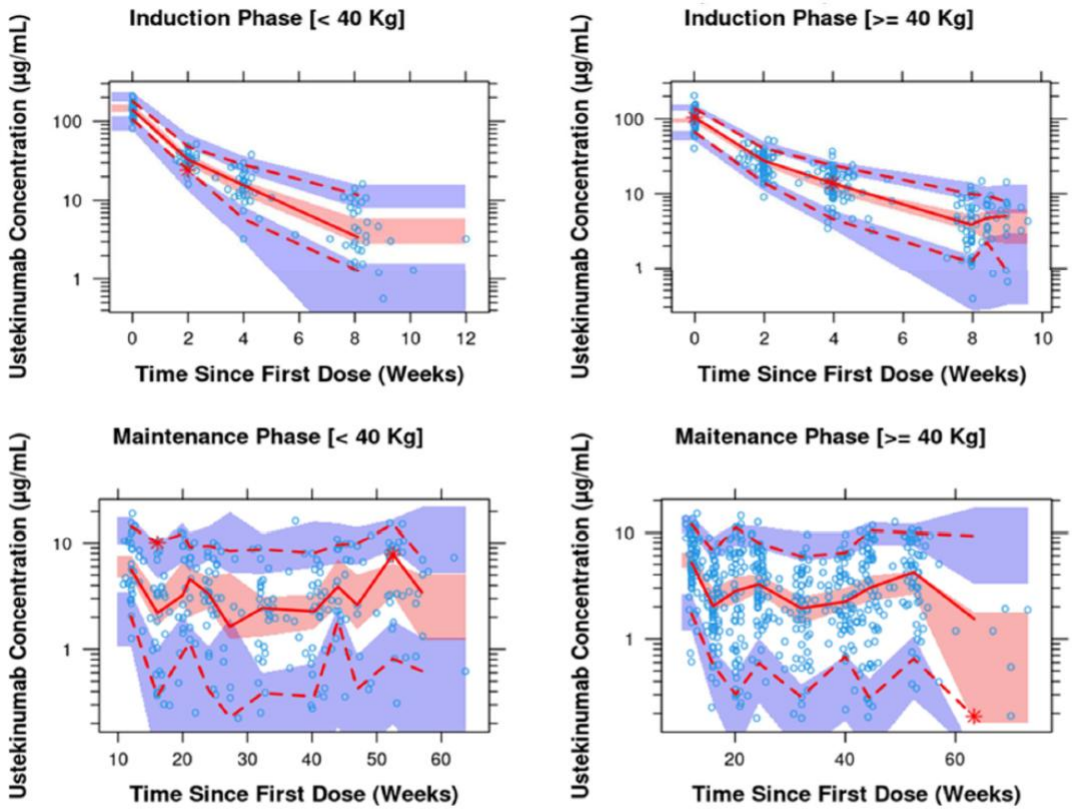


Abbreviations: CWRES=conditional weighted residuals; DV=observations; GOF=goodness-of-fit; IPRED=individual prediction; PRED=population prediction; TSFD=time since first dose.
Note: The black solid line is the line of identity or the zero line, and the red solid line is the trend line. The blue circles are the observations. The top panels and the bottom panels represent the pediatric participants with body weight <40 kg and ≥40 kg, respectively.

The VPC shows that the final paediatric PopPK model adequately captured the median concentration-time profiles of ustekinumab, as well as the associated variabilities across the treatment phase (

Figure 5).

Figure 5: VPCs Using the Final Pediatric Model for the Pediatric Dataset of CNTO1275PUC3001 Stratified by Treatment Phase and Weight Cutoff of 40 kg



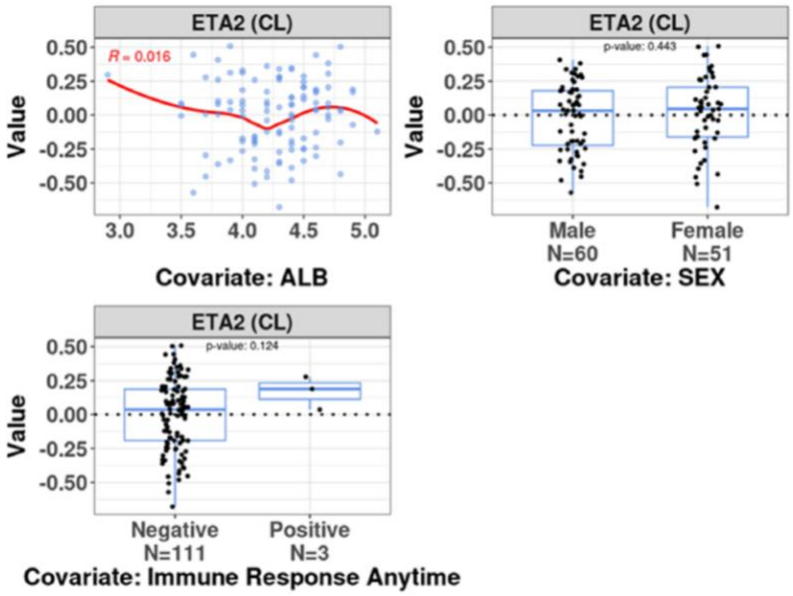
Abbreviations: CI=confidence interval; IV=intravenous; LLOQ=lower limit of quantification; SC=subcutaneous; VPC=visual predictive check.

Note: The upper panels show the time course following IV induction treatment, stratified by body weight <40 kg and ≥40 kg, whereas the lower panels show the time course following SC maintenance treatment, stratified by body weight <40 kg and ≥40 kg. Blue circles are observed data. Solid red lines are medians, dashed red lines are the 5th and 95th percentiles of the observations. The shaded red area represents the 95% CI of the median and the shaded blue areas represent the 95% CI of the 5th and 95th percentiles predicted by the model. Concentrations below LLOQ are set to LLOQ/2 for plotting VPC on the log scale.

The ETA versus covariate plots for the paediatric model are shown in

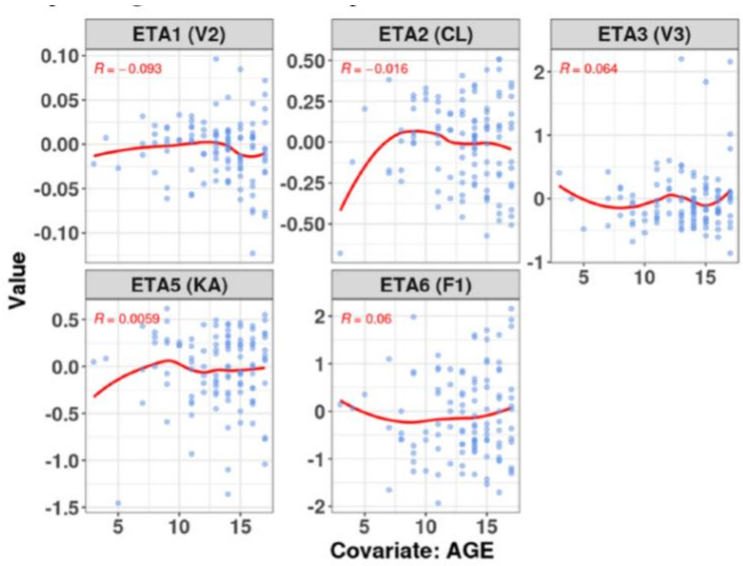
Figure 6 There were no remaining trends between random effects and covariates, indicating that the BSV in the paediatric PK was well explained by the covariate relationships that were already included in the paediatric model. As shown in Figure 7, there was no correlation between age and ETA on CL, V2, V3, and Q, suggesting that ustekinumab disposition parameters do not change with age within the paediatric participants, once the body weight effect is accounted for.

Figure 6: Scatterplot of ETAs Versus Covariates for the Final Pediatric Model



Abbreviations: ALB=baseline serum albumin; CL=clearance; ETA=individual random effect; R=the correlation value of ETA vs continuous covariate.
Note: The blue and black dots represent the individual random effects, and the solid red line represents the loess trend line.

Figure 7: Scatterplot of Age Versus ETAs on Disposition Parameters for the Final Pediatric Model



Abbreviations: CL=clearance; ETA=individual random effect; F1=bioavailability; KA=first-order absorption rate constant; R=the correlation value of ETA vs continuous covariate; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

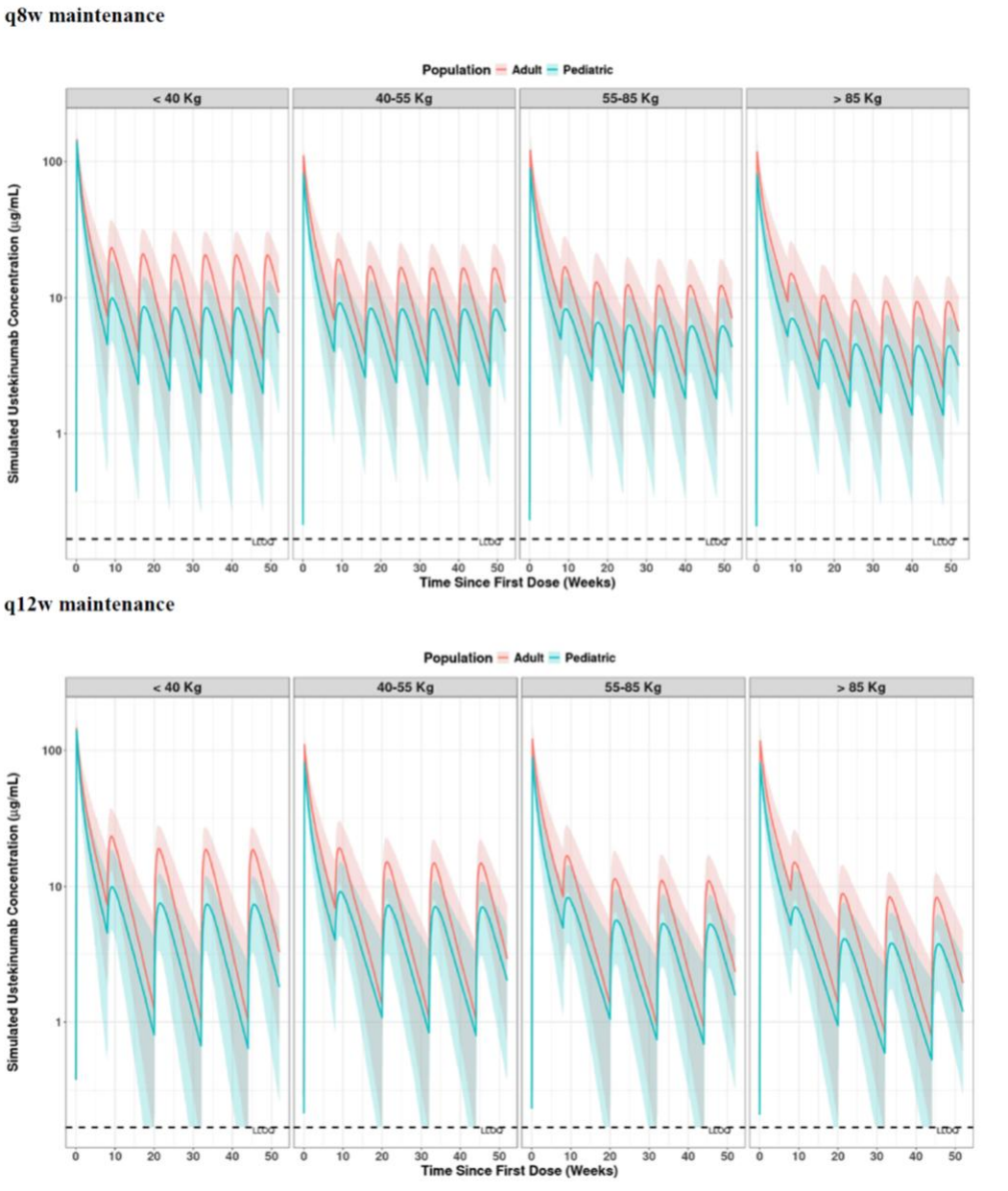
PK simulations

Simulations were performed to compare the systemic exposures in paediatric participants with UC following the proposed dose regimens with those in adults who received the approved adult dose regimen (i.e., weight-tier induction doses followed by 90 mg SC q12w or q8w).

Comparison of simulated PK between paediatric and adult participants by weight groups

The overlay of simulated PK profiles in adult and paediatric participants stratified by weight groups is shown in Figure 8. Median concentrations were higher in adults than paediatric participants; however, the concentration-time profiles of ustekinumab in paediatric participants overlapped with those in adult participants, where the predicted C_{trough} in more than 80% of paediatric participants fell within the 90% prediction interval of adult exposures following either induction or maintenance treatment across weight groups.

Figure 8: Comparison of the Simulated Serum Concentration-time Profiles of Ustekinumab by Weight Group in Pediatric and in Adult Participants



Abbreviations: IV=intravenous; LLOQ=lower limit of quantification; PK=pharmacokinetic(s); qXw=every X weeks.
Note: Lines represent medians of the simulated values. Shaded regions represent the 5th to 95th percentile ranges. The upper and lower panel show PK profiles of ustekinumab with single IV induction treatment followed by 90 mg q8w or 90 mg q12w maintenance treatment, respectively. For each weight group, simulations were performed based on 1,000 virtual pediatric or adult participants.

Additional simulations of PK profiles in paediatric participants stratified into body weight classes 10 to <20 kg, 20 to <30 kg, and 30 to <40 kg were performed, and these exposures were compared with

model-predicted exposure in adults and paediatric participants ≥40 kg. Boxplots summaries of ustekinumab exposure metrics (C_{max} and C_{trough}) following IV induction and SC maintenance ustekinumab treatment are presented in Figure 9 and Figure 10, respectively. Overall, systemic ustekinumab exposures during induction and maintenance in the different body weight subgroups of participants <40 kg (10 to <20 kg, 20 to <30 kg, and 30 to <40 kg) following the proposed BSA-adjusted dosage were comparable to those who received approved ustekinumab doses in the ≥40 kg group. Furthermore, these ustekinumab exposures were generally within the range of those established to be safe and effective in the adult UC population.

Figure 9: Ustekinumab Exposure Metrics (Cmax and Ctrough) by Body Weight Subgroups, Following the Proposed BSA-adjusted IV Induction Doses for Pediatric Participants With UC <40 kg, or Body Weight Tiered Fixed IV Induction Doses in Pediatric Participants with UC ≥40 kg

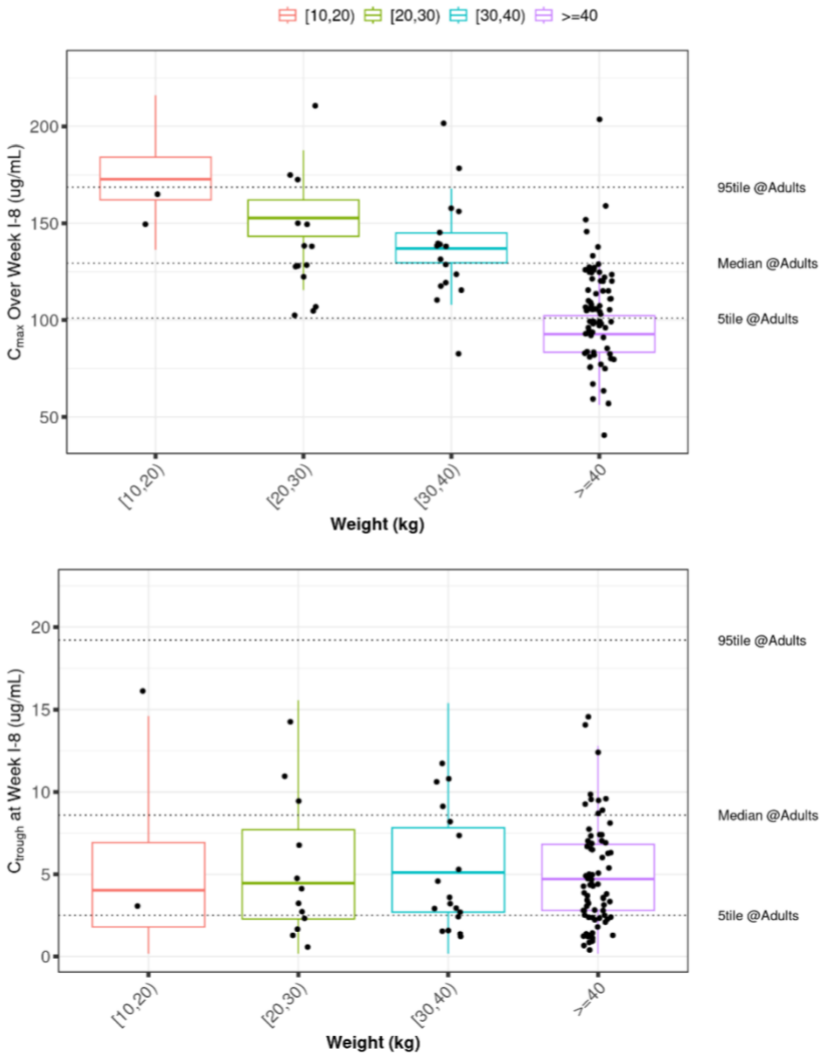


Figure 10: Ustekinumab Exposure Metrics (Cmax and Ctrough) by Body Weight Subgroups, Following the Proposed BSA-adjusted IV Induction Doses for Pediatric Participants With UC <40 kg, or Body Weight Tiered Fixed IV Induction Doses in Pediatric Participants with UC ≥40 kg

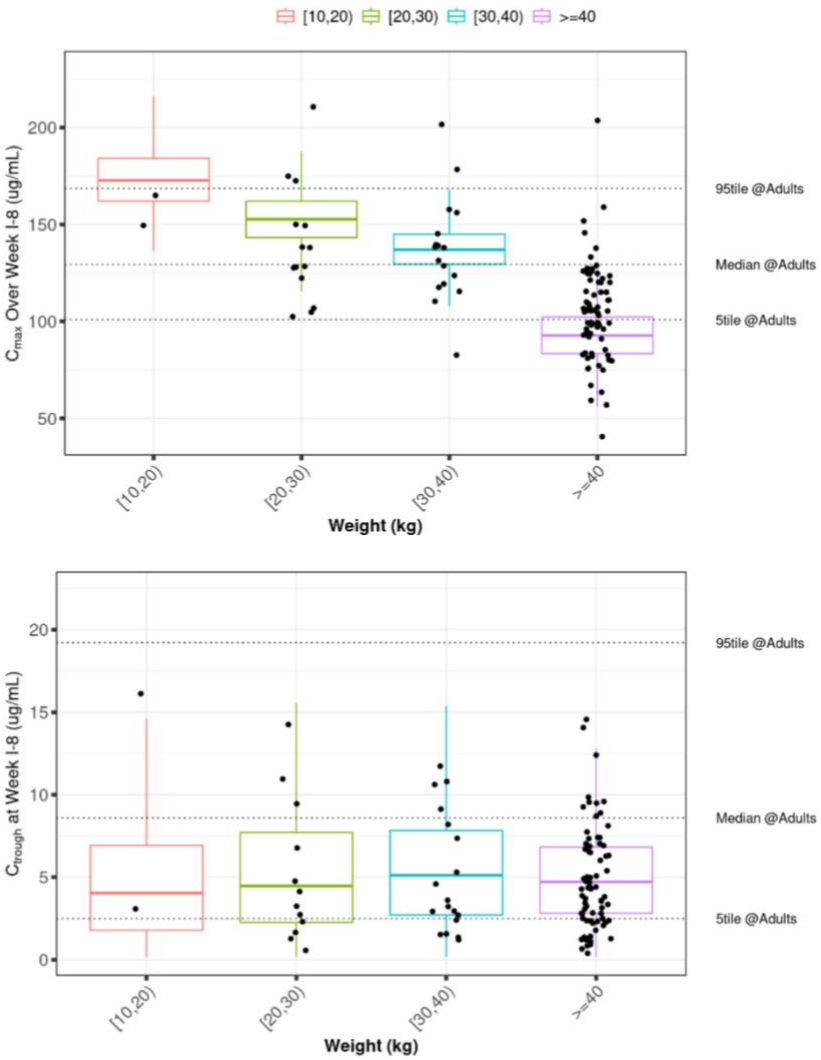
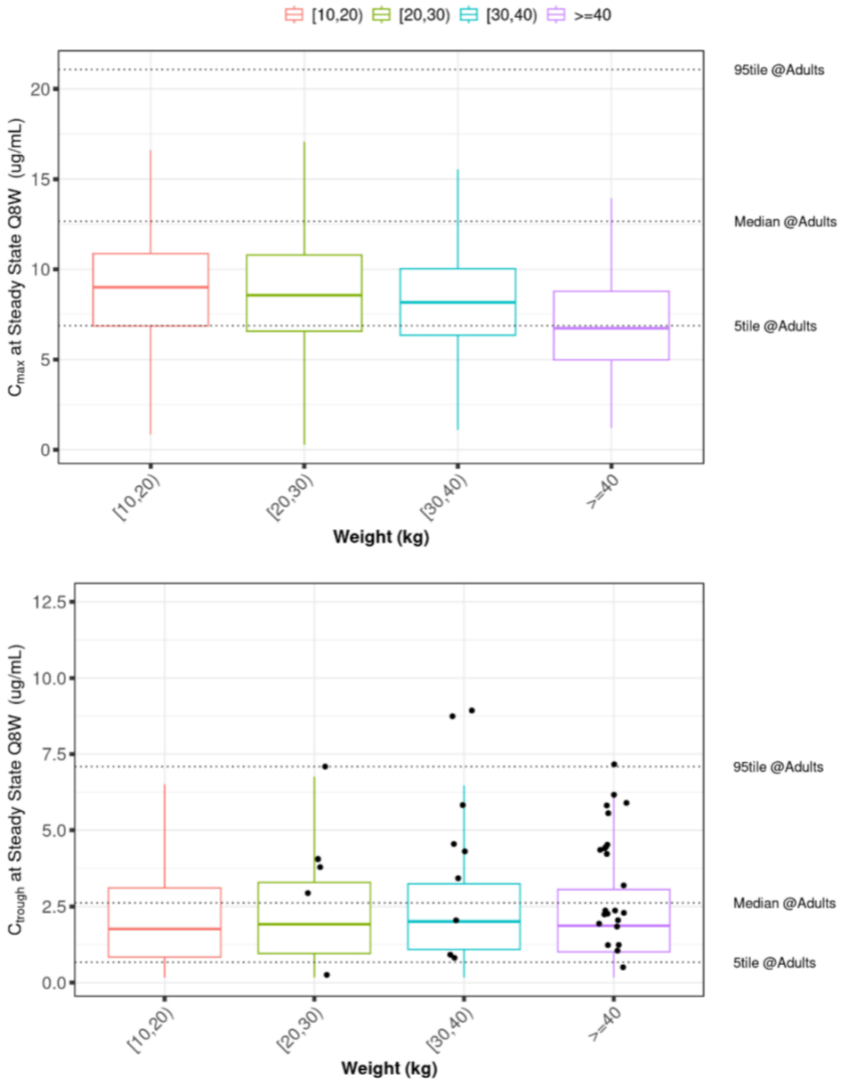
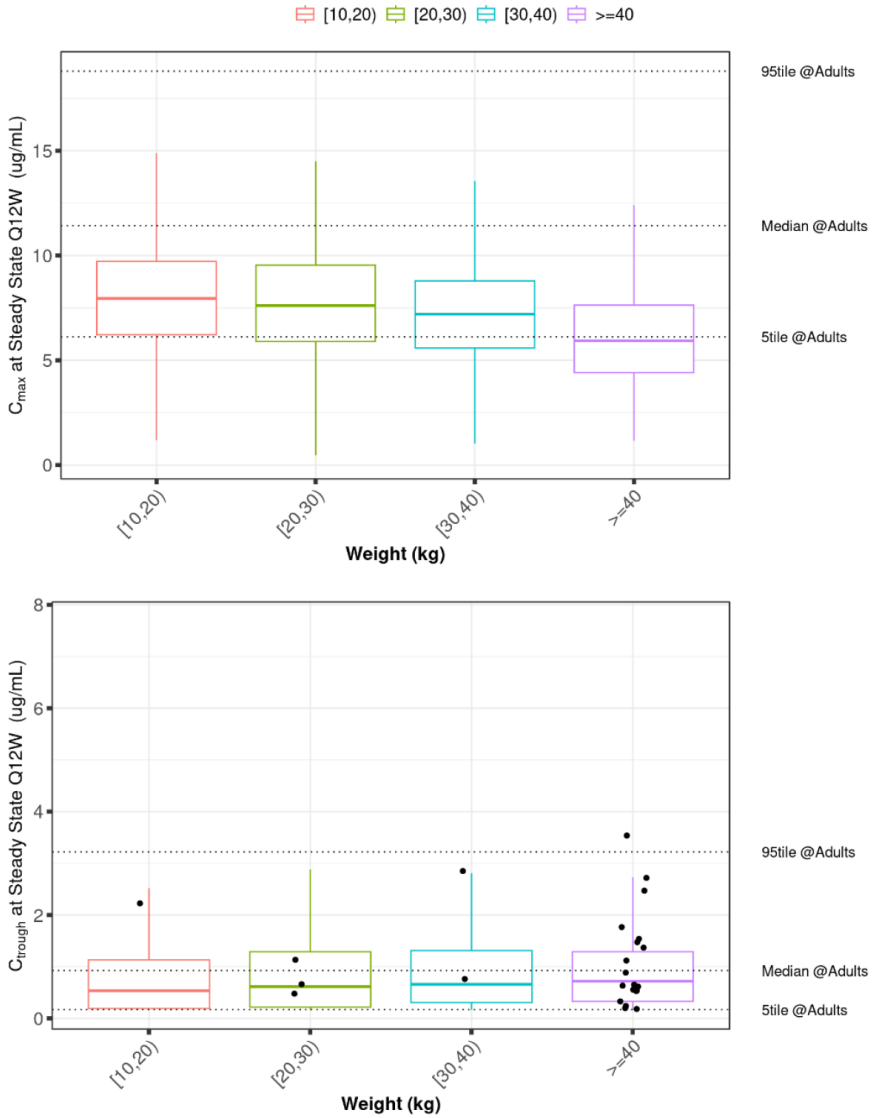


Figure 11: Ustekinumab Exposure Metrics (Steady-State Cmax and Ctrough) by Body Weight Subgroups, Following the Proposed BSA-adjusted SC Doses for Pediatric Participants With UC <40 kg, or Approved Fixed SC Maintenance Doses in Pediatric Participants with UC ≥40 kg

2A: q8w Dosing



2B: q12w Dosing



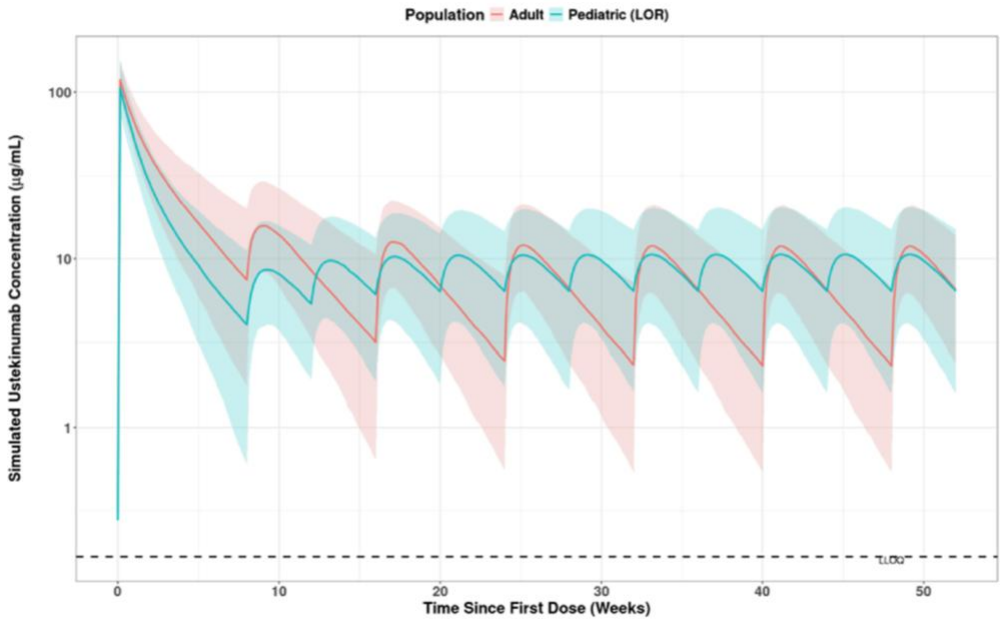
Comparison of simulated PK between paediatrics receiving q4w SC maintenance treatment and adults receiving q8w SC maintenance treatment

The median (range) individual post hoc estimate of CL for the 21 participants who entered into the optional Exposure Optimisation Sub-study with LOR and low ustekinumab exposure (i.e., an 8-week, steady-state, trough concentration <1.4 µg/mL) was 0.271 (0.086 to 0.552) L/day, which is higher compared with those participants who did not enter the sub-study (0.205 [0.046 to 0.453] L/day). The median (range) body weight of paediatric LOR participants was 46.4 (14.2-78) kg.

The overlay of simulated PK profiles in paediatric LOR participants who received either 60 mg/m^2 or 90 mg q4w SC maintenance treatment and adults receiving 90 mg q8w SC maintenance treatment is shown in Figure 12. The ustekinumab concentration-time profiles in paediatric participants largely overlapped with those in adult participants. Peak concentrations were similar, whilst troughs were 178% higher in paediatrics following q4w treatment compared with adults following q8w treatment, resulting in a 32.6% increase in AUC_{ss},q8w in paediatrics.

Simulations were also done where all paediatric participants were switched to q4w treatment irrespective of LOR status, as a worst-case sensitivity analysis, and compared with adults receiving q8w SC maintenance treatment. In this simulation, C_{trough} was 209% higher in paediatrics following q4w treatment compared with adults following q8w treatment, resulting in a 44.2% increase in AUC_{ss},q8w in paediatrics.

Figure 12: Comparison of the Simulated Serum Concentration-time Profiles of Ustekinumab in Pediatric Participants From CNTO1275PUC3001 Who Lost Response and Received Either 60 mg/m2 (Weight <40 kg) or 90 mg q4w (Weight ≥40 kg) SC Maintenance Treatment With Those in Adult Participants From CNTO1275UCO3001 Receiving the 90 mg q8w SC Maintenance Treatment



Abbreviations: EBE=empirical Bayesian estimate; LLOQ=lower limit of quantification; LOR=loss of response; qXw=every X weeks; SC=subcutaneous.
Note: Lines represent medians of the simulated values. Shaded regions represent the 5th to 95th percentile ranges. Comparison was made between 1,000 pediatric participants (sampling with replacement from the 21 pediatric LOR participants in CNTO1275PUC3001) and 822 adult participants from CNTO1275UCO3001. The individual post hoc EBE parameters from the final pediatric model and the updated adult model were used for pediatric and adult simulations, respectively.

2.3.3. Pharmacodynamics

Mechanism of action

Ustekinumab is a human IgG1κ mAb that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signalling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of UC. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

Immunogenicity

Phase 3 CD Study CNTO1275PUC3001

Induction period

Among the 108 paediatric participants who received induction ustekinumab and had appropriate samples, no participant was positive for antibodies to ustekinumab through Week I-8.

Maintenance period

Of the 97 ustekinumab-treated paediatric participants with appropriate samples, 2 (2.1%) were positive for antibodies to ustekinumab through Week M-44. Both participants were positive for NAbs.

Exposure optimisation substudy (EOS)

Among paediatric participants who entered the EOS and had appropriate samples, 1 (5.3%) of 19 participants was positive for antibodies to ustekinumab.

Comparison of immunogenicity between paediatric and adult participants with UC

The incidence of antibodies to ustekinumab was comparable between paediatric and adult participants with UC. Using the same assay, 2.1% of paediatric participants were positive for antibodies to ustekinumab compared with 4.6% of the adult UC participants.

Comparison of immunogenicity between paediatric participants with UC and CD

The incidence of antibodies to ustekinumab was comparable between paediatric participants with UC (Study CNTO1275PUC3001) and CD (Study CNTO1275CRD3004). Using the same assay, 2.1% of paediatric participants with UC were positive for antibodies to ustekinumab compared with 3.3% of paediatric participants with CD.

2.3.4. PK/PD modelling

Exposure-response analyses for efficacy

The main objectives of these analyses were to characterise the relationships between ustekinumab exposure and clinical efficacy endpoints in paediatric UC participants and to assess the similarity of these E-R relationships with those adult UC participants.

Methods

The analyses were performed using data from the Phase 3 paediatric UC study (CNTO1275PUC3001). To evaluate similarity between paediatric and adult UC participants, ER analyses based on data from the adult Phase 3 UC study (CNTO1275UCO3001) were used.

The analyses were performed for 3 clinical efficacy endpoints, including clinical remission and clinical response at Week I-8 in relation to $C_{trough,weekI8}$, and clinical remission at Week M-44 in relation to $C_{trough,weekM44}$. The analysis methods for each endpoint are provided in Table 7.

Table 7: Summary of E-R Analyses for Efficacy Endpoints in CNTO1275PUC3001

Efficacy Endpoint	Analysis Method
Clinical remission at Week I-8 (global primary endpoint)	Graphical exploratory analysis and modeling analysis
Clinical remission at Week M-44 (US-specific endpoint)	Graphical exploratory analysis and modeling analysis
Clinical response at Week I-8	Graphical exploratory analysis

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

Individual popPK parameter estimates were used to derive individual ustekinumab exposure metrics ($C_{trough,weekI8}$ and $C_{trough,weekM44}$).

For the exploratory graphical analyses, the proportion of participants achieving the endpoint at Week I-8 (induction phase) and at Week M-44 (maintenance phase) were plotted by ustekinumab exposure tertile groups based on their model-predicted individual exposures.

For the modelling analyses, firstly, similarity in the ER relationship between paediatric participants and adults was assessed graphically by fitting a logistic smooth function. Then, covariate relationships that were significant in the adult ER model were evaluated graphically, including biologic failure status and baseline Mayo score for clinical remission at Week I-8 and remission status for clinical remission at Week M-44. Covariate relationships that were not evident in the paediatric data were not included in the model. Finally, the paediatric data were fitted with a nonlinear logistic regression model, with additive placebo and E_{max} drug effects on the logit scale, which was based on the prior knowledge from the adult E-R model. A GOF plot was used to compare the observed and model-predicted proportions of participants in clinical remission at Week I-8 and Week M-44 in the predicted exposure tertile bins.

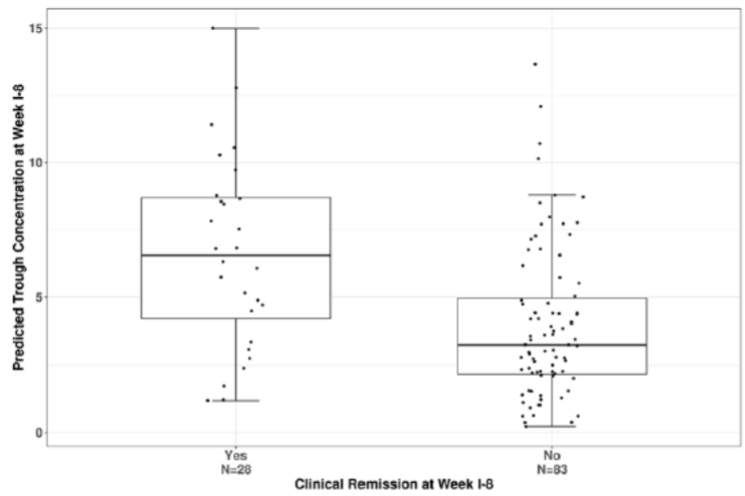
Results

- Clinical Remission at Week I-8

Exploratory graphical analyses

Figure 13 shows the distribution of model-predicted $C_{trough,weekI8}$ in paediatric participants with and without clinical remission at Week I-8. $C_{trough,weekI8}$ overlapped between pediatric participants with and without clinical remission, with numerically higher median $C_{trough,weekI8}$ observed in those with clinical remission.

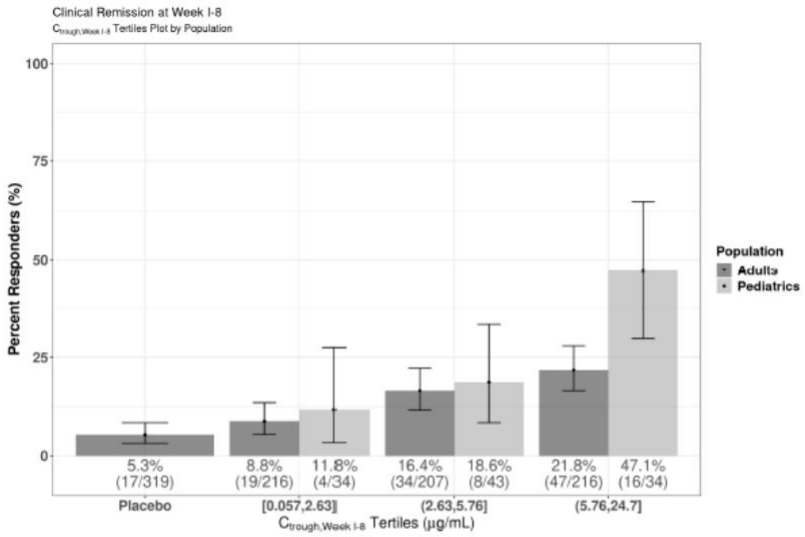
Figure 13: Comparison of Model-predicted Ctrough,week IS Between Pediatric Participants With or Without Clinical Remission at Week I-8 in Study CNTO1275PUC3001



Abbreviations: CI=confidence interval; C_{trough}=trough concentration; N=number of participants; Week I-X=Induction Week X.
Note: Error bars are the 95% CIs of response rates. Black dots are the model-predicted individual $C_{trough,Week\ I8}$. Clinical remission at Week I-8 in pediatric participants was summarized in participants who had measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m^2 (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275PUC001 (N=111).

Figure 14 shows the E-R relationship of paediatric participants compared to that of adult participants. A similar positive E-R trend was observed, with a higher (but more variable) clinical remission rate in paediatric participants in each predicted $C_{trough,weekI8}$ tertile group. Overall, the clinical remission rate at Week I-8 was higher in paediatric participants (28/111 [25.2%]) compared with adult participants (49/319 [15.3%]).

Figure 14: E-R Relationship for Clinical Remission at Week I-8 Versus Predicted Ctrough,weekIs in Pediatric Study CNTO1275PUC3001 and Adult Study CNTO1275UCO3001

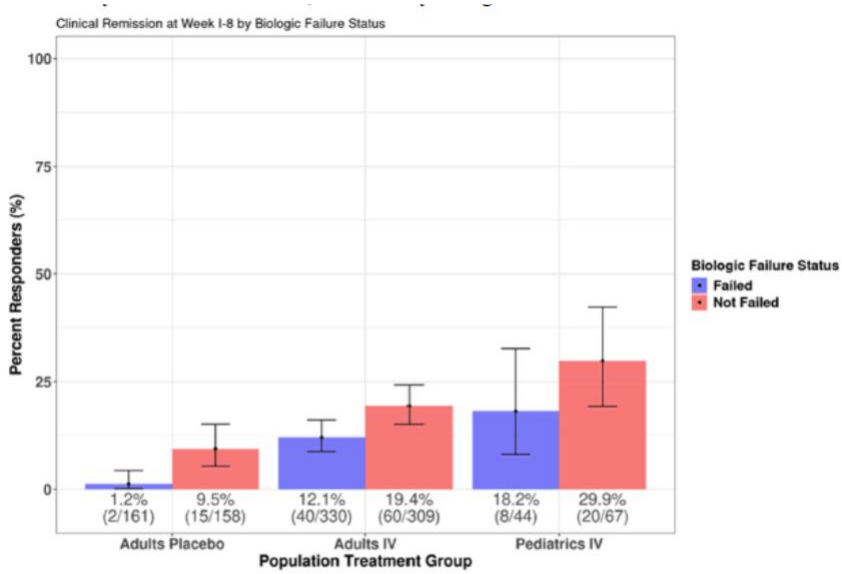


Abbreviations: CI=confidence interval; $C_{trough,weekI8}$=trough concentration for IV induction dose at Week I-8; E-R=exposure-response; IV=intravenous; N=number of participants; Week I-X=Induction Week X.

Note: Error bars are the 95% CIs of response rates in the respective exposure tertile groups. The E-R relationship in adults was summarized in participants who received ustekinumab 130 mg or ~6 mg/kg and placebo at Week I-0 from CNTO1275UCO3001 (N=958). The E-R relationship in pediatric participants was summarized in participants who had measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m^2 (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275PUC3001 (N=111). Exposure tertile cutoffs for $C_{trough,weekI8}$ were based on pooled data from pediatric Study CNTO1275PUC3001 and adult Study CNTO1275UCO3001.

Similar to adults, at a given concentration, the clinical remission rate at Week I-8 was higher in the biologic non-failure population compared with the biologic failure population in paediatric participants (Figure 15).

Figure 15: Clinical Remission at Week I-8 in Pediatric Study CNTO1275PUC3001 and Adult Study CNTO1275UCO3001, Stratified by Biologic Failure Status

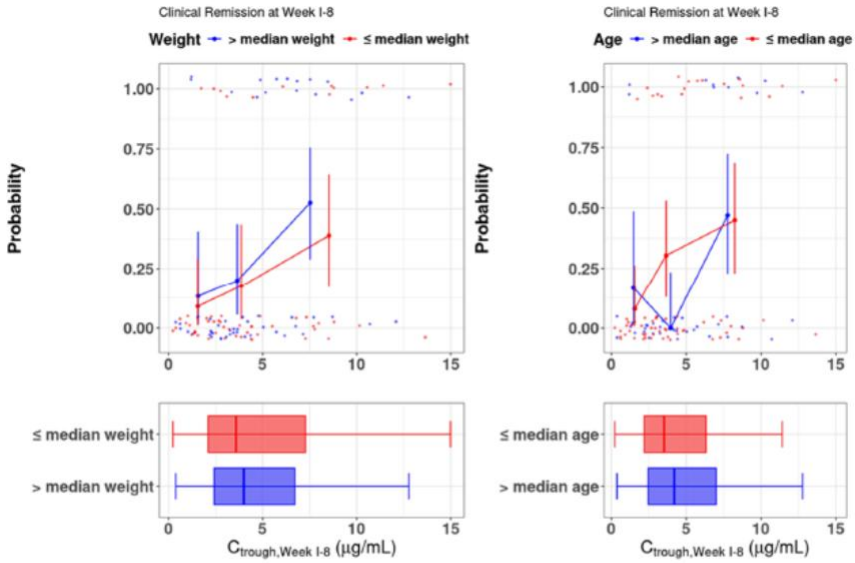


Abbreviations: CI=confidence interval; IV=intravenous; Week I-X=Induction Week X.

Note: Error bars are the 95% CIs of response rates by biologic failure status. 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 CNTO1275UCO3001 (N=958). Clinical remission at Week I-8 in pediatric participants was summarized in participants who had measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m^2 (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275PUC3001 (N=111).

The E-R relationship of clinical remission at Week I-8 and the predicted $C_{trough,weekI8}$ in paediatric participants by age group or weight group is shown in Figure 16. Age and weight had no clear effect on the E-R relationship; the 95% CIs of the clinical remission rate across the $C_{trough,weekI8}$ tertile groups were largely overlapping.

Figure 16: E-R Relationship of Clinical Remission at Week I-8 Versus the Predicted $C_{trough\ week18}$ in Pediatric Study CNTO1275PUC3001, Stratified by Weight Group (Left) or Age Group (Right)



Abbreviations: CI=confidence interval; $C_{trough,weekI8}$=trough concentration for IV induction dose at Week I-8; E-R=exposure-response; IV=intravenous; Week I-X=Induction Week X.

Note: Connected dots with error bars are the observed median and 95% CIs of probability in the respective exposure tertile groups. Dots at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders, respectively, which were predicted based on the actual dose regimen and individual PopPK model parameter estimates in pediatric participants who had measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m^2 (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275PUC3001 (N=111). Box plots at the bottom represent the distribution of the individual model-predicted exposure metrics in subgroups.

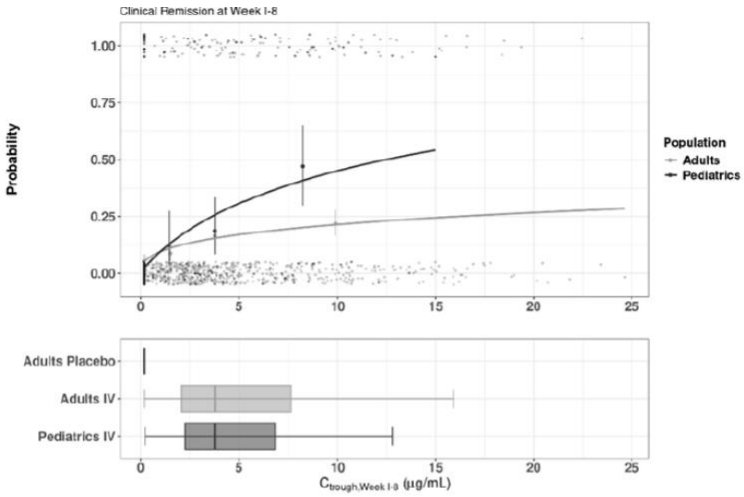
Note: Stratification for age was as follows: 3-14 years versus 14-17 years. Stratification for weight was as follows: 13.6-47 kg versus 47 kg-80 kg.

Modelling analysis

In the graphical exploration, the positive ER trend appeared stronger in paediatric participants compared with adults (

Figure 17).

Figure 17: Linear Logistic Regression of Clinical Remission at Week I-8 and $C_{trough\ week18}$ in Adult and Pediatric Participants



Abbreviations: CI=confidence interval; $C_{trough,week18}$=most recent trough concentration prior to Week I-8; E-R=exposure-response; IV=intravenous; N=number of participants; PopPK=population pharmacokinetic(s); SC=subcutaneous; Week I-X=Induction Week X.

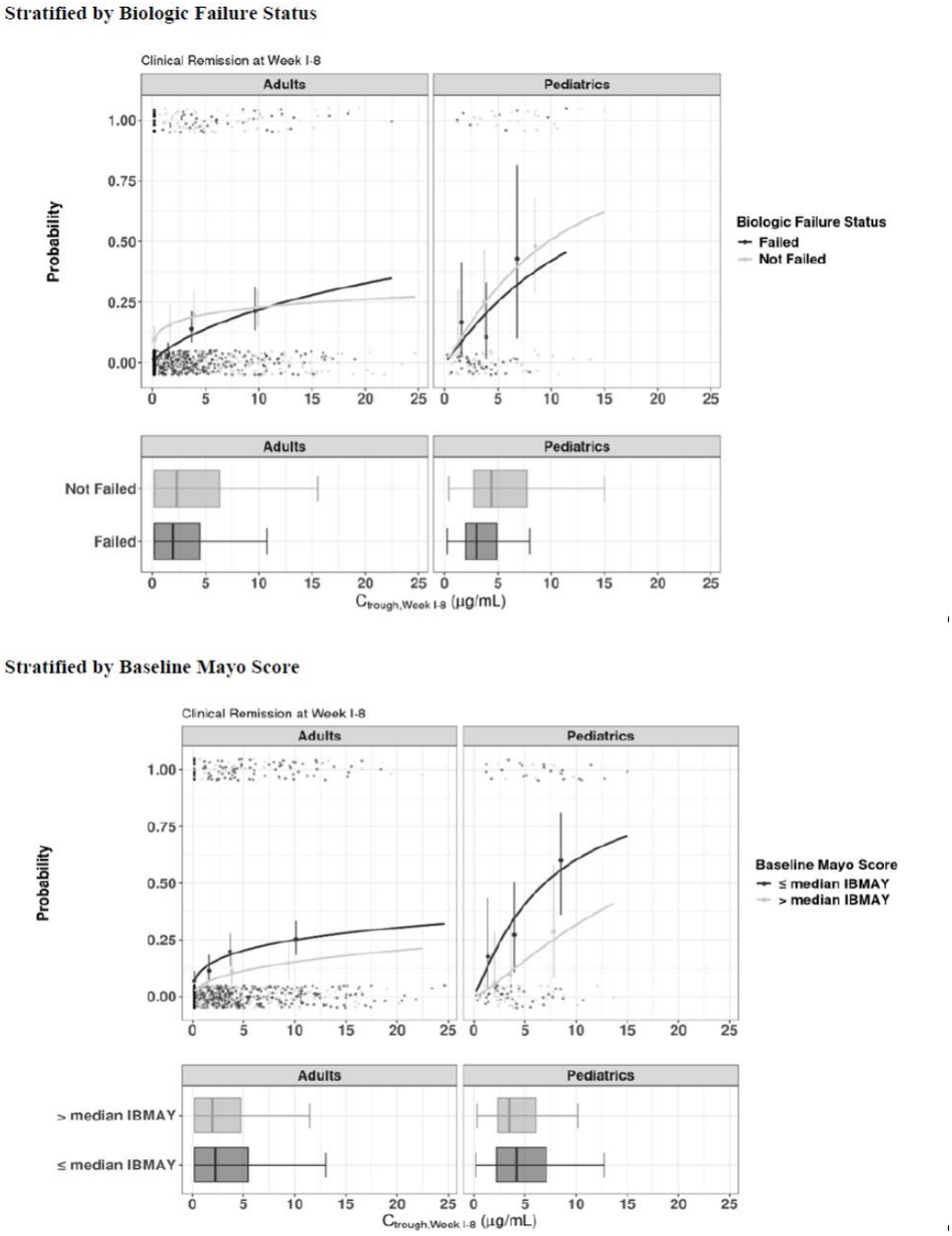
Note: Solid dots with error bars are the observed median and 95% CIs of the probability in the respective exposure tertile groups. The smoothed solid lines are logistic regression model-predicted E-R relationships of clinical remission at Week I-8 in adult or pediatric participants. The intercept in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

Note: Dots at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders for clinical remission at Week I-8, respectively, where the black dots represent the placebo group from adult studies and light and dark grey dots represent adult or pediatric participants receiving IV induction treatment, respectively. The individual exposure metrics were predicted based on actual doses and individual PopPK model parameter estimates in pediatric participants who received IV induction regimens of 60 mg/m^2 (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) in CNTO1275PUC3001 (N=111) or adult participants who received IV induction regimens of placebo, 130 mg, or ~6 mg/kg in CNTO1275UCO3001 (N=958). Box plots at the bottom represent the distribution of the individual model-predicted exposure metrics in the placebo group from adults, and adults from CNTO1275UCO3001 or pediatrics from CNTO1275PUC3001 receiving IV induction treatment.

The effect of biologic failure status and baseline Mayo score on the ER relationship were similar in adult and paediatric participants, where participants who had previously failed biologic therapy or had a baseline Mayo score higher than the median score have lower clinical remission rate (

Figure 18).

Figure 18: Linear Logistic Regression of Clinical Remission at Week I-8 and Ctrough,weekIs in Adults and Pediatric Participants, Stratified by Covariates of Interest



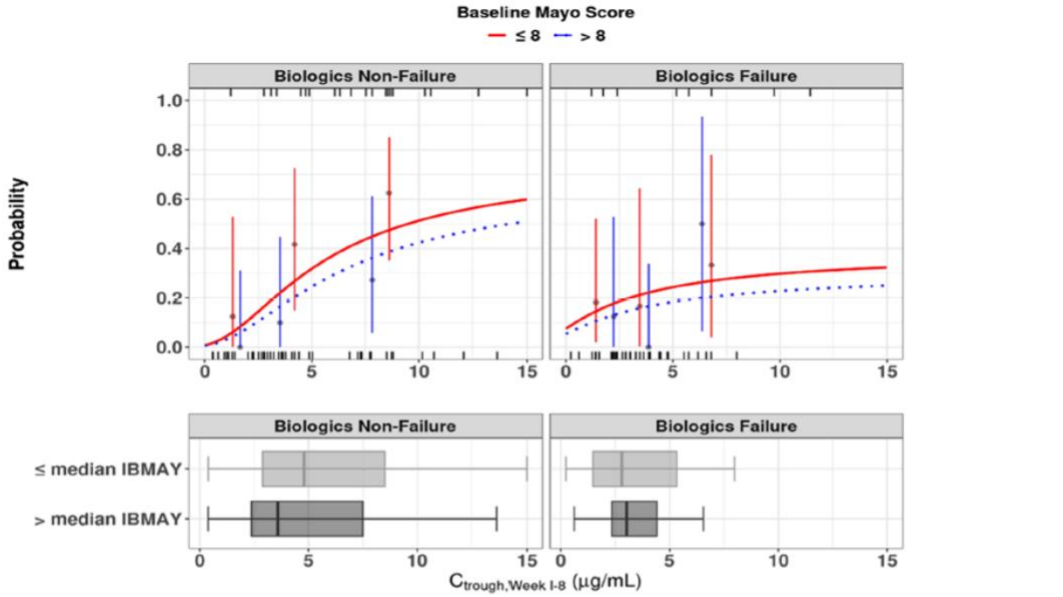
The E-R relationship between $C_{trough,weekI8}$ and clinical remission at Week I-8 in paediatric participants was adequately characterised by an E_{max} model with an additive placebo effect on the logit scale. As no placebo data were available in paediatric participants, the placebo effect was fixed (by fixing the intercept of the linear logistic regression model) to that from the adult model and assumed to be the same. The effect of biologic failure status and baseline Mayo score on the placebo effect and effect of biologic failure status on E_{max} were retained from the adult model. Parameter estimates of the final paediatric ER model are presented in Table 8. A GOF plot of the final model is shown in Figure 19. The larger RSE for EC50 (78%) was likely the result of the limited data at low concentrations due to the large induction dose.

Table 8: Clinical Remission at Week I-8 Final E_{max} E-R Model Parameter Estimates

Parameter	Estimate (%RSE)
Placebo effect (β)	
β_0	-4.82 Fixed
Biologic Failure	2.31 Fixed
Baseline Mayo Score	-3.05 Fixed
E_{max}	
$E_{max,0}$	6.09 (22%)
Biologic Failure	-1.08 (33%)
EC_{50} (µg/mL)	
$EC_{50,0}$	2.50 (78%)

Abbreviations: β=placebo effect; β_0=intercept; $EC_{50,0}$ or EC_{50}=half maximal effective concentration; $E_{max,0}$ or E_{max}=maximum drug effect; E-R=exposure-response; RSE=relative standard error; Week I-X=Induction Week X.

Figure 19: GOF Plot of the Final Pediatric Emax Model for Clinical Remission at Week I-8 in Pediatric Participants From CNTO1275PUC3001 Stratified by Biologic Failure Status and Baseline Mayo Score



Abbreviations: CI=confidence interval; $C_{trough,weekI8}$=trough concentration for IV induction dose at Week I-8; E_{max}=maximum drug effect; E-R=exposure-response; GOF=goodness-of-fit; IBMAY=imputed baseline Mayo score; IV=intravenous; N=number of participants; PopPK=population pharmacokinetic(s); Week I-X=Induction Week X.

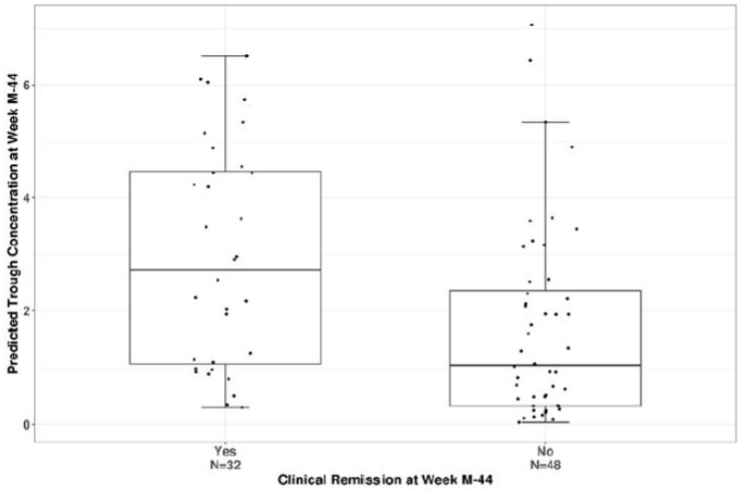
Note: Dots are the observed median of the probability in the respective exposure tertile groups, and the vertical bars are the observed 95% CI. The solid smooth curves represent the model-predicted E-R relationships for subgroups stratified by biologic failure status and baseline Mayo score stratified as above or below median Mayo score, while other covariates were fixed to be the same as the reference group in the final model. Short vertical lines at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders, respectively, which were predicted based on the actual dose regimen and individual PopPK model parameter estimates in pediatric participants across the full body weight range who received ~6 mg/kg ustekinumab at Week I-0 from CNTO1275PUC3001 (N=111). Box plots at the bottom of the figure represent the distribution of the individual model-predicted exposure metrics in subgroups of pediatric participants.

- Clinical remission at Week M-44

Exploratory graphical analyses

Figure 20 shows the distribution of model-predicted $C_{trough,weekM44}$ in paediatric participants with and without clinical remission at Week M-44. $C_{trough,weekM44}$ overlapped between paediatric participants with and without clinical remission, with numerically higher median $C_{trough,weekM44}$ observed in those with clinical remission.

Figure 20: Comparison of Model-predicted $C_{trough,weekM44}$ Between Pediatric Participants With or Without Clinical Remission at Week M-44 in Study CNTO1275PUC3001

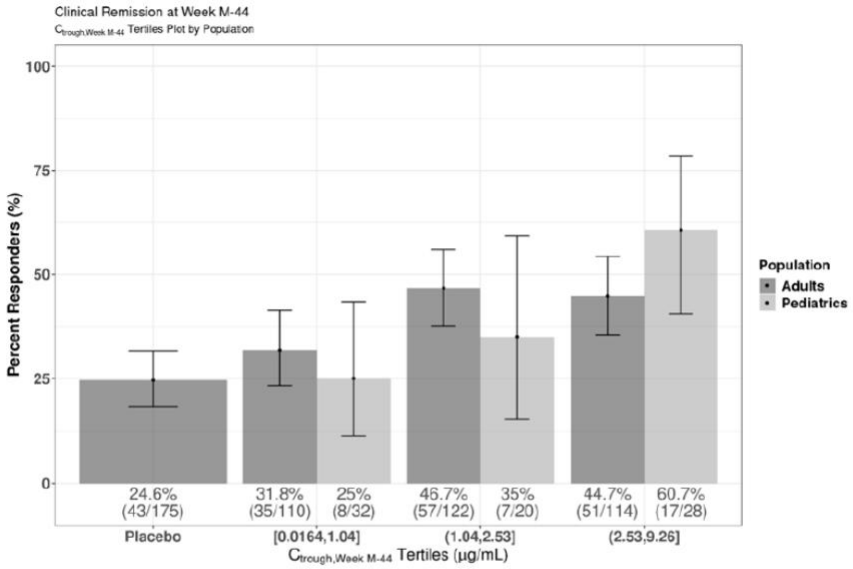


Abbreviations: CI=confidence interval; $C_{trough,WeekM44}$=trough concentration at Week M-44; N=number of participants; qXw=every X weeks; SC=subcutaneous; Week M-X=Maintenance Week X.

Note: Error bars are the 95% CIs of response rates. Black dots are the model-predicted individual $C_{trough,WeekM44}$. Clinical remission at Week M-44 in pediatric participants was summarized in participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m^2 (weight <40 kg) or 90 mg (weight ≥40 Kg) q8w or q12w in CNTO1275PUC3001 (N=80).

Figure 21 shows the E-R relationship of clinical remission at Week M-44 in paediatric participants compared with adult participants. A similar E-R trend was observed for clinical remission at Week M-44 in relation to predicted $C_{trough,weekM44}$ in adult and paediatric participants, with comparable clinical remission rate in paediatric participants across predicted $C_{trough,weekM44}$ tertile groups. Overall, the clinical remission rate at Week M-44 in paediatric participants was comparable to that in adult participants (32 [40%] of 80 paediatric participants and 143 [41%] of 346 adult participants).

Figure 21: E-R Relationship for Clinical Remission at Week M-44 Versus Predicted $C_{trough,weekM44}$ in Pediatric Study CNTO1275PUC3001 and Adult Study CNTO1275UCO3001

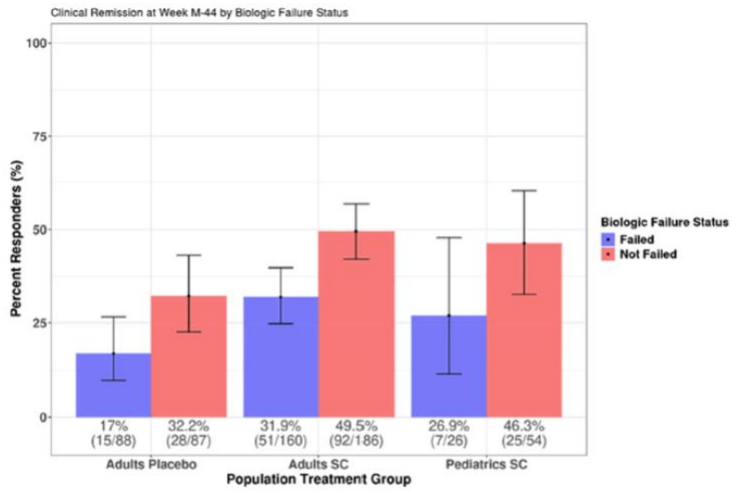


Abbreviations: CI=confidence interval; $C_{trough,weekM44}$=most recent trough concentration prior to Week M-44; E-R=exposure-response; N=number of participants; qXw=every X weeks; SC=subcutaneous; Week M-X=Maintenance Week X.

Note: Error bars are the 95% CIs of response rates in the respective exposure tertile groups. The E-R relationship in adults was summarized in participants who were randomized to receive SC maintenance regimens of placebo, 90 mg q8w, or 90 mg q12w in CNTO1275UCO3001 (N=521). The E-R relationship in pediatric participants was summarized in participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m^2 (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275PUC3001(N=80). Exposure tertile cutoffs for $C_{trough,weekM44}$ were based on pooled data from pediatric Study CNTO1275PUC3001 and adult Study CNTO1275UCO3001.

Similar to adults, the clinical remission rate at Week M-44 was higher in the biologic non-failure population compared with the biologic failure population in paediatric participants (Figure 22).

Figure 22: Clinical Remission at Week M-44 in Pediatric Study CNTO1275PUC3001 and Adult Study CNTO1275UCO3001, Stratified by Biologic Failure Status

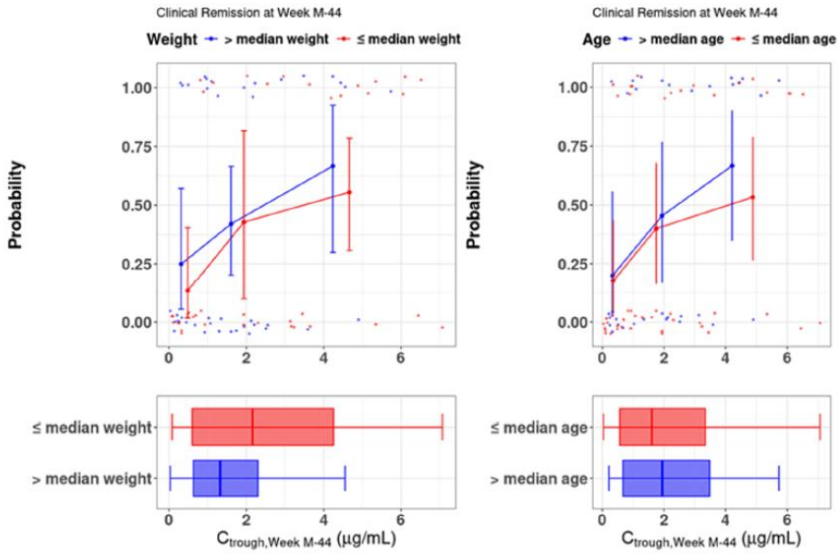


Abbreviations: CI=confidence interval; N=number of participants; qXw=every X weeks; SC=subcutaneous; Week M-X=Maintenance Week X.

Note: Error bars are the 95% CIs of response stratified by biologic failure status. Clinical remission at Week M-44 in adults was summarized in participants who were randomized to receive SC maintenance regimens of placebo, 90 mg q8w, or 90 mg q12w in CNTO1275UCO3001 (N=521). The E-R relationship in pediatric participants was summarized in participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m^2 (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275PUC3001(N=80).

The E-R relationship of clinical remission at Week M-44 and the predicted $C_{trough,weekM44}$ in paediatric participants stratified by age group or weight group is shown in Figure 23. Age and weight had no clear effect on the E-R relationship; the 95% CIs of clinical remission rate across the $C_{trough,weekM44}$ tertile groups were largely overlapping.

Figure 23: E-R Relationship of Clinical Remission at Week M-44 Versus the Predicted $C_{trough,weekM44}$ in Pediatric Study CNTO1275PUC3001, Stratified by Weight Group (Left) or Age Group (Right)



Abbreviations: CI=confidence interval; $C_{trough,weekM44}$=most recent trough concentration prior to Week M-44; E-R=exposure-response; N=number of participants; PopPK=population pharmacokinetic(s); SC=subcutaneous; Week M-X=Maintenance Week X.

Note: Connected dots with error bars are the observed median and 95% CIs of probability in the respective exposure tertile groups. Dots at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders, respectively, which were predicted based on the actual dose regimen and individual PopPK model parameter estimates in pediatric participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m^2 (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275PUC3001 (N=80). Box plots at the bottom represent the distribution of the individual model-predicted exposure metrics in subgroups.

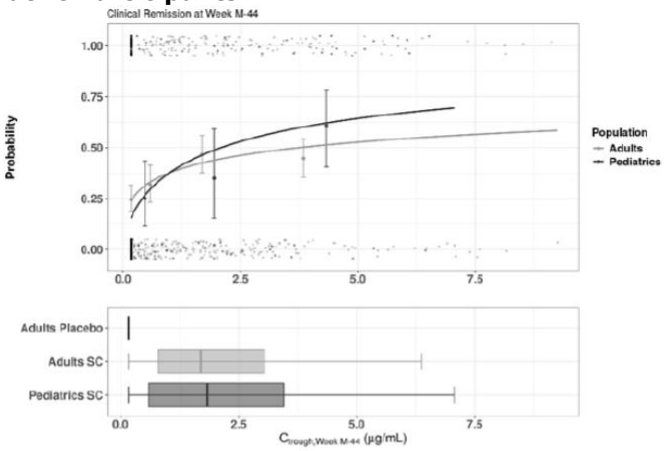
Note: Stratification for age was as follows: 3-14 years versus 14-17 years. Stratification for weight was as follows: 13.6-46.9 kg versus 46.9 kg-80.0 kg.

Modelling analysis

The graphical exploration demonstrated a similar E-R trend in clinical remission at Week M-44 with respect to $C_{trough,weekM44}$ in adult and pediatric participants (

Figure 24).

Figure 24: Linear Logistic Regression of Clinical Remission at Week M-44 and $C_{trough,weekM44}$ in Adult and Pediatric Participants



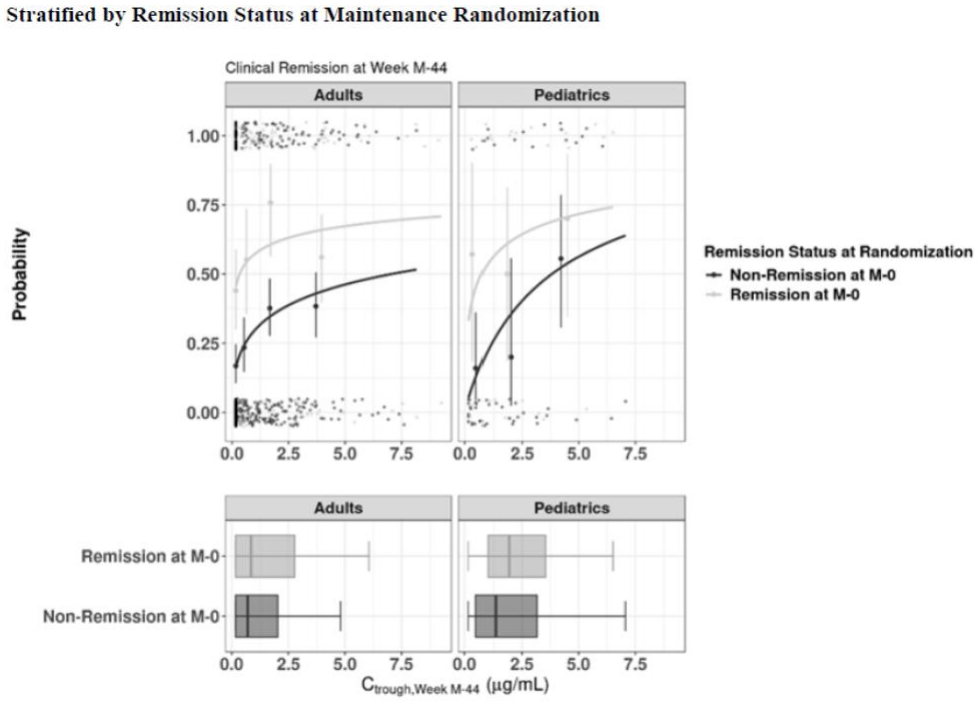
Abbreviations: CI=confidence interval; $C_{trough,weekM44}$=most recent trough concentration prior to Week M-44; E-R=exposure-response; N=number of participants; PopPK=population pharmacokinetic(s); qXw=every X weeks; SC=subcutaneous; Week M-X=Maintenance Week X.

Note: Solid dots with error bars are the observed median and 95% CIs of probability in the respective exposure tertile groups. The smoothed solid lines are logistic regression model-predicted E-R relationships of clinical remission at Week M-44 in adult or pediatric participants. The intercept in the pediatric model was fixed to that of the adult model.

Note: Dots at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders for clinical remission at Week M-44, respectively, where the black dots represent the placebo group from adult studies and light and dark grey dots represent adult or pediatric participants receiving SC maintenance treatment, respectively. The individual exposure metrics were predicted based on actual doses and individual PopPK model parameter estimates in pediatric participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m^2 (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275PUC3001 (N=80) or adult participants who were randomized to receive SC maintenance regimens of placebo, 90 mg q8w, or 90 mg q12w in CNTO1275UCO3001 (N=521). Box plots at the bottom represent the distribution of the individual model-predicted exposure metrics in the placebo group from adults, and adults from CNTO1275UCO3001 or pediatrics from CNTO1275PUC3001 receiving SC maintenance treatment.

The effect of remission status at maintenance randomisation on the ER relationship was similar in adult and paediatric participants, where participants who are already in remission at Week I-8 have a higher probability of achieving remission at Week M-44 relative to those that are not in remission at Week I-8 (Figure 25).

Figure 25: Linear Logistic Regression of Clinical Remission at Week M-44 and $C_{trough,\ weekM44}$ in Adults and Pediatric Participants, Stratified by Covariates of Interest



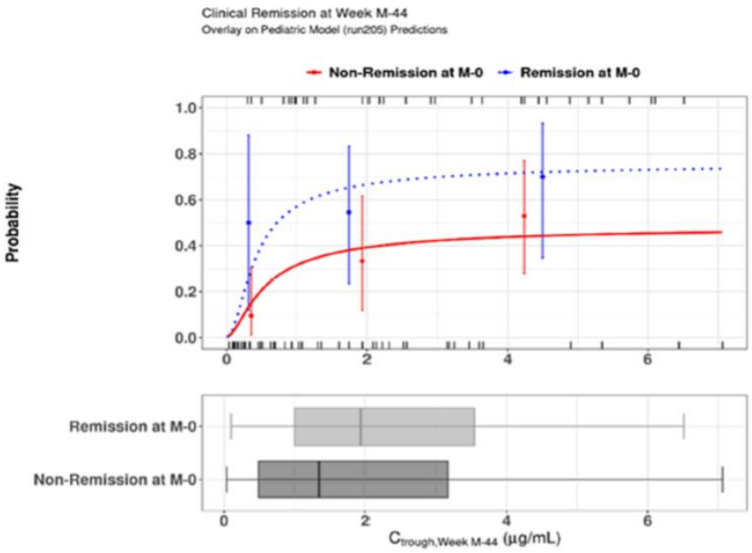
The E-R relationship between $C_{trough,weekM44}$ and clinical remission at Week M-44 in paediatric participants who were induction responders was adequately characterised by an E_{max} model with an additive placebo effect on the logit scale. The effect of remission status at maintenance randomisation on the placebo effect was retained from the previously established adult E-R model. After accounting for this covariate effect, the overall E-R trend suggested a lower placebo effect than that estimated in adults (-1.63). Therefore, the placebo effect was fixed to a lower value (-6). Accordingly, the covariate effect of remission status at randomisation on the placebo response was dropped and was instead added as an effect on E_{max}. Parameter estimates of the final E-R model are presented in Table 9. A GOF plot for the final ER model is shown in Figure 26.

Table 9: Clinical Remission at Week M-44 Final E_{max} E-R Model Parameter Estimates

Parameter	Estimate (%RSE)
Placebo effect (β)	
β_0	-6 Fixed
E_{max}	
$E_{max,0}$	5.95 (8%)
Remission Status at Randomization	0.185 (48%)
EC_{50} (µg/mL)	
$EC_{50,0}$	0.139 (54%)

Abbreviations: β=placebo effect; β_0=intercept; $EC_{50,0}$ or EC_{50}=half maximal effective concentration; $E_{max,0}$ or E_{max}=maximum drug effect; E-R=exposure-response; RSE=relative standard error; Week M-X=Maintenance Week X.

Figure 26: GOF Plot of Final Pediatric E_{max} Model for Clinical Remission at Week M-44 in Pediatric Participants From CNTO1275PUC3001 Stratified by Remission Status at Randomization



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

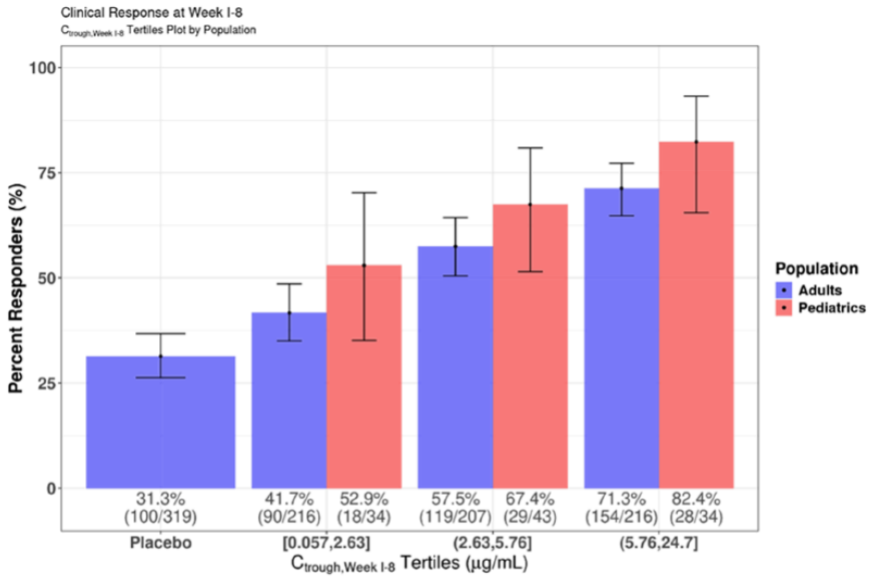
Note: Red and blue dots are the observed median of the probability in the respective exposure tertile groups stratified by remission status at randomization. The solid smooth curve represents the model-predicted E-R relationship of the final model. Short vertical lines at the lower and upper part of the plotting area represent the individual model-predicted exposure metrics in nonresponders and responders, respectively, which were predicted based on the actual dose regimen and individual PopPK model parameter estimates in pediatric participants who were induction responders and randomized to receive SC maintenance regimens of 60 mg/m^2 (weight <40 kg) or 90 mg (weight ≥40 kg) q8w or q12w in CNTO1275PUC3001 (N=80). Box plot at the bottom of the figure represents the distribution of the individual model-predicted exposure metrics in pediatric participants receiving SC maintenance treatment stratified by remission status at maintenance randomization.

- Clinical response at Week I-8

Exploratory graphical analysis

Figure 27 shows the E-R relationship for clinical response at Week I-8 in paediatric participants compared with adult participants. A similar positive E-R trend was observed in adult and paediatric participants, with a numerically higher clinical response rate in paediatric participants in each $C_{trough,weekI8}$ tertile group relative to adults.

Figure 27: E-R Relationship of Clinical Response at Week I-8 in Pediatric Study CNTO1275PUC3001 and Adult Study CNTO1275UCO3001



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

Note: Error bars are the 95% CIs of response rates in the respective exposure tertile groups. The E-R relationship in adults was summarized in participants who received ustekinumab 130 mg or ~6 mg/kg and placebo at Week I-0 from CNTO1275UCO3001 (N=958). The E-R relationship in pediatric participants was summarized in participants who had measurable ustekinumab concentrations after receiving ustekinumab 250 mg/m^2 (weight <40 kg) or ~6 mg/kg (weight ≥40 kg) at Week I-0 from CNTO1275PUC3001 (N=111). Exposure tertile cutoffs for $C_{trough,weekI8}$ were based on pooled data from pediatric Study CNTO1275PUC3001 and adult Study CNTO1275UCO3001.

Exposure-response analyses for safety

For these analyses, the ustekinumab concentrations were divided into quartiles, and the proportions of paediatric participants experiencing selected safety events (ie, infections, serious infections, and SAEs) were summarised**.** The induction analyses were performed using ustekinumab concentration at Week I-8 (Week 8), while the maintenance analyses were performed using the average steady-state trough concentration, in CNTO1275PUC3001.

There was no relationship between ustekinumab exposure and selected safety events at the dose levels evaluated in the paediatric study (

Table 10).

Table 10: Number of Participants With 1 or More Treatment-emergent Infections, Serious Infections, and Serious Adverse Events by Serum Ustekinumab Concentration Quartiles at Week I-8 (Week 8) and by Average Steady-state Trough Serum Ustekinumab Concentration Quartiles From Week M-0 Through Week M-44 (CNTO1275PUC3001)

	CNTO1275PUC3001							
	Ustekinumab Concentrations at Week I-8[a]				Ustekinumab Concentrations at Average Steady-State Trough[b, c]			
	<1st Quartile	≥1st Quartile and <2nd Quartile	≥2nd Quartile and <3rd Quartile	≥3rd Quartile	<1st Quartile	≥1st Quartile and <2nd Quartile	≥2nd Quartile and <3rd Quartile	≥3rd Quartile
Analysis set: PK Analysis Set	21	21	21	21	18	19	19	19
Average duration of follow-up (weeks)	8.07	8.16	8.10	8.07	43.08	43.95	43.72	44.49
Average exposure (number of administrations)	1.00	1.00	1.00	1.00	9.78	9.63	9.11	9.37
Participants with 1 or more treatment-emergent infections	7 (33.3%)	3 (14.3%)	5 (23.8%)	4 (19.0%)	14 (77.8%)	14 (73.7%)	12 (63.2%)	9 (47.4%)
Participants with 1 or more serious infection	0	1 (4.8%)	0	0	0	0	0	0
Participants with 1 or more serious adverse events	2 (9.5%)	1 (4.8%)	2 (9.5%)	0	1 (5.6%)	0	0	2 (10.5%)

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

Note: Quartile is calculated based on ustekinumab concentration at Week I-8 for all participants from CNTO1275PUC3001 regardless of the induction dosing. 1st quartile=2.34509 µg/mL, 2nd quartile=3.84425 µg/mL, 3rd quartile=7.20027 µg/mL.

Note: Quartiles are calculated based on ustekinumab concentration at steady-state visits for all participants from CNTO1275PUC3001 regardless of the induction dosing received. In case of q8w, trough serum ustekinumab concentrations at Week M-24 and Week M-32 are averaged. In case of q12w, trough serum ustekinumab concentrations at Week M-24 and Week M-36 are averaged. 1st quartile=0.597885 µg/mL, 2nd quartile=1.548195 µg/mL, 3rd quartile=3.616315 µg/mL.

Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 28.0.

Note: Infections as assessed by the investigator.

[a] PK Analysis Set was used.

[b] PK Randomized Analysis Set was used.

[c] CNTO1275PUC3001, include all participants who were randomized (induction responders and nonresponders) into the maintenance period of the study (Week M-0), received at least 1 administration of ustekinumab during maintenance, and have at least one post Week M-0 blood sample collection in maintenance.

Note: Participants in CNTO1275PUC3001 who dose adjusted are counted in the treatment group they were randomized to at Week M-0, and their data from the time of dose adjustment or substudy onward are not included.

2.3.5. Discussion on clinical pharmacology

The clinical programme for ustekinumab in paediatric patients with UC comprised a single open-label paediatric Phase 3 study (CNTO1275PUC3001), supported by the extrapolation of safety and efficacy from adults with UC using exposure matching to bridge between populations. Therefore, a key objective of this submission was to demonstrate that the proposed paediatric doses would provide systemic exposures to ustekinumab that are comparable to those observed in adults receiving the approved adult doses.

Bioanalytical methods

There are sufficient data to provide documentation of a robust PK method.

Study CNT01275PUC3001: Phase 3 study in paediatric participants with UC

In this study, ustekinumab concentrations observed in the paediatric UC participants generally fell within the exposure range observed in adults with UC. However, there were a limited number of participants in the 2 to <6-year age group (n=3) and in the <20 kg body weight group (n=2).

Population PK analysis

The paediatric PopPK model was developed based on paediatric data from Study CNTO1275PUC3001. The final model described the data well. Model parameters were estimated with good precision (RSE <20% for most of the structural parameters) and there were no apparent trends in the GOF plots. The VPCs showed that the predictive performance of the model was adequate.

A formal covariate analysis was not conducted as the paediatric data were too limited (N=111). Body weight was appropriately included as a covariate on clearance and volume parameters *a priori,* with standard fixed coefficients. The only other covariates included in the final paediatric model were those found significant in the adult model (albumin, sex, and immune response status), which were re-estimated for the paediatric model. This approach is acceptable given the limited data from the paediatric study (N=111). Further, there were no remaining trends in the ETA versus covariate plots for the paediatric model, which indicates that the paediatric PK was adequately explained by the included covariates. Age did not impact PK after accounting for body weight.

The typical population values of CL, V2, ka, and F1 in paediatric UC participants with a median body weight of ~70 kg were 0.29 L/day, 4.32 L, 0.08 day^{-1}, and 0.75, respectively. These are reasonably consistent with those estimated in adult UC participants with a median body weight of ~70 kg (0.18 L/day, 3.02 L, 0.14 day^{-1}, and 0.87, respectively), although CL and V2 are higher in paediatric patients. Notably, the paediatric values are comparable to those estimated in paediatric CD participants (0.29 L/day, 4.06 L, 0.18 day^{-1} and 0.81, respectively) with a median body weight of ~70 kg.

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

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

Exposure-response analyses for efficacy

Following ustekinumab treatment in paediatric participants, positive E-R trends were observed for efficacy outcomes during induction and maintenance.

Induction: Clinical remission at Week I-8

The exploratory graphical analyses for clinical remission at Week I-8 showed a similar positive E-R trend in paediatric and adult UC participants, but with a higher proportion of paediatric participants in clinical remission vs adults.

The nonlinear logistic regression model for clinical remission at Week I-8 was based on the previously established adult E-R model and exploratory plots for potential covariate effects. The ER relationship was adequately characterised by an E_{max} model. The placebo effect was fixed to the adult value as there were no paediatric placebo data. Model parameters that were estimated were not too different from those in the adult ER model - E_{max} was 6.05 in the paediatric model and 3.95 in the adult model, and the EC_{50} was 2.50 ug/mL in the paediatric model and 1.71 ug/mL in the adult model. However, EC_{50} was poorly

estimated with a large %RSE (78%) and the larger RSE was thought to be the result of the limited data at low concentrations due to the large induction dose.

Consistent with adult participants, influential covariates on the ER relationship in paediatric patients included biologic failure status and baseline Mayo score. Participants who had previously failed biologic therapy and had a baseline Mayo score above the median had a lower placebo response and a lower probability of remission at Week I-8. The E-R relationship was not affected by age or body weight.

Maintenance: Clinical remission at Week M-44

The exploratory graphical analyses for clinical remission at Week M-44 also showed a similar positive E-R trend in paediatric and adult UC participants, but with both a higher and lower proportion of paediatric participants in clinical remission vs adults depending on the trough tertile. The overall clinical remission rate at Week M-44 in paediatric participants was comparable with that in adult participants.

Consistent with the paediatric ER modelling for clinical remission at Week I-8, the nonlinear logistic regression model for clinical remission at Week M-44 (maintenance) was also based on the previously established adult model and exploratory plots for potential covariate effects. The E-R relationship was adequately characterised by an E_{max} model. The estimated E_{max} in the paediatric ER model (5.95) was higher than that in adults (1.37), while the EC_{50} estimate was lower (0.14 µg/mL in the paediatric model versus 0.59 µg/mL in the adult model). Both E_{max} and EC_{50} were estimated with relatively low precision (RSEs of ~50%). After accounting for covariate effects, the placebo response had to be fixed to a lower value (−6) than the adult model (−1.63), despite the absence of paediatric placebo data.

Consistent with adults, remission status at randomisation was an influential covariate on the ER relationship, resulting in a lower probability of being in remission at M-44 in those who were not already in remission at randomisation. Consistent with the induction analyses, the E-R relationship was not affected by age or body weight during maintenance.

In conclusion, the exposure–response relationships for ustekinumab appear similar in paediatric and adult participants, with a clear, positive ER trend in both populations. Furthermore, covariate effects identified as influential in adults appeared to have comparable influence in paediatric participants, and neither age nor weight affected the ER relationship. There are some limitations in the modelling analyses—particularly the reliance on previously developed adult models— however, the observed positive trends suggest ER similarity between the two populations.

Exposure-response analyses for safety

Similar to adult participants with UC, there was no association between serum ustekinumab concentrations and selected safety events including infections, serious infections, and SAEs in paediatric participants with UC.

Immunogenicity

The incidence of antibodies to ustekinumab was low in paediatric participants with UC (2.1%), which is consistent with the immunogenicity profile of ustekinumab in adult participants with UC (4.6%) and paediatric participants with CD (3.3%). Given the low incidence of antibodies to ustekinumab, the impact of immunogenicity on PK, efficacy, or safety could not be determined. As mentioned in the SmPC section 5.1 "Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with both increased clearance and reduced efficacy of ustekinumab, except in patients with Crohn's disease or ulcerative colitis where no reduced efficacy was observed."

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology data support the conclusion that the proposed ustekinumab doses for paediatric UC patients (≥2 years) will result in ustekinumab exposures that are comparable to those established to be safe and effective in the adult UC population.

2.4. Clinical efficacy

2.4.1. Dose response study

The PK, safety, and efficacy of ustekinumab have previously been evaluated in a Phase 1 study of paediatric participants with Crohn's disease (CNTO1275CRD1001, n=44). In that study, dose regimens comprising of 1 of 2 ustekinumab IV induction doses (3 mg/kg for participants <40 kg or 130 mg for participants ≥40 kg [approximating a 130 mg dose in adults], or 9 mg/kg for participants <40 kg and 390 mg for participants ≥40 kg [approximating a 6 mg/kg dose in adults]) followed by a single ustekinumab SC maintenance dose regimen (2 mg/kg for participants <40 kg and 90 mg for participants ≥40 kg [approximating a 90 mg dose in adults]) were evaluated. The totality of the data (efficacy and safety) from CNTO1275CRD1001 supported the use of the higher induction dose regimen along with the tested maintenance dose according to the MAH.

The pivotal clinical trial CNTO1275PUC3001, hence forth referred to as UNIFI Jr, is further assessing dose response in the paediatric population.

2.4.2. Main study (UNIFI Jr)

Study Title: A Phase 3 Study of the Efficacy, Safety and Pharmacokinetics of Ustekinumab as Open-label Intravenous Induction Treatment Followed by Randomised Double-blind Subcutaneous Ustekinumab Maintenance in Paediatric Participants (2 to <18 Years of Age) with Moderately to Severely Active Ulcerative Colitis

Study Number: CNTO1275PUC3001

Methods

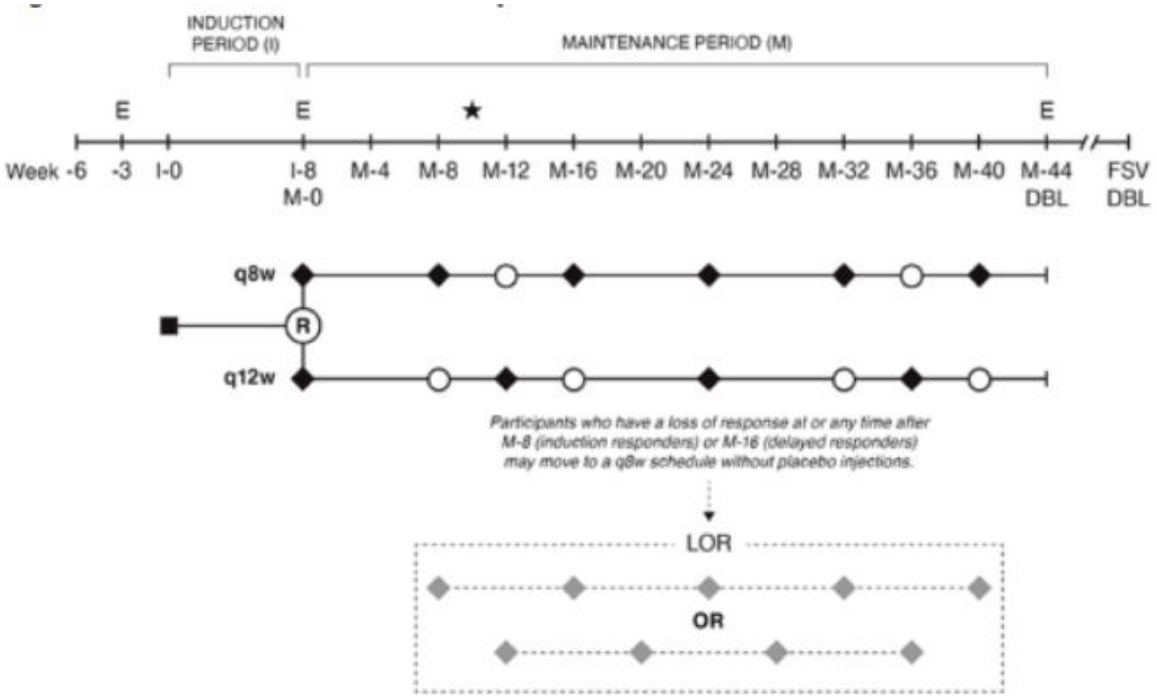
UNIFI Jr was a Phase 3, multicentre, interventional study consisting of an open-label induction period with a single IV ustekinumab dose followed by a maintenance period with a randomised, double-blind, parallel-group, 2-arm study design, exploring 2 different SC ustekinumab maintenance dose regimens.

The planned duration of the study periods was the following:

1. 8 weeks in the induction period.
2. 44 weeks in the maintenance period.
3. At least 16 weeks in the optional exposure optimisation sub study (EOS).
4. 20 weeks of safety follow up after the last study intervention administration.

The expected duration of the study was 74 weeks, including 6 weeks of screening, 48 weeks of treatment (8 weeks in the induction period followed by 40 weeks of treatment in the maintenance period) with study intervention and 20 weeks of safety follow-up after the last study intervention administration.

Figure 28: Schematic Overview of the Study (CSR Figure 1)



■ = Intravenous ustekinumab: 250 mg/m² IV for participants with <40 kg body weight; 260 mg IV for participants with ≥40 kg to ≤55 kg body weight; 390 mg IV for participants with >55 kg to ≤85 kg body weight; 520 mg IV for participants with >85 kg body weight.

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

○ = SC Placebo

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

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

DBL = Database Lock E = Endoscopy FSV = Final Safety Visit LOR = Loss of Response R = Randomization

Study participants

Key Inclusion Criteria

- 2 to <18years of age with a body weight ≥10 kg.
- Medically stable on the basis of physical examination, medical history, vital signs, and clinical laboratory tests performed at screening.
- Must have had UC diagnosed prior to screening and must have biopsy confirmation that is consistent with a diagnosis of UC (e.g., crypt distortion, crypt abscess, and goblet cell depletion).
- Have moderately to severely active UC, defined as a baseline Mayo score of 6 through 12, inclusive, with a screening Mayo endoscopy subscore ≥2 as determined by a central review of the video of the endoscopy.
- Prior or current medication for UC must include at least one of the following:

- Have received biologic therapy (ie, TNFα antagonist or vedolizumab) for the treatment of paediatric UC and have had ≥2-half-lives washout duration prior to first administration of study intervention and have a documented history of failure to respond to or not tolerate treatment;

OR

- Be naïve to biologic therapy or have not demonstrated a history of failure to respond to, or tolerate a biologic therapy and have a prior or current UC medication history that includes at least 1 of the following:

  1.1 Inadequate response to or failure to tolerate current treatment with oral or IV corticosteroids or immunomodulators (6-MP, AZA, or MTX)

  2.1 History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA or MTX)

  3.1 History of corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of UC)

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

- Must meet concomitant medication criteria prior to the first administration of study intervention.
- If previously receiving enteral nutrition providing more than 80% of daily caloric needs, therapy must have been stopped for at least 4 weeks prior to Week I-0.
- A participant who has had extensive colitis for≥8 years, or disease limited to the left side of the colon for ≥10 years, must:
  - Have had a full colonoscopy to assess for the presence of dysplasia within 1 year before the first administration of study intervention.

  OR

  - Have a full colonoscopy with surveillance for dysplasia as the baseline endoscopy during the screening period. Results from these surveillance biopsies must be negative for dysplasia (low-grade, high-grade, or indeterminant) prior to the first administration of study intervention.
- Have negative stool results for enteric pathogens.

Key Exclusion Criteria

- Have severe, extensive colitis as evidenced by:
  - Investigator judgment that the participant is likely to require a colectomy within 12 weeks of Week I-0.

  OR

  - Symptom complex at screening or Week I-0 visit that includes at least 4 of the following:

    1.1 Diarrhoea with ≥6 bowel movements/day with macroscopic blood in stool

    2.1 Focal severe or rebound abdominal tenderness

3.1 Persistent fever (≥37.5°C) for more than 5 days

4.1 Persistent tachycardia for more than 5 days

5.1 Anaemia (haemoglobin <8.5 g/dL)

- Have UC limited to the rectum only or to <20 cm of the colon.
- Have severe, fixed symptomatic stenosis of the large or small intestine.
- Require, or required within the 2 months prior to screening, surgery for active GI bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage, or other conditions possibly confounding the evaluation of benefit from study intervention treatment.
- Presence or history of colonic or small bowel obstruction within 6 months prior to screening, confirmed by objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the colon or small bowel proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy).
- Have evidence of Crohn's disease:
    - Small intestinal or ileal disease by upper GI small bowel follow-through, ileocolonoscopy with histology, video capsule endoscopy, or magnetic resonance enterography.
    - Noncaseating and non-mucin granulomas that are suggestive of a diagnosis of Crohn's disease on colonoscopy.
    - Skip lesions on colonoscopy including absolute rectal sparing, with a normal rectum both endoscopically and histologically.
    - Perianal disease.
- Have a history of latent or active granulomatous infection, histoplasmosis, or coccidioidomycosis, or have had a nontuberculous mycobacterial infection prior to screening.

Treatments

For the induction period, ustekinumab was supplied as a single-use, 1 dose strength to be diluted to an appropriate concentration for IV administration. For participants ≥40 kg, doses were based on a weight-tiered induction dose, which was the same as the existing approved adult dose regimen. For participants <40 kg, doses were BSA-adjusted for 250 mg/m^2 IV.

For the maintenance period, ustekinumab was supplied as a single-use, sterile solution in 2 mL vials. For randomised participants with body weight <40 kg; ustekinumab 90 mg/mL could be used for SC administration at a dose strength of 45 mg in 0.5 mL nominal volume. For randomised participants with body weight ≥40 kg, ustekinumab was supplied in a pre-filled syringe ustekinumab (PFS-U) in a strength of 90 mg in 1 mL nominal volume for SC administration.

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

- **Ustekinumab q8w**: 90 mg SC for ≥40 kg body weight or 60 mg/m2 SC for <40 kg body weight. Participants received ustekinumab at Weeks M-0, M-8, M-16, M-24, M-32, and M-40 and matching placebo at Weeks M-12 and M-36 to maintain the blind.
- **Ustekinumab q12w:** 90 mg SC for ≥40 kg body weight or 60 mg/m2 SC for <40 kg body weight. Participants received ustekinumab at Weeks M-0, M-12, M-24, and M-36, and matching placebo at Weeks M-8, M-16, M-32, and M-40 to maintain the blind.

Concomitant medication criteria are as follows:

Corticosteroids

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

5-Aminosalicylates, MTX, 6-MP, and AZA Compounds

- If receiving oral 5-ASA compounds, the dose must have been stable for at least 2 weeks prior to Week I-0.
- If oral or rectal 5-ASA compounds have been discontinued, they must have been stopped for at least 2 weeks prior to Week I-0.
- If receiving MTX, 6-MP, or AZA, the participant must have been taking them for ≥12 weeks and on a stable dose for at least 4 weeks prior to Week I-0.
- If the MTX, 6-MP, or AZA have been recently discontinued, they must have been stopped for at least 4 weeks prior to Week I-0.

Antibiotics

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

Exclusionary concomitant or previous medical therapies within the specified period:

- Has ever received ustekinumab or a biologic agent targeting IL-12/23 or IL-23, including but not limited to briakinumab, guselkumab, mirikizumab (formerly LY-3074828), and risankizumab.
- Has ever received thalidomide or related agents.
- Has received natalizumab within 12 months of Week I-0.
- Has received agents that deplete B- or T- cells (e.g., rituximab, alemtuzumab, or visilizumab) within 12 months of Week I-0 or continue to manifest depletion of B or T cells more than 12 months after completion of therapy with lymphocyte depleting agents.
- Has received vedolizumab with <2 half-lives washout period prior to Week I-0.
- Has received other immunomodulatory agents (e.g., 6-thioguanine [6-TG], cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil [MMF]) within 8 weeks prior to Week I-0.

- Has received anti-TNF α biologic agents with <2 half-lives washout period prior to Week I-0.
- Has used any investigational intervention within 4 weeks prior to Week I-0 or
- within 5 half-lives of the investigational intervention, whichever is longer.
- Has used apheresis (i.e., Adacolumn apheresis, Cellsorba apheresis) within 2 weeks prior to Week I-0.
- Has used laxatives, except preparations for endoscopy or other procedures, within 1 week prior to screening procedures.
- Has an indwelling catheter.
- Is on total (complete) or partial (supplemental) parenteral nutrition or anticipated to require during enrolment in the study. If recently on total (complete) or partial (supplemental) parenteral nutrition, must have stopped therapy at least <3 weeks before first administration of study intervention.
- Is on rectal therapy for UC with either 5-ASA medications or corticosteroids.
- Is on IV steroids.
- Is on more than one antibiotic prescribed for the treatment of UC.

Objectives

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

The primary objective and primary endpoint in this study was to assess clinical remission in moderately to severely active UC in paediatric participants. The assessment timepoint for clinical remission was different for countries outside of the United States (global timepoint of Week I-8) and the United States (US-specific timepoint of Week M-44).

Primary Objectives

- To evaluate the efficacy of ustekinumab dosing in inducing clinical remission in paediatric participants with moderately to severely active UC.
- To evaluate the safety profile of ustekinumab in paediatric participants with moderately to severely active UC.
- To evaluate ustekinumab exposure (PK).

Secondary Objectives

- 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 Clinical Endpoint

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

Secondary Endpoints (Induction Period)

- Clinical response at Week I-8.
- Symptomatic remission at Week I-8.
- Clinical remission at Week I-8 as assessed by the PUCAI score.
- Endoscopic improvement at Week I-8.
- Histologic-endoscopic mucosal improvement at Week I-8.

Secondary Endpoints (Maintenance Period)

- Clinical remission at Week M-44.
- Symptomatic remission at Week M-44.
- Clinical remission at Week M-44 as assessed by the PUCAI score.
- Endoscopic improvement at Week M-44.
- Corticosteroid-free clinical remission at Week M-44.
- Clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44 among participants who received corticosteroids at Week I-0.
- Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8.
- Histologic-endoscopic mucosal improvement at Week M-44.

No statistical comparisons were made. Comparisons were made descriptively with adult populations, to both placebo and ustekinumab intervention groups. Data were summarised using descriptive statistics.

Sample size

Approximately 100 participants were to be enrolled in this study. All participants entering maintenance were to be randomised to one of two maintenance doses. The study would continue enrolling until at least 80 responders (i.e., induction responders at Week I-8 or delayed responders at Week M-8) have been attained. Approximately 24 participants were to be <40 kg, including approximately 5 participants <30 kg.

With a sample size of approximately 100 participants enrolled (which would include approximately 80 responders [induction responders at Week I-8 or delayed responders at WeekM-8]) and assuming 90% of the participants in this study are biologic failures, the precision (i.e., half width of the 95% confidence interval [CI]) in estimating the true proportion of paediatric participants in clinical remission at Week I-8 is 7.1% (assuming the proportion of participants in clinical remission is 15.5% at Week I-8 [based on a weighted average from the biologic-failure population (14.5%; ~6 mg/kg treatment group) and from the non-biologic-failure population (24.4%; ~6 mg/kg treatment group)] from the ustekinumab adult study CNTO1275UCO3001).

Randomisation

The induction phase of the study is open label. For the maintenance phase, participants (induction responders and induction nonresponders) were to be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomisation schedule. Participants were to be stratified by response status at Week I-8 (induction responder/induction nonresponder) and weight (<40 kg, ≥40 kg).

Blinding (masking)

To maintain the study blind during the maintenance period, placebo injections were used, and they will be identical in appearance to ustekinumab. The investigator will not be provided with randomisation codes. The codes will be maintained within the interactive web response system (IWRS), which has the functionality to allow the investigator to break the blind for an individual participant.

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

If a participant had documented LOR and the investigator wished to evaluate if the participant would be eligible for the Exposure Optimisation Substudy, the site was informed of the participants exposure (i.e., low [<1.4 μg/mL] or normal).

Unblinding

The blind during the maintenance period should not be broken until the Week M-44 analyses of the maintenance period had been completed. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant.

The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

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

Key Study Assessment

The Mayo score consists of 4 sub scores (stool frequency, rectal bleeding, endoscopy findings, and physician's global assessment [PGA]), each of which is rated on a scale from 0 to 3, indicating normal to severe activity. The Mayo score is calculated as the sum of the 4 sub scores and values range from 0 to 12.

A Mayo score of 3 to 5 points indicates mildly active disease; a score of 6 to 10 indicates moderately active disease; and a score of 11 to 12 indicates severe disease.

Clinical remission: Defined by Mayo sub scores as a stool frequency sub score of 0 or 1, a rectal bleeding sub score of 0, and an endoscopy sub score of 0 or 1 with no friability present on the endoscopy, where the stool frequency sub score had not increased from induction baseline.

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

Clinical response: A decrease from baseline in the Modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding sub score of ≥1 or a rectal bleeding sub score of 0 or 1.

Partial Mayo score: The partial Mayo score is the Mayo score without the endoscopy sub score, and values range from 0 to 9. Partial Mayo scores are calculated using stool frequency, rectal bleeding, and Physician Global Assessment (PGA) data.

Loss of Response: Participants in the maintenance period who meet the following criteria will be considered to have LOR:

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

OR

- An absolute partial Mayo score ≥7 points at 2 consecutive visits at least 7 days apart.

Histologic-endoscopic mucosal improvement based on GS is defined as achieving a combination of histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system) and endoscopic improvement (a Mayo endoscopy sub-score of 0 or 1 with no friability present in the endoscopy).

Histologic-endoscopic mucosal improvement based on RHI is defined as achieving a combination of histologic improvement (Robart Histopathology Index ≤ 9 with sub-scores of 0 for neutrophils in the epithelium and without erosions or ulcers) and endoscopic improvement (a Mayo endoscopy sub-score of 0 or 1 with no friability present in the endoscopy).

IMPACT-III is a self-administered IMPACT-III questionnaire is validated and applicable for children and adolescents ≥10 years of age with IBD. The questionnaire comprises 35 questions that cover the domains of Bowel symptoms (7 items), Systemic symptoms (3 items), Emotional functioning (7 items), Social functioning (12 items), Body image (3 items), and Tests and treatments (3 items). The score ranges from 35 to 175, with a higher score indicating better quality of life.

Explatory TUMMY-UC was utilised to measure PRO HRQoL in pediatrics. The EMA Guideline CHMP/EWP/18463/2006 Rev.1 identified that no validated paediatric PRO (pPRO) for the evaluation of symptoms is currently available. The TUMMY-UC questionnaire was developed as a non-invasive PRO tool to score disease-related signs and symptoms in pediatric UC. There are 2 versions of the TUMMY-UC questionnaire: the TUMMY-UC PRO for children 8 to <18 years old which is completed by the patient and the TUMMY-UC obsRO which is completed by caregivers of children <8 years old. The TUMMY-UC includes 8 components (abdominal pain, stool frequency and consistency (Bristol stool consistency chart), amount and frequency of rectal bleeding, urgency, weakness, and nocturnal stooling) with total scores ranging from 0 to 114, with higher scores being indicative of more severe disease. It has undergone Qualification Advice at EMA; see TUMMY-UC CSR dated 25 March 2022 (CSR EMA/SA/0000075690 2022).

Statistical methods

Data were summarised using descriptive statistics. Continuous variables were summarised using the number of observations, mean, SD, median, interquartile 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 are reported. Graphical data displays (e.g., line plots) may have also been used to summarise the data.

Unless otherwise specified, the Mayo endoscopy sub score as obtained during the central review of the video of the endoscopy was used for all efficacy analyses involving the Mayo endoscopy sub score. Additionally, for all endpoints that require achievement of a Mayo endoscopy sub score of 0 or 1, the endpoints were considered to not have been met if friability was present on endoscopy.

Unless otherwise specified, all efficacy and safety analyses were based on randomised study intervention. Efficacy was summarised for all participants who receive at least 1 dose of ustekinumab in the sub study. All data were reported as observed analysis. Data were not imputed for any missing values, with the composite strategy applied where intercurrent events were incorporated as an unfavourable outcome in the assessment of the treatment effect.

There was no formal hypothesis testing and therefore no multiplicity adjustments were made in this study.

Table 11: Populations for Analyses (Protocol and Amendments Table 8)

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

Participants with intercurrent events (ICEs) in categories 1-3, and 5 by Week I-8 were considered to not be in clinical remission at Week I-8

Table 12: Intercurrent events and their corresponding strategies:

ICEs	Strategy for Addressing ICEs and Its Description
1. Had a colectomy (partial or full) or ostomy	**Composite Strategy:** A participant with this ICE is considered to not have achieved clinical remission after this event; the occurrence of this ICE has been captured in the variable definition.
2. Discontinued study intervention due to lack of efficacy or an AE of worsening of UC	**Composite Strategy:** Same as above
3. Had prohibited changes in UC medications (for details, see Section 6.8)	**Composite Strategy:** Same as above
4. Discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infections)	**Hypothetical Strategy:** A participant with this ICE is considered to have missing data at and after the event occurred.
5. Discontinued study intervention due to reasons other than ICEs 2 or 4 as described above	**Composite Strategy:** Same as above

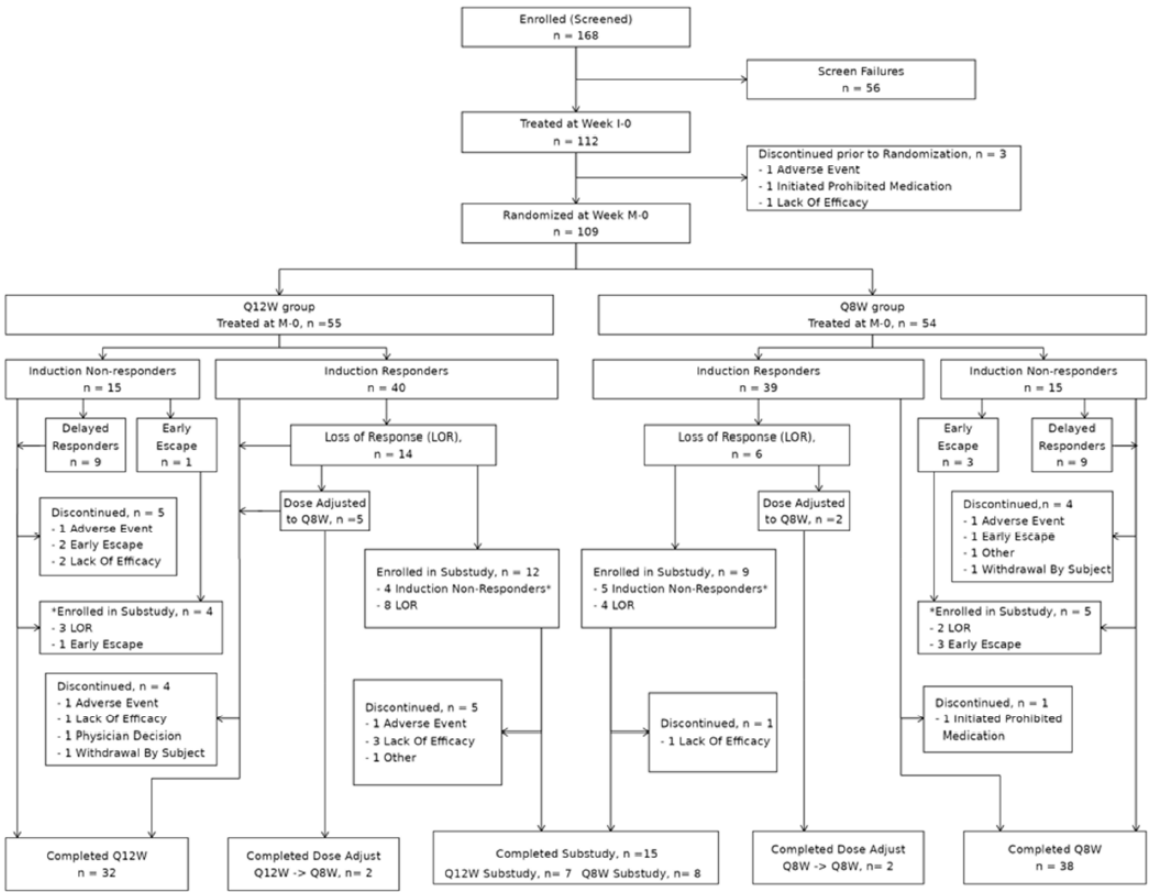
Results

Participant flow

Of the 168 participants screened for this study, 112 participants were enrolled with a total of 109 participants being randomised to maintenance treatment with ustekinumab SC q12w (n=55) or q8w (n=54) at 32 study sites across 8 countries.

A total of 3 (2.7%) of 112 participants in the study and 14 (12.8%) of 109 randomised participants discontinued study intervention during the induction and maintenance periods, respectively. The primary reason for discontinuation was Early escape and Lack of efficacy (3 participants each, 2.8%) with the remaining reasons accounting for <2% each. A higher proportion of participants discontinued study treatment in the q12w treatment group (9, 16.4%) compared to the q8w treatment group (5, 9.3%).

One (0.9%) of 112 participants in the study terminated study participation during the induction period due to withdrawal by parent or guardian while a total of 10 (9.2%) of 109 randomised participants terminated study participation during the maintenance period. The most common reasons for termination during the maintenance period were withdrawal by parent or guardian (6, 5.5%) and withdrawal by participant (3, 2.8%). More participants in the q12w treatment group (7, 12.7%) than the q8w treatment group (3, 5.6%) terminated study participation.



Exposure Optimisation Substudy (EOS) Participants

A total of 22 participants enrolled into the EOS. Participants who experienced a LOR or were induction nonresponders with low 8-week steady state trough ustekinumab exposure of <1.4 µg/ml were eligible to enrol in the optional q4w EOS.

- Four (3.7%) participants (q12w: n=1; q8w: n=3) were induction nonresponder participants with low ustekinumab exposure levels who met the early escape criteria by Week M-8.
- Eighteen (18.6%) participants (q12w: n=12; q8w: n=6) were randomised into the maintenance period of the main study and experienced a confirmed LOR and had low ustekinumab exposure levels.

Although a total of 13 participants from the q12w treatment group and 9 participants from the q8w treatment group enrolled in the EOS, 1 participant who entered the EOS from the q12w treatment group did not receive treatment during the EOS and was therefore not considered to be a part of the Substudy Analysis Set.

Of the 21 participants in the Substudy Analysis Set, 16 (76.2%) completed the EOS (9 participants from the q12w treatment group and 7 participants from the q8w treatment group). The reasons for the 5 (23.8%) participants who terminated EOS participation early included lost to follow-up, withdrawal by parent or guardian, and withdrawal by participant due to lack of improvement.

A total of 6 (28.6%) of 21 participants discontinued treatment during the EOS (5 participants from the q12w treatment group and 1 participant from the q8w treatment group). The reasons for EOS treatment discontinuation included lack of efficacy and AE of worsening UC.

Seven participants treated in the EOS had a major protocol deviation (MPD). One participant initiated upadacitinib 45 mg per day (oral) because of worsening of UC during study participation. The remaining MPDs were listed as "other," with the most common deviation criterion being that Week M-44 visits were not performed as per protocol schedule. Most of these Week M-44 visit deviations were due to participant's entry into the EOS.

Overall, the demographic and clinical characteristics of the EOS participants at Week I-0 were similar to those of the main study participants except for the following:

- More than half of the EOS participants were male (14 [66.7%] of 21 participants versus 51 [45.5%] of 112 participants).
- A numerically higher proportion of EOS participants had a history of biologic failure (12 [57.1%] of 21 participants versus 44 [39.3%]) of 112 participants.

Conduct of the study

No participants were unblinded during the maintenance period from Week M-0 through Week M-44.

Amendments

The UNIFI Jr clinical trial has had three amendments, two of which were implemented before the first participant screening on the 17th of March 2021, while the third amendment occurred on the 21st of May 2021 but had no significant change to the design of the study.

- **Amendment 3 (21 May 2021)**
  - **Overall Rationale for the Amendment:** Participants will be required to be up to date with measles and varicella immunisations per local immunisation guidelines for immunocompromised participants. The serum pregnancy test was replaced with a urine pregnancy test to decrease participant burden; liver safety stopping algorithm/follow-up assessments and Coronavirus 2019 (COVID-19) language was updated; and tables were added to the optional Exposure Optimisation Substudy, to clarify additional dosing and visit possibilities/activities.
- **Amendment 2 (02 February 2021)**
  - **Overall Rationale for the Amendment:** An optional Exposure Optimisation Substudy for induction nonresponders who have a low steady-state, 8 weeks post-dose ustekinumab concentration, and for induction responders and delayed responders who lose response during maintenance and have a low steady-state, 8 weeks postdose ustekinumab concentration has been added.
- **Amendment 1 (16 September 2020)**
  - **Overall Rationale for the Amendment:** The study design was changed per Food and Drug Administration's (FDA) recommendation. For participants ≥40 kg, dosing will be based on a weight-tiered induction dose which is the same as the approved adult dosing regimen. For participants <40 kg, dosing will be body surface area (BSA) adjusted to minimise the variability of ustekinumab exposure across the lower paediatric weight.

Protocol Deviations

A total of 20 (17.9%) of 112 study participants and 33 (30.3%) of 109 randomised participants had an MPD during the induction and maintenance periods, respectively. The most common Major Protocol Deviations (MPDs) during both the induction and maintenance periods were classified as "other" (14.3% and 29.4%, respectively). Most of the "other" deviations were due to missing faecal samples, out of window visits, and insufficient diaries completed.

Table 13: Summary of Subjects With Major Protocol Deviations Through Week I-8; Full Analysis Set (CSR, Table 5)

	Ustekinumab IV
Analysis set: Full	112
Subjects with major protocol deviations	20 (17.9%)
Entered but did not satisfy criteria	2 (1.8%)
Received incorrect IV dose during induction	2 (1.8%)
Developed withdrawal criteria but not withdrawn	0
Received a disallowed concomitant treatment	0
Other	16 (14.3%)
Missed visit/assessment due to COVID-19	0

Table 14: Summary of Subjects With Major Protocol Deviations From Week M-0 through Week M-44; Full Analysis Set (CSR, Table 6)

	Ustekinumab IV				
		Ustekinumab SC			
	Not randomized*	q12w	q8w	Combined	Total
Analysis set: Full	3	55	54	109	112
Subjects with major protocol deviations	0	17 (30.9%)	16 (29.6%)	33 (30.3%)	33 (29.5%)
Received a disallowed concomitant treatment	0	2 (3.6%)	1 (1.9%)	3 (2.8%)	3 (2.7%)
Developed withdrawal criteria but not withdrawn	0	0	0	0	0
Entered but did not satisfy criteria	0	0	0	0	0
Received incorrect dose during maintenance	0	0	0	0	0
Other	0	16 (29.1%)	16 (29.6%)	32 (29.4%)	32 (28.6%)
Missed visit/assessment due to COVID-19	0	0	0	0	0

During the maintenance period, 3 participants received a disallowed concomitant treatment. Two participants in the q12w treatment group initiated rescue therapy (1 participant received rectal budenofalk during induction and 1 participant received budenoside without meeting the LOR criteria), and 1 participant in the q8w treatment group failed to taper steroids after LOR as per protocol.

Three (2.7%) participants had study selection criteria deviations:

- 1 participant received the prohibited medication rectal 5-ASA (start date before Week I-0).
- 1 participant received the prohibited medication tacrolimus (start date before Week I-0).
- 1 participant had a baseline Mayo score of 4 reported at Week I-0. This participant was randomised to the q8w treatment group but was discontinued after Week M-0 when the study team identified that the participant did not meet inclusion criteria.

A total of 2 (1.8%) participants had deviations in ustekinumab administration that were not considered to be clinically significant.

- 1 participant received an incorrect dose of ustekinumab treatment during the induction period on Day 1. This participant received a dose of 267.5 mg (an excess of 2.5 mg) that was slightly higher than the correct dose.
- 1 participant in the q8w treatment group received an incorrect dose of ustekinumab treatment during the induction period on Day 1. This participant received a dose of 307.5 mg (a difference of 7.5 mg) that was slightly lower than the correct dose.

Nine (8.0%) of 112 participants in the study had minor protocol deviations due to COVID-19- related missing visits and assessments.

Baseline data

The majority of participants were white, and more than half were female. Negative BMI z scores were observed for both female (mean [SD] and median of -0.06 [0.821] and -0.09, respectively; range: -1.3; 2.1) and male (mean [SD] and median of -0.19 [0.883] and -0.31, respectively; range: -1.7; 2.7) participants, with 14 (12.5%). While negative mean BMI z-scores were observed for both treatment groups, the mean (SD) value was numerically lower in the q8w treatment group (-0.24 [0.692]) compared with the q12w treatment group (-0.02 [0.985]).

The sample size in the younger age groups (notably in participants 2 to <6 years of age [n=3]) and the <30 kg (n=13) and ≥30 to <40 kg (n=14) weight subgroups were too small for the induction responder population to draw any meaningful conclusions on demographic characteristics. There were too few participants who were delayed responders at Week M-8 (n=18) to draw any meaningful conclusions.

In general, the baseline demographics for the q12w and q8w treatment groups were balanced.

Table 15: Summary of Demographics at Baseline; Full Analysis Set (CSR, Table 8)

	Ustekinumab IV				
		Ustekinumab SC			
	Not randomized*	q12w	q8w	Combined	Total
Analysis set: Full	3	55	54	109	112
Age, years					
N	3	55	54	109	112
Mean (SD)	11.3 (3.06)	13.2 (3.37)	13.3 (2.80)	13.2 (3.09)	13.2 (3.09)
Median	12.0	14.0	14.0	14.0	14.0
Range	(8; 14)	(3; 17)	(4; 17)	(3; 17)	(3; 17)
IQ range	(8.0; 14.0)	(11.0; 16.0)	(12.0; 15.0)	(11.0; 16.0)	(11.0; 15.5)
2-<12 years	1 (33.3%)	16 (29.1%)	13 (24.1%)	29 (26.6%)	30 (26.8%)
2-<6 years	0	2 (3.6%)	1 (1.9%)	3 (2.8%)	3 (2.7%)
6-<12 years	1 (33.3%)	14 (25.5%)	12 (22.2%)	26 (23.9%)	27 (24.1%)
12-<18 years	2 (66.7%)	39 (70.9%)	41 (75.9%)	80 (73.4%)	82 (73.2%)
Sex					
N	3	55	54	109	112
Female	3 (100.0%)	28 (50.9%)	30 (55.6%)	58 (53.2%)	61 (54.5%)
Male	0	27 (49.1%)	24 (44.4%)	51 (46.8%)	51 (45.5%)
Race					
N	3	55	54	109	112
American Indian or Alaska Native	0	0	0	0	0
Asian	0	7 (12.7%)	6 (11.1%)	13 (11.9%)	13 (11.6%)
Black or African American	0	1 (1.8%)	1 (1.9%)	2 (1.8%)	2 (1.8%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	2 (66.7%)	46 (83.6%)	46 (85.2%)	92 (84.4%)	94 (83.9%)
Multiple	0	0	0	0	0
Not reported	0	0	1 (1.9%)	1 (0.9%)	1 (0.9%)
Unknown	1 (33.3%)	1 (1.8%)	0	1 (0.9%)	2 (1.8%)
Weight, kg					
N	3	55	54	109	112
Mean (SD)	38.4 (8.07)	47.9 (15.86)	46.6 (13.49)	47.2 (14.68)	47.0 (14.59)
Median	40.0	47.0	47.2	47.0	46.9
Range	(30; 46)	(14; 80)	(14; 76)	(14; 80)	(14; 80)
IQ range	(29.6; 45.5)	(37.2; 57.7)	(36.0; 57.4)	(36.1; 57.4)	(36.1; 57.2)
<40 kg	1 (33.3%)	15 (27.3%)	18 (33.3%)	33 (30.3%)	34 (30.4%)
<30 kg	1 (33.3%)	8 (14.5%)	7 (13.0%)	15 (13.8%)	16 (14.3%)

	Ustekinumab IV				
		Ustekinumab SC			
	Not randomized*	q12w	q8w	Combined	Total
≥30 - <40 kg	0	7 (12.7%)	11 (20.4%)	18 (16.5%)	18 (16.1%)
≥40 kg	2 (66.7%)	40 (72.7%)	36 (66.7%)	76 (69.7%)	78 (69.6%)
≥40 - ≤55 kg	2 (66.7%)	22 (40.0%)	18 (33.3%)	40 (36.7%)	42 (37.5%)
>55 - ≤85 kg	0	18 (32.7%)	18 (33.3%)	36 (33.0%)	36 (32.1%)
>85 kg	0	0	0	0	0
Body mass index Z score#					
N	3	55	54	109	112
Mean (SD)	0.33 (0.352)	-0.02 (0.985)	-0.24 (0.692)	-0.13 (0.856)	-0.12 (0.849)
Median	0.18	-0.06	-0.33	-0.24	-0.22
Range	(0.1; 0.7)	(-1.7; 2.7)	(-1.6; 2.1)	(-1.7; 2.7)	(-1.7; 2.7)
IQ range	(0.07; 0.73)	(-0.86; 0.81)	(-0.70; 0.06)	(-0.80; 0.27)	(-0.79; 0.29)

*Subjects received ustekinumab at Week I-0 in induction but not randomized at Week M-0 in maintenance.
#Age and sex-specific

Baseline UC Disease characteristics

The median (range) duration of disease was 1.2 years (0-11 years).

- The majority of participants had extensive UC (67.0%) compared with UC being limited to the left side of the colon (33.0%).
- 91.7% of participants had moderate disease and 7.4% of participants had severe disease based on the Mayo score.

In general, the baseline UC disease characteristics for the q12w and q8w treatment groups were similar.

A total of 108 (96.4%) of 112 participants had a complete Mayo score at Week I-0. Three participants each were missing subscores for stool frequency and rectal bleeding, while 1 participant was missing the PGA score because the score was entered after the visit and did not transfer correctly. A total of 19

(17.0%) of 112 participants had a history of COVID-19; the outcome was considered recovered or resolved in all 19 participants.

Baseline UC disease characteristics across the q12w and q8w treatment groups by age and weight subgroups were generally similar to those for the whole study population. Baseline UC disease characteristics for all responders (both induction and delayed responders) were similar to those for the whole study population.

Table 16: Summary of Baseline UC Disease Characteristics; Full Analysis Set (CSR, Table 9)

	Ustekinumab IV				
		Ustekinumab SC			
	Not randomized*	q12w	q8w	Combined	Total
Analysis set: Full	3	55	54	109	112
Age at diagnosis, years					
N	3	55	54	109	112
Mean (SD)	8.2 (4.49)	11.0 (3.75)	11.6 (3.09)	11.3 (3.44)	11.2 (3.48)
Median	7.0	12.1	11.8	11.9	11.8
Range	(4; 13)	(2; 17)	(2; 17)	(2; 17)	(2; 17)
Ulcerative colitis disease duration, years					
N	3	55	54	109	112
Mean (SD)	3.2 (3.87)	2.3 (2.18)	1.7 (1.64)	2.0 (1.94)	2.0 (1.99)
Median	1.0	1.5	1.2	1.3	1.2
Range	(1; 8)	(0; 11)	(0; 9)	(0; 11)	(0; 11)
Extent of ulcerative colitis disease					
N	3	55	54	109	112
Limited to left side of colon	1 (33.3%)	19 (34.5%)	17 (31.5%)	36 (33.0%)	37 (33.0%)
Extensive	2 (66.7%)	36 (65.5%)	37 (68.5%)	73 (67.0%)	75 (67.0%)
PUCAI Score					
N	3	55	54	109	112
Mean (SD)	66.7 (17.56)	53.5 (12.97)	51.5 (16.10)	52.5 (14.57)	52.9 (14.74)
Median	65.0	55.0	55.0	55.0	55.0
Range	(50; 85)	(25; 85)	(5; 80)	(5; 85)	(5; 85)
Mayo Score[a]					
N	2	54	52	106	108
Mean (SD)	8.0 (0.00)	8.4 (1.44)	8.4 (1.50)	8.4 (1.46)	8.4 (1.45)
Median	8.0	8.5	8.0	8.0	8.0
Range	(8; 8)	(6; 11)	(4; 12)	(4; 12)	(4; 12)
IQ range	(8.0; 8.0)	(7.0; 9.0)	(7.5; 9.0)	(7.0; 9.0)	(7.0; 9.0)
Severity of disease by Mayo Score					
N	2	54	52	106	108
No active disease (Mayo Score ≤ 2)	0	0	0	0	0
Mild (Mayo Score ≥3 -<6)	0	0	1 (1.9%)	1 (0.9%)	1 (0.9%)
Moderate (Mayo score 6-10)	2 (100.0%)	49 (90.7%)	48 (92.3%)	97 (91.5%)	99 (91.7%)
Severe (Mayo >10)	0	5 (9.3%)	3 (5.8%)	8 (7.5%)	8 (7.4%)

	Ustekinumab IV				
		Ustekinumab SC			
	Not randomized*	q12w	q8w	Combined	Total
Severity of endoscopy subscore					
N	3	55	54	109	112
Moderate (endoscopy subscore=2)	2 (66.7%)	30 (54.5%)	29 (53.7%)	59 (54.1%)	61 (54.5%)
Severe (endoscopy subscore=3)	1 (33.3%)	25 (45.5%)	25 (46.3%)	50 (45.9%)	51 (45.5%)
C-reactive protein (CRP), mg/L					
N	3	55	54	109	112
Mean (SD)	2.23 (2.916)	7.31 (14.422)	6.29 (12.786)	6.81 (13.583)	6.68 (13.424)
Median	0.60	2.00	1.30	1.70	1.65
Range	(0.5; 5.6)	(0.1; 69.0)	(0.1; 81.6)	(0.1; 81.6)	(0.1; 81.6)
Abnormal CRP (>3 mg/L)	1 (33.3%)	20 (36.4%)	21 (38.9%)	41 (37.6%)	42 (37.5%)
Fecal calprotectin concentrations, mg/kg					
N	3	46	44	90	93
Mean (SD)	1861.7 (1522.25)	3830.3 (3558.93)	4223.9 (5432.80)	4022.7 (4550.11)	3953.0 (4497.35)
Median	2495.0	2575.5	2470.5	2474.0	2494.0
Range	(125; 2965)	(36; 15621)	(252; 25792)	(36; 25792)	(36; 25792)
Abnormal fecal calprotectin (>250 mg/kg)	2 (66.7%)	43 (93.5%)	44 (100.0%)	87 (96.7%)	89 (95.7%)
Fecal lactoferrin concentrations, µg/g					
N	3	46	46	92	95
Mean (SD)	167.4 (113.32)	410.5 (353.49)	356.1 (270.60)	383.3 (314.24)	376.5 (311.95)
Median	127.9	259.2	283.5	275.8	268.5
Range	(79; 295)	(4; 1000)	(30; 1000)	(4; 1000)	(4; 1000)
Abnormal fecal lactoferrin (>7.24 µg/g)	3 (100.0%)	44 (95.7%)	46 (100.0%)	90 (97.8%)	93 (97.9%)

Key: CRP=C-reactive protein; IQ=interquartile; SD=standard deviation.
Note: N's for each parameter reflect non-missing values.
* Subjects received ustekinumab at Week I-0 in induction but not randomized at Week M-0 in maintenance.
[a] Mayo Score is based on Central Endoscopy Score

Prior Medication and Therapy

A total of 111 (99.1%) of 112 participants in the study had a history of inadequate response, intolerance, or dependence to conventional therapy with corticosteroids and/or 6-MP/AZA/MTX. The remaining participant only had a documented failure to prior biological therapy. Proportions were generally similar across the q12w and q8w treatment groups, although a numerically higher proportion of participants in the q8w treatment group had an inadequate response and/or intolerance to immunomodulators compared with the q12w treatment group.

A total of 44 (39.3%) of 112 participants in the study had a history of biological treatment failure. All participants without a history of biologic failure were biologic naïve (68 [60.7%] of 112 participants). Overall, all responders (both induction and delayed responders) had a similar history of corticosteroid and immunomodulator failure, biological failure, and UC medication use.

Table 17: Summary of Corticosteroid and Immunomodulator Prior Failure Status; Full Analysis Set (CSR, Table 10)

	Ustekinumab IV	Ustekinumab SC			
	Not randomized*	q12w	q8w	Combined	Total
Analysis set: Full	3	55	54	109	112
Subjects with inadequate response, intolerance, or dependence to corticosteroids and/or 6-MP/AZA/MTX	3 (100.0%)	54 (98.2%)	54 (100.0%)	108 (99.1%)	111 (99.1%)
Corticosteroids					
Subjects with inadequate response, intolerance or dependence to corticosteroids	2 (66.7%)	49 (89.1%)	46 (85.2%)	95 (87.2%)	97 (86.6%)
Subjects with inadequate response	1 (33.3%)	34 (61.8%)	31 (57.4%)	65 (59.6%)	66 (58.9%)
Subjects intolerant	0	4 (7.3%)	2 (3.7%)	6 (5.5%)	6 (5.4%)
Subjects dependent	2 (66.7%)	26 (47.3%)	26 (48.1%)	52 (47.7%)	54 (48.2%)
Immunomodulators (AZA, 6-MP or MTX)					
Subjects with inadequate response or intolerance to immunomodulators (6-MP/AZA/MTX)	1 (33.3%)	21 (38.2%)	27 (50.0%)	48 (44.0%)	49 (43.8%)
Subjects with inadequate response	1 (33.3%)	19 (34.5%)	26 (48.1%)	45 (41.3%)	46 (41.1%)
Subjects intolerant	0	4 (7.3%)	3 (5.6%)	7 (6.4%)	7 (6.3%)

Note: Subjects may appear in more than 1 category.
* Subjects received ustekinumab at Week I-0 in induction but not randomized at Week M-0 in maintenance.

Concomitant Therapy

At baseline, the majority (93.8%) of participants were receiving UC-related concomitant medications. The most frequently used concomitant medication across the combined q12w and q8w treatment groups was oral 5-ASA (74.1% of participants). Proportions were similar across the q12w and q8w treatment groups. Baseline UC-related concomitant medication use for all responders (both induction and delayed responders) was similar to those in the overall study population.

Table 18: Summary of UC-related Concomitant Medications at Baseline; Full Analysis Set (CSR, Table 11)

	Ustekinumab IV	Ustekinumab SC			
	Not randomized*	q12w	q8w	Combined	Total
Analysis set: Full	3	55	54	109	112
Subjects who received any of the following UC medications	2 (66.7%)	50 (90.9%)	53 (98.1%)	103 (94.5%)	105 (93.8%)
Any Antibiotic use	0	0	0	0	0
Corticosteroid use	1 (33.3%)	25 (45.5%)	23 (42.6%)	48 (44.0%)	49 (43.8%)
Oral/Rectal Corticosteroid use (excluding budesonide and beclomethasone dipropionate)	1 (33.3%)	15 (27.3%)	12 (22.2%)	27 (24.8%)	28 (25.0%)
Budesonide[a]	0	10 (18.2%)	10 (18.5%)	20 (18.3%)	20 (17.9%)
Beclomethasone dipropionate[a]	0	0	1 (1.9%)	1 (0.9%)	1 (0.9%)
Immunomodulatory drugs	0	18 (32.7%)	26 (48.1%)	44 (40.4%)	44 (39.3%)
6-mercaptopurine/azathioprine	0	18 (32.7%)	25 (46.3%)	43 (39.4%)	43 (38.4%)
Methotrexate	0	0	1 (1.9%)	1 (0.9%)	1 (0.9%)
Oral 5-Aminosalicylate	1 (33.3%)	39 (70.9%)	43 (79.6%)	82 (75.2%)	83 (74.1%)

* Subjects received ustekinumab at Week I-0 in induction but not randomized at Week M-0 in maintenance.
[a] Including oral or rectal
Note: Subjects may appear in more than one category.
Note: Baseline is defined as the observation at Week I-0

Dose Modification

Overall, 10 (9.2%) of 109 randomised participants met the early escape criteria as induction nonresponders; 5 of these participants had low exposure and 4 entered the EOS. Additionally, during maintenance, 26 (26.8%) of 97 responders (both induction and delayed responders) experienced a confirmed LOR.

- Seven (6.4%) of 109 randomised participants had a dose adjustment to q8w or a sham adjustment (remained in q8w). Eight responders had normal ustekinumab levels and a confirmed LOR. Of note, 1 responder with normal ustekinumab levels in the q12w treatment group had a confirmed LOR but did not dose adjust to q8w due to a malfunction of the IWRS system and regained response without intervention.
- A total of 18 (18.6%) of 97 responders who had low ustekinumab levels and a confirmed LOR entered the EOS to be dose escalated to ustekinumab q4w. Of note, 1 participant who entered the EOS from the q12w treatment group did not receive treatment during the EOS and was therefore not considered to be a part of the Substudy Analysis Set.

Table 19: Summary of Early Escape and Loss of Response During the Maintenance Period; Safety Randomised Analysis Set (CSR, Table 12)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w[a]	q8w[a]	Combined
Analysis set: Safety Randomized	55	54	109
Total number of subjects who met early escape criteria	5 (9.1%)	5 (9.3%)	10 (9.2%)
Total number of subjects who had low exposure	2 (3.6%)	3 (5.6%)	5 (4.6%)
Total number of subjects who entered substudy	1 (1.8%)	3 (5.6%)	4 (3.7%)
All Responder (at Week I-8 or Week M-8)	49	48	97
Total number of subjects who experienced a confirmed loss of response[b]	18 (36.7%)	8 (16.7%)	26 (26.8%)
Total number of subjects who had low exposure	12 (24.5%)	6 (12.5%)	18 (18.6%)
Total number of subjects who entered substudy	12 (24.5%)	6 (12.5%)	18 (18.6%)

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

Numbers analysed

Unless otherwise noted, efficacy analyses were based on all study participants (Full Analysis Set [FAS]; n=112) for endpoints through Week I-8 and the induction responders (Full Clinical Responder Analysis Set [FASCR]; n=79) for endpoints from Week M-0 through Week M-44; participants were analysed according to the intervention group to which they were randomised regardless of the intervention they actually received.

For selected endpoints, a population set that included both induction responders (clinical responders at Week I-8/M-0) and delayed responders (clinical responders at Week M-8) was analysed (All Responder Analysis Set [FASRES]; n=97). All randomised participants (Safety Randomised Analysis Set [SASR]; n=109) were analysed for the exploratory endpoint of TUMMY-UC/Observer TUMMY-UC.

No participants missed a study intervention administration from Week I-0 through Week M-44. All 112 participants received the full scheduled IV ustekinumab induction dose at Week I-0 except for 1 participant who did not complete the dose due to an infusion reaction. During maintenance, no participants missed a study intervention administration due to AEs or other reasons, including COVID-19 related reasons.

Table 20: Number of Subjects in Each Analysis Set; All Enrolled Analysis Set (CSR, Table 7)

	Ustekinumab IV				
		Ustekinumab SC			
	Not randomized*	q12w	q8w	Combined	Total
All Enrolled[a]	3	55	54	109	112
Full Analysis Set	3	55	54	109	112
Full Clinical Responder Analysis Set	0	40 (72.7%)	39 (72.2%)	79 (72.5%)	79 (70.5%)
All Responder Analysis Set	0	49 (89.1%)	48 (88.9%)	97 (89.0%)	97 (86.6%)
Safety Analysis Set	3 (100.0%)	55 (100.0%)	54 (100.0%)	109 (100.0%)	112 (100.0%)
Safety Randomized Analysis Set	0	55 (100.0%)	54 (100.0%)	109 (100.0%)	109 (97.3%)
Safety Clinical Responder Analysis Set	0	40 (72.7%)	39 (72.2%)	79 (72.5%)	79 (70.5%)
PK Analysis Set	2 (66.7%)	55 (100.0%)	54 (100.0%)	109 (100.0%)	111 (99.1%)
PK Clinical Responder Analysis Set	0	40 (72.7%)	39 (72.2%)	79 (72.5%)	79 (70.5%)
PK All Responder Analysis Set	0	49 (89.1%)	48 (88.9%)	97 (89.0%)	97 (86.6%)
Immunogenicity Analysis Set	3 (100.0%)	55 (100.0%)	54 (100.0%)	109 (100.0%)	112 (100.0%)
Immunogenicity Clinical Responder Analysis Set	0	40 (72.7%)	39 (72.2%)	79 (72.5%)	79 (70.5%)
Immunogenicity All Responder Analysis Set	0	49 (89.1%)	48 (88.9%)	97 (89.0%)	97 (86.6%)
Substudy Analysis Set	0	12 (21.8%)	9 (16.7%)	21 (19.3%)	21 (18.8%)

Note: Clinical response and Delayed response status are determined by the IWRS.
* Subjects received ustekinumab at Week I-0 in induction but not randomized at Week M-0 in maintenance.
[a]Excluding Screen Failure subjects

Outcomes and estimation

Primary Endpoint

The global primary endpoint was clinical remission at Week I-8. This endpoint was assessed among all 112 participants (Full Analysis Set) in the study using the Global Primary Estimand. At Week I-8, 25.0% of participants achieved clinical remission.

Table 21: Primary Endpoint Analysis (Global Primary Estimand): Number of Subjects in Clinical Remission at Week I-8; Full Analysis Set (CSR, Table 13)

	Ustekinumab IV
Analysis set: Full	112
Week I-8	
N	112
Subjects in clinical remission[a,b,c,d]	28 (25.0%)
95% CI for proportion of subjects in clinical remission[e]	(17.9%, 33.8%)

Note: Global Primary Estimand handles the ICEs with a combination of the composite and hypothetical strategies as described in footnote c.
[a] Clinical remission is defined by Mayo subscores as: a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.
[b] ICEs include: (1) Subjects who had a colectomy (partial or full) or ostomy, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of UC, (3) Had prohibited changes in UC medications, (4) Discontinued study intervention due to COVID-19 reasons (excluding COVID-19 infections), (5) Discontinued study intervention for reasons other than those in 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.

ICE Primary Endpoint

Through Week I-8, 3 (2.7%) of 112 participants had at least 1 ICE. One participant had an ICE of "surgery," 1 had an ICE categorised as "discontinuation due to lack of efficacy or AE of worsening UC," and 2 participants had an ICE categorised as "discontinued study intervention due to reasons other than lack of efficacy or an AE of worsening UC or COVID-19-related reasons". Supplementary analyses performed for the global primary endpoint provided the same results as the primary analysis.

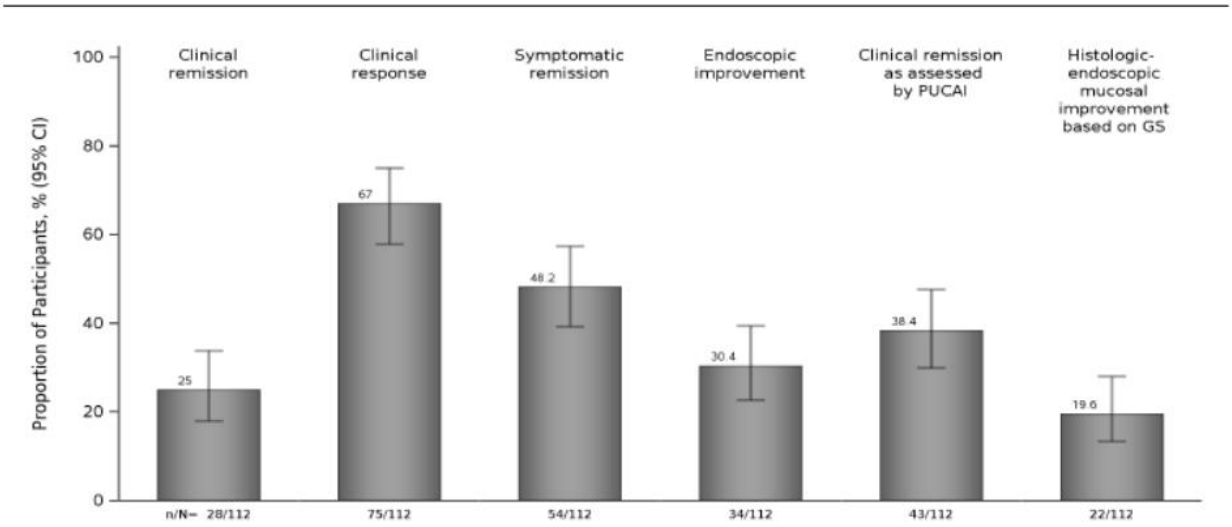
Sensitivity Analysis Primary Endpoint

Almost all participants (103 [92.0%] of 112 participants) had complete Mayo scores at Week I-8. Two participants were missing all 4 Mayo scores as they discontinued study intervention prior to visit Week I-8. Sensitivity analyses performed for the global primary endpoint were consistent with and supported the robustness of the primary analysis

Secondary Efficacy Analysis (Induction Period)

At Week I-8, the proportions of ustekinumab-treated paediatric participants who achieved clinical response, symptomatic remission, and endoscopic improvement were numerically higher than those of ustekinumab-treated adult participants in the Phase 3 study CNTO1275UCO3001.

Figure 29: Histogram with Confidence Interval of Primary and Secondary Endpoints at Week I-8; Full Analysis Set (CSR, Figure 7)



Note: Clinical remission is defined by Mayo subscores as: a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.
Note: Clinical response is defined as a decrease from baseline in the Modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. Endoscopy subscore was based on assessment by the central endoscopist.
Note: Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline.
Note: Clinical remission as assessed by PUCAI is defined as PUCAI score <10
Note: Endoscopic improvement is defined as a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
Note: Histologic-endoscopic mucosal improvement based on GS is defined as achieving a combination of histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system) and endoscopic improvement (a Mayo endoscopy sub-score of 0 or 1 with no friability present in the endoscopy).

Secondary Efficacy Analysis (Maintenance Period)

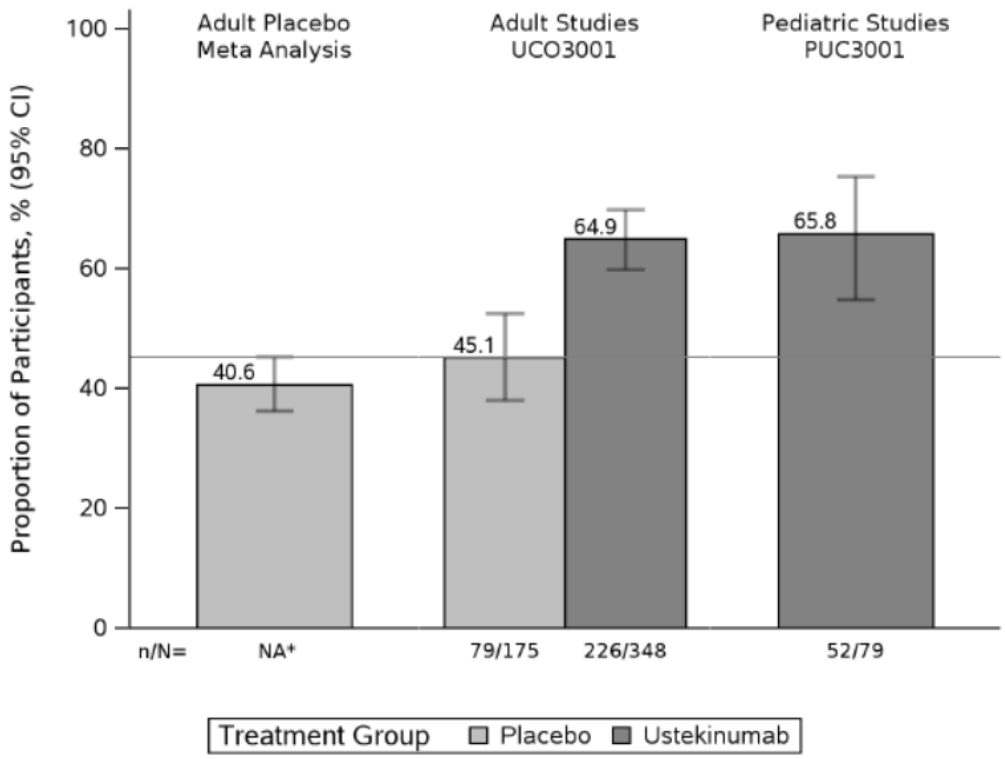
Numerically higher (>10%) response rates were observed for induction responders in the q8w treatment group compared with those in the q12w treatment group for most secondary endpoints.

At Week M-44, the proportions of ustekinumab-treated paediatric participants who achieved symptomatic remission, clinical response, and endoscopic improvement were similar to those of ustekinumab-treated adult participants in the Phase 3 study CNTO1275UCO3001.

Clinical remission at Week M-44 was a global secondary endpoint and the US-specific primary endpoint. At Week M-44, 32 (40.5%) of 79 induction responders in the combined treatment group (q12w: 13 [32.5%] of 40 participants; q8w: 19 [48.7%] of 39 participants) achieved clinical remission.

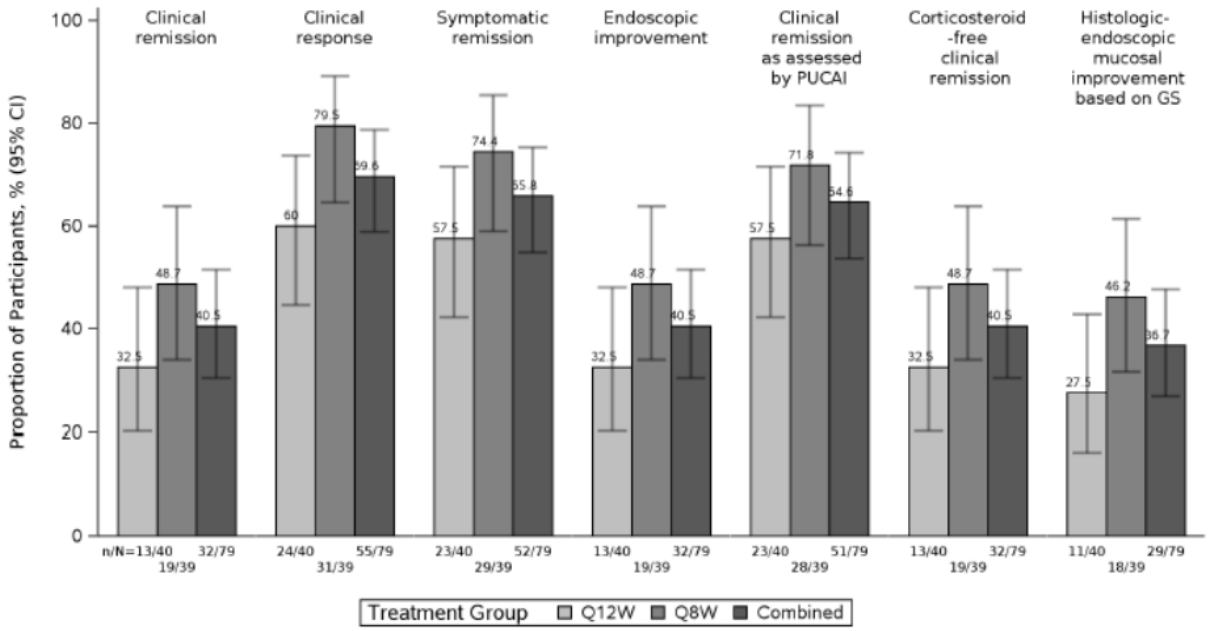
At Week M-44, 52 (65.8%) of 79 induction responders in the combined treatment group (q12w: 23 [57.5%] of 40 participants; q8w: 29 [74.4%] of 39 participants) achieved symptomatic remission. The lower bound of the 95% CI for the proportion of ustekinumab-treated paediatric participants in symptomatic remission at Week M-44 (54.8%) was higher than the upper bound of the 95% CI for the proportion of placebo-treated adult participants in symptomatic remission at approximately 1 year (45.17%) based on the meta-analysis from 3 adult studies in UC.

Figure 30: Secondary Endpoint Symptomatic Remission at Week M-44: Studies CNTO1275UCO3001 and CNTO1275PUC3001; Full Clinical Responder Analysis Set (CSR, Figure 8)



* at NA on x-axis: The following 3 aggregate study level adult placebo proportion of subjects in remission are included in the meta-analysis: LUCENT 2 study 71/179 (39.7%) at Week 40 , QUASAR_phase_3_m study 71/190 (37.4%) at Week 44, UNIFI_m study 79/175 (45.1%) at Week 44. The total number of subjects is 544.
Note: This graph is adopted from table TEFSEC08_GU and TEFPSADU02.
Note: The horizontal reference line on the graph represents the upper bound of the 95% CI from the adult placebo meta-analysis.
Note: Clinical response and Delayed response status are determined by the IWRS.

Figure 31: Histogram with Confidence Interval of Primary and Key Endpoints at Week M-44; Full Clinical Responder Analysis Set (CSR, Figure 9)



Note: Clinical remission is defined by Mayo subscores as: a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.
Note: Clinical response is defined as a decrease from baseline in the Modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. Endoscopy subscore was based on assessment by the central endoscopist.
Note: Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline.
Note: Clinical remission as assessed by PUCAI is defined as PUCAI score <10
Note: Endoscopic improvement is defined as a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
Note: Corticosteroid-free clinical remission is defined as a Mayo stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline; and not receiving corticosteroids for at least 90 days prior to Week M-44.
Note: Histologic-endoscopic mucosal improvement based on GS is defined as achieving a combination of histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system) and endoscopic improvement (a Mayo endoscopy sub-score of 0 or 1 with no friability present in the endoscopy).
Note: Refer to individual tables TEFSEC07G, TEFTEROTH15, TEFSEC08GU, TEFSEC11GU, TEFSEC09GU, TEFSEC12GU and TEFSEC15GU respectively.
Note: Clinical response used for Full Clinical Responder Analysis Set are determined by the IWRS.

Tertiary Efficacy Analysis

Clinical remission was summarised using 3 alternative definitions at both Week I-8 and Week M-44.

1. Clinical Remission at Week I-8, defined as a Mayo stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 (excluding friability) – 19.6% and 27.8% respectively.
2. Clinical Remission at Week I-8, defined as a Mayo absolute stool number ≤3, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 (excluding friability) – 25% and 40.5%% respectively.

3. Clinical Remission at Week I-8, defined as a Mayo score ≤2 points, with no individual subscore >1 (excluding friability) – 23.2% and 39.2% respectively.

Clinical Remission: A total of 16 (20.3%) of 79 induction responders in the combined treatment group were in remission at both Week I-8 and Week M-44, with similar results for the q12w (7 [17.5%] of 40 participants) and q8w (9 [23.1%] of 39 participants) treatment groups.

Symptomatic Remission: A total of 36 (45.6%) of 79 induction responders were in symptomatic remission at both Week I-8 and Week M-44; a numerically higher proportion of these participants were in the q8w treatment group compared with the q12w treatment group.

Clinical Remission as Assessed by PUCAI Score: A total of 32 (78.0%) of 41 participants who achieved clinical remission as assessed by the PUCAI score at Week I-8 remained in clinical remission as assessed by the PUCAI score at Week M-44.

Other Clinical Efficacy Endpoints

- **Clinical Response as Assessed by Mayo Score:** At Week I-8, 78 (69.6%; 95% CI: 60.6%, 77.4%) of 112 participants were in clinical response. At Week M-44, 56 (70.9%; 95% CI: 60.1%, 79.7%) of induction responders maintained clinical response. The proportion of induction responders who maintained clinical response was numerically higher in the q8w treatment group (32 [82.1%; 95% CI: 67.3%, 91.0%] of 39 participants) compared with the q12w treatment group (24 [60%; 95% CI: 44.6%, 73.7%] of 40 participants).
- **Clinical Response as Assessed by Modified Mayo Score:** At Week I-8, 80 (71.4%; 95% CI: 62.5%, 79.0%) of 112 participants were in clinical response. At Week M-44, 55 (69.6%; 95% CI: 58.8%, 78.7%) of 79 induction responders in the combined treatment group maintained clinical response. The proportion of induction responders who maintained clinical response was numerically higher in the q8w treatment group (31 [79.5%; 95% CI: 64.5%, 89.2%] of 39 participants) compared with the q12w treatment group (24 [60.0%; 95% CI: 44.6%, 73.7%] of 40 participants).
- **Clinically Important Change in the PUCAI Score:** A reduction in the PUCAI score of 20 points (from baseline) was considered a clinically important change. Through Week I-8, 93 (83.0%; 95% CI: 75.0%, 88.9%) of 112 participants in the study had a clinically important change in the PUCAI score. Through Week M-44, 56 (70.9% [95% CI: 60.1%, 79.7%]) of 79 induction responders in the combined treatment group had a clinically important change in the PUCAI score. The proportion of induction responders with a clinically important change in the PUCAI score was numerically higher in the q8w treatment group (32 [82.1%; 95% CI: 67.3%, 91.0%] of 39 participants) compared with the q12w treatment group (24 [60.0%; 95% CI: 44.6%, 73.7%] of 40 participants).

Change From Baseline (Week I-0) for Mayo Scores, Modified Mayo Scores, Partial Mayo Scores, Mayo Subscores, and Stool Frequency and Rectal Bleeding Subscores

- **Mayo:** The mean (SD) and median reduction in the Mayo score from baseline to Week I-8 was -4.3 (2.43) and -5.0, respectively. The mean (SD) and median reduction in the Mayo score from baseline to Week M-44 was -4.8 (3.34) and -6.0, respectively, for induction responders in the combined treatment group (q12w: -3.8 [3.33] and -5.0; q8w: -5.8 [3.08] and -7.0).
- **Modified Mayo:** The mean (SD) and median reduction in the Modified Mayo score from baseline to Week I-8 was -3.0 (1.92) and -3.0, respectively. The mean (SD) and median reduction in the Modified Mayo score from baseline to Week M-44 was -3.3 (2.47) and -

4.0, respectively, for induction responders in the combined treatment group (q12w: -2.5 [2.35] and -3.0; q8w: -4.1 [2.35] and -5.0).

- **Partial Mayo:** The mean (SD) and median reduction in the partial Mayo score from baseline to Week I-8 was -3.6 (2.09) and -4.0, respectively. The mean (SD) and median reduction in the partial Mayo score from baseline to Week M-44 was -3.8 (2.67) and -5.0, respectively, for induction responders in the combined treatment group (q12w: -3.0 [2.69] and -4.0y; q8w: -4.6 [2.43] and -5.0).
- **Mayo Subscores:** Among all treated participants, the mean (SD) and median reductions from baseline to Week I-8 were as follows:
    - Stool frequency score: -1.1 (1.04) and -1.0.
    - Rectal bleeding score: -1.3 (0.86) and -1.0.
    - Endoscopy final score: -0.7 (0.84) and 0.0.
    - PGA score: -1.2 (0.84) and -1.0.
- **Mayo Subscores:** Among the Week I-8 induction responders in the q8w and q12w treatment groups, the mean (SD) and median reductions from baseline to Week M-44 for the combined treatment group were as follows:
    - Stool frequency score: -1.1 (0.99) and -1.0 (q12w: -0.7 [0.85] and -0.5; q8w: -1.4 [1.01] and -1.5).
    - Rectal bleeding score: -1.3 (1.01) and -2.0 (q12w: -1.1 [1.06] and -1.5; q8w: -1.5 [0.92] and -2.0).
    - Endoscopy final score: -0.9 (1.05) and -1.0 (q12w: -0.7 [0.88] and 0.0; q8w: -1.1 [1.17] and -1.0).
    - PGA score: -1.4 (1.04) and -2.0 (q12w: -1.3 [1.15] and -2.0; q8w: -1.6 [0.91] and -2.0).

Endoscopic Normalisation

At Week I-8, 10 (8.9%: 95% CI: 4.9%, 15.7%) of 112 participants in the study achieved endoscopic normalisation. At Week M-44, 15 (19.0%) of 79 induction responders in the combined treatment group achieved endoscopic normalisation. A numerically higher proportion of induction responders in the q8w treatment group (10 [25.6%; 95% CI: 14.6%, 41.1%] of 39 participants) achieved endoscopic normalisation compared with participants in the q12w treatment group (5 [12.5%; 95% CI: 5.5%, 26.1%] of 40 participants); however, the CIs overlapped.

Average Daily Prednisone-Equivalent Corticosteroid Dose

The average daily prednisone-equivalent corticosteroid dose was decreased at Week I-8 and Week M-44, indicating a reduction in corticosteroid dependence. At Week I-8, the mean (SD) prednisone-equivalent corticosteroid dose was 2.9 (8.55) compared with 5.6 (12.54) at baseline. At Week M-44, the mean (SD) reduction in average daily corticosteroid use from baseline for the combined treatment group was -3.8 (9.7) (q12w: -3.2 [8.4]; q8w: -4.4 [10.9]).

Growth and Nutritional Parameters

At baseline, based on observed scores, mean (SD) BMI z-scores were below zero in female (-0.056 [0.8214]; median: -0.088) and male (-0.192 [0.8827]; median: -0.310) participants. At Week M-44, change from baseline BMI z-scores showed an increase in both the q12w and q8w treatment groups.

- The mean (SD) iron serum level was 7.712 (10.0631) µmol/L at baseline and 14.901 (9.6400) µmol/L at Week M-44 for the combined treatment group. At Week M-44 in the combined treatment group, iron serum values shifted from low to normal for 21 of 58 participants, remained normal for 15 participants, and shifted from normal to low for 4 participants.
- The mean (SD) 25-hydroxyvitamin D value was 70.281 (33.7321) nmol/L at baseline and 69.601 (28.2459) nmol/L at Week M-44 for the combined treatment group. At Week M-44 in the combined treatment group, 25-hydroxyvitamin D values shifted from low to normal for 7 of 56 participants, remained normal for 36 participants, and shifted from normal to low for 4 participants.
- The mean (SD) MMA value was 141.840 (62.4210) nmol/L at baseline and 154.203 (92.8775) nmol/L at Week M-44 for the combined treatment group. At Week M-44 in the combined treatment group, MMA values stayed normal (0 to 378 nmol/L) for 55 of 57 participants and improved from high to normal for 1 participant.

C-Reactive Protein

Improvement in CRP, which was achieved by Week I-4 (mean [SD] and median change -3.83 [12.082] mg/L and -0.60 mg/L). At Week I-8, the mean (SD) and median change from baseline in CRP concentrations was -2.75 (12.161) mg/L and -0.45 mg/L, respectively. Additionally, among the 42 participants with elevated CRP levels (>3 mg/L) at Week I-0, 21 (50.0%) participants had normalised CRP levels (≤3 mg/L) at Week I-8.

At M-44, the mean (SD) and median change in CRP concentrations were -3.67 (13.911) mg/L and 0.00 mg/L, respectively, in the combined treatment group at Week M-44 (q12w:-2.94 [13.850] mg/L and 0.00 mg/L; q8w: -4.41 [14.114] mg/L and -0.20 mg/L).

Fecal Calprotectin

Improvement in fecal calprotectin, which was achieved by Week I-4 (mean [SD] change -2059.4 [5386.56] mg/kg). At Week I-8, the mean (SD) and median change from baseline in fecal calprotectin was -2157.4 (4203.30) mg/kg and -1103.0 mg/kg, respectively. Additionally, among the 89 participants with abnormal fecal calprotectin levels (>250 mg/kg) at Week I-0, 20 (22.5%) participants had normalised fecal calprotectin levels (≤250 mg/kg) at Week I-8.

At M-44, the mean (SD) and median change from Week I-0 in fecal calprotectin of -2427.6 (4593.26) mg/kg and -899.0 mg/kg, respectively, in the combined treatment group (q12w: -1198.6 [2061.66] mg/kg and -216.5 mg/kg; q8w: -3884.2 [6159.12] mg/kg and -1244.0 mg/kg).

Quality of Life

The IMPACT-III total score ranges from 35 to 175 with a higher score indicating that patients have a good overall health related quality of life (HRQoL). The MAH indicates that 0.5 SD as reasonable threshold for establishing clinically meaningful improvement in HRQoL concepts (Homco 2019; Norman 2003). Mean change scores for the combined treatment group (≥10 years of age) indicated that total score improvement from baseline in the IMPACT-III approached 1 SD at Week I-8 (21.6) and exceeded 1 SD at Week M-44 (26.3).

Table 22: Summary of Change From Baseline in IMPACT-III Scores at Week M-44 for Participants at Least 10 Years of Age at Week I-0; Full Clinical Responder Analysis Set (CSR, Table 16)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: Full Clinical Responder	40	39	79
Subjects ≥10 years of age at Week I-0	31 (77.5%)	35 (89.7%)	66 (83.5%)
IMPACT-III Scores			
Baseline[a]			
N	29	30	59
Mean (SD)	106.7 (24.40)	103.6 (19.86)	105.1 (22.07)
Median	105.0	105.5	105.0
Range	(67; 157)	(56; 140)	(56; 157)
Week I-8			
N	24	29	53
Mean (SD)	125.8 (21.64)	125.1 (20.29)	125.4 (20.71)
Median	127.0	129.0	127.0
Range	(79; 156)	(84; 162)	(79; 162)
Week I-8 change from baseline[b,c]			
N	23	25	48
Mean (SD)	19.1 (19.00)	23.9 (17.13)	21.6 (18.02)
Median	10.0	21.0	18.0
Range	(-9; 52)	(-2; 62)	(-9; 62)
Week M-44			
N	20	25	45
Mean (SD)	126.9 (29.42)	135.1 (20.29)	131.4 (24.81)
Median	130.5	135.0	134.0
Range	(52; 162)	(97; 170)	(52; 170)
Week M-44 change from baseline[b,c]			
N	19	22	41
Mean (SD)	18.2 (23.44)	33.2 (17.37)	26.3 (21.52)
Median	8.0	31.0	26.0
Range	(-15; 55)	(0; 60)	(-15; 60)

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 colectomy (partial or full) or ostomy, (2) Discontinued study intervention due to lack of efficacy or an AE of worsening of UC, (3) Had prohibited changes in UC medications, (4) Rescue medication used (initiation or increase above baseline) for treatment of LOR after Week M-8 for responders and Week M-16 for delayed responders, (5) Dose adjusted after Week M-8 (including both study interventions), (6) Discontinued study intervention due to COVID-19 reasons (excluding COVID-19 infections), (7) Discontinued study intervention for reasons other than those in ICEs 2 or 6.
[c] ICEs strategies: Subjects with ICEs 1-5, and 7 prior to Week M-44 are considered to have no change from baseline at Week M-44 (ie, composite strategy). Subjects with ICE 6 prior to Week M-44 are considered to have missing data from the time of the event onward (ie, hypothetical strategy).
Note: Clinical response and Delayed response status are determined by the IWRS.

During induction, TUMMY-UC scores improved in participants ≥8 years at Week I-8 compared with baseline, with a mean (SD) and median (IQR) change from baseline of -34.3 (28.98) and -35.0 (-53.0; -16.0), respectively. This improvement in TUMMY-UC scores was maintained in induction responders ≥8 years old at Week M-44, with a mean (SD) and median (IQR) change from baseline of -39.2 (25.90) and -41.0 (-52.5, -22.5), respectively, for the combined treatment group. Both q12w and q8w treatment groups showed a similar median (IQR) change from baseline (q12w: -36.0 [-50.5, -20.0]; q8w: -42.5 [-58.5, -31.5]).

To note, baseline values were not recorded for participants <8 years (Observer TUMMY-UC), and there were too few participants <8 years with data at Week I-8 and Week M-44 (n=2 at both Week I-8 and Week M-44) to draw any meaningful conclusions for this age group.

Table 23: Summary of Values and Change From Baseline in Tummy UC From Week M-0 Through Week M-44; Safety Randomised Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab SC					
	Baseline Age					
	<8 years			>=8 years		
	q12w	q8w	Combined	q12w	q8w	Combined
Analysis set: Safety Randomized	3	3	6	52	51	103
Week M-44[a]						
N	1	1	2	36	42	78
Mean (SD)	29.0 (-)	0.0 (-)	14.5 (20.51)	20.3 (17.50)	17.1 (16.40)	18.6 (16.88)
Median	29.0	0.0	14.5	15.5	13.5	14.0
IQ range	(29.0; 29.0)	(0.0; 0.0)	(0.0; 29.0)	(8.0; 33.5)	(4.0; 22.0)	(4.0; 27.0)
Range	(29; 29)	(0; 0)	(0; 29)	(0; 62)	(0; 61)	(0; 62)
Change from baseline						
Week M-44[a]						
N	0	0	0	35	40	75
Mean (SD)	-	-	-	-33.4 (24.26)	-41.9 (29.30)	-37.9 (27.22)
Median	-	-	-	-35.0	-41.5	-38.0
IQ range	-	-	-	(-50.0; -21.0)	(-58.5; -23.0)	(-52.0; -21.0)
Range	-	-	-	(-97; 38)	(-104; 20)	(-104; 38)

Key Efficacy Endpoints by Baseline Subgroups

Subgroup analyses by baseline age and weight were performed to examine the consistency of the key efficacy endpoints of clinical remission, clinical response, symptomatic remission, clinical remission defined by PUCAI score, endoscopic improvement, and histologic-endoscopic mucosal improvement.

The consistency of treatment effect for the primary endpoint of clinical remission at Week I-8 was evaluated for subgroups based on demographics, UC disease characteristics, UC-related concomitant medication usage and UC-related medication history using the Global Primary Estimand. The results for these subgroup analyses were generally consistent with those observed in the overall study population.

At Week I-8, clinical remission proportions were numerically higher among participants with weight <40 kg (11 [32.4%; 95% CI: 19.1%, 49.2%] of 34 participants) compared with participants with weight ≥ 40 kg (17 [21.8%; 95% CI: 14.1%, 32.2%) of 78 participants) and participants without biologic failure (20 [29.4%; 95% CI: 19.9%, 41.1%] of 68 participants) compared with participants with biologic failures (8 [18.2%; 95% CI: 9.5%, 32.0%) of 44 participants), although the CIs overlapped.

Across every assessed key endpoint, Ustekinumab was less effective at M-44 in the 2-<12 age group (N=22) compared to the 12-<18 age group (N=57). For participants 2-<6 years, there was only an N of 3. For Week I-8, results were similar across key efficacy endpoints in the 2-<12 age group when compared to the 12-<18 age group.

Table 24: Tertiary Endpoint Analysis: Number of Subjects Achieving Key Efficacy Endpoint at Week M-44 by Baseline Age; Full Clinical Responder Analysis Set (CSR, TEFTERKEYEFF02)

	Baseline Age					
	2-<12 years			12-<18 years		
	q12w	q8w	Combined	q12w	q8w	Combined
Analysis set: Full Clinical Responder	11	11	22	29	28	57
Week M-44						
N	11	11	22	29	28	57
Subjects in clinical remission[a1],b,c,d	2 (18.2%)	3 (27.3%)	5 (22.7%)	11 (37.9%)	16 (57.1%)	27 (47.4%)
95% CI for proportion of subjects in clinical remission [e]	(5.1%, 47.7%)	(9.7%, 56.6%)	(10.1%, 43.4%)	(22.7%, 56.0%)	(39.1%, 73.5%)	(35.0%, 60.1%)
Week M-44						
N	11	11	22	29	28	57
Subjects in symptomatic remission[a2],b,c,d	4 (36.4%)	8 (72.7%)	12 (54.5%)	19 (65.5%)	21 (75.0%)	40 (70.2%)
95% CI for proportion of subjects in symptomatic remission [e]	(15.2%, 64.6%)	(43.4%, 90.3%)	(34.7%, 73.1%)	(47.3%, 80.1%)	(56.6%, 87.3%)	(57.3%, 80.5%)
Week M-44						
N	11	11	22	29	28	57
Subjects in clinical remission as assessed by the PUCAI score[a3],b,c,d	5 (45.5%)	8 (72.7%)	13 (59.1%)	18 (62.1%)	20 (71.4%)	38 (66.7%)
95% CI for proportion of subjects in clinical remission as assessed by the PUCAI score [e]	(21.3%, 72.0%)	(43.4%, 90.3%)	(38.7%, 76.7%)	(44.0%, 77.3%)	(52.9%, 84.7%)	(53.7%, 77.5%)
Week M-44						
N	11	11	22	29	28	57
Subjects in endoscopic improvement[a4],b,c,d	2 (18.2%)	3 (27.3%)	5 (22.7%)	11 (37.9%)	16 (57.1%)	27 (47.4%)
95% CI for proportion of subjects in endoscopic improvement [e]	(5.1%, 47.7%)	(9.7%, 56.6%)	(10.1%, 43.4%)	(22.7%, 56.0%)	(39.1%, 73.5%)	(35.0%, 60.1%)
Week M-44						
N	11	11	22	29	28	57
Subjects in corticosteroid-free clinical remission[a5],b,c,d	2 (18.2%)	3 (27.3%)	5 (22.7%)	11 (37.9%)	16 (57.1%)	27 (47.4%)
95% CI for proportion of subjects in corticosteroid-free clinical remission [e]	(5.1%, 47.7%)	(9.7%, 56.6%)	(10.1%, 43.4%)	(22.7%, 56.0%)	(39.1%, 73.5%)	(35.0%, 60.1%)
Week M-44						
N	11	11	22	29	28	57
Subjects in histologic-endoscopic mucosal improvement based on GS[a6],b,c,d	1 (9.1%)	3 (27.3%)	4 (18.2%)	10 (34.5%)	15 (53.6%)	25 (43.9%)
	Baseline Age					
	2-<12 years			12-<18 years		
	q12w	q8w	Combined	q12w	q8w	Combined
95% CI for proportion of subjects in histologic-endoscopic mucosal improvement based on GS [e]	(1.6%, 37.7%)	(9.7%, 56.6%)	(7.3%, 38.5%)	(19.9%, 52.7%)	(35.8%, 70.5%)	(31.8%, 56.7%)
Week M-44						
N	11	11	22	29	28	57
Subjects in histologic-endoscopic mucosal improvement based on RHI[a7],b,c,d	1 (9.1%)	3 (27.3%)	4 (18.2%)	8 (27.6%)	12 (42.9%)	20 (35.1%)
95% CI for proportion of subjects in histologic-endoscopic mucosal improvement based on RHI [e]	(1.6%, 37.7%)	(9.7%, 56.6%)	(7.3%, 38.5%)	(14.7%, 45.7%)	(26.5%, 60.9%)	(24.0%, 48.1%)
Subjects who are in clinical remission[a1] at Week I-8	5 (45.5%)	3 (27.3%)	8 (36.4%)	6 (20.7%)	13 (46.4%)	19 (33.3%)
Week M-44						
N	5	3	8	6	13	19
Number of subjects in clinical remission among subjects who are in clinical remission at Week I-8 [a1],b,c,d	2 (40.0%)	1 (33.3%)	3 (37.5%)	5 (83.3%)	8 (61.5%)	13 (68.4%)
95% CI for proportion of subjects in clinical remission among subjects who are in clinical remission at Week I-8 [e]	(11.8%, 76.9%)	(6.1%, 79.2%)	(13.7%, 69.4%)	(43.6%, 97.0%)	(35.5%, 82.3%)	(46.0%, 84.6%)
Subjects who received corticosteroid at Week I-0	3 (27.3%)	2 (18.2%)	5 (22.7%)	14 (48.3%)	14 (50.0%)	28 (49.1%)
Week M-44						
N	3	2	5	14	14	28
Number of subjects in corticosteroid-free clinical remission[a5],b,c,d	1 (33.3%)	0	1 (20.0%)	6 (42.9%)	9 (64.3%)	15 (53.6%)
95% CI for proportion of subjects in corticosteroid-free clinical remission[e]	(6.1%, 79.2%)		(3.6%, 62.4%)	(21.4%, 67.4%)	(38.8%, 83.7%)	(35.8%, 70.5%)

Across every assessed key endpoint, Ustekinumab was less effective at M-44 in participants weighing <30kg (N=13) compared to those weighing ≥30-<40kg (N=14) (same dosing strategy induction 250 mg/m2 and maintenance 60 mg/m2). A similar trend occurred for participants weighing <40kg (N=27) compared to those weighing ≥40kg (N=52) bar "Subjects in clinical remission as assessed by the PUCAI score".

Table 25: Tertiary Endpoint Analysis: Number of Subjects Achieving Key Efficacy Endpoint at Week M-44 by Baseline Weight; Full Clinical Responder Analysis Set (CSR, TEFTERKEYEFF07)

	Ustekinumab SC					
	Baseline Weight					
	<40 kg			≥40 kg		
	q12w	q8w	Combined	q12w	q8w	Combined
Analysis set: Full Clinical Responder	12	15	27	28	24	52
Week M-44						
N	12	15	27	28	24	52
Subjects in clinical remission [a1],b,c,d	3 (25.0%)	6 (40.0%)	9 (33.3%)	10 (35.7%)	13 (54.2%)	23 (44.2%)
95% CI for proportion of subjects in clinical remission [e]	(8.9%, 53.2%)	(19.8%, 64.3%)	(18.6%, 52.2%)	(20.7%, 54.2%)	(35.1%, 72.1%)	(31.6%, 57.7%)
Week M-44						
N	12	15	27	28	24	52
Subjects in symptomatic remission [a2],b,c,d	5 (41.7%)	12 (80.0%)	17 (63.0%)	18 (64.3%)	17 (70.8%)	35 (67.3%)
95% CI for proportion of subjects in symptomatic remission [e]	(19.3%, 68.0%)	(54.8%, 93.0%)	(44.2%, 78.5%)	(45.8%, 79.3%)	(50.8%, 85.1%)	(53.8%, 78.5%)
Week M-44						
N	12	15	27	28	24	52
Subjects in clinical remission as assessed by the PUCAI score [a3],b,c,d	6 (50.0%)	12 (80.0%)	18 (66.7%)	17 (60.7%)	16 (66.7%)	33 (63.5%)
95% CI for proportion of subjects in clinical remission as assessed by the PUCAI score [e]	(25.4%, 74.6%)	(54.8%, 93.0%)	(47.8%, 81.4%)	(42.4%, 76.4%)	(46.7%, 82.0%)	(49.9%, 75.2%)
Week M-44						
N	12	15	27	28	24	52
Subjects in endoscopic improvement [a4],b,c,d	3 (25.0%)	6 (40.0%)	9 (33.3%)	10 (35.7%)	13 (54.2%)	23 (44.2%)
95% CI for proportion of subjects in endoscopic improvement [e]	(8.9%, 53.2%)	(19.8%, 64.3%)	(18.6%, 52.2%)	(20.7%, 54.2%)	(35.1%, 72.1%)	(31.6%, 57.7%)
Week M-44						
N	12	15	27	28	24	52
Subjects in corticosteroid-free clinical remission [a5],b,c,d	3 (25.0%)	6 (40.0%)	9 (33.3%)	10 (35.7%)	13 (54.2%)	23 (44.2%)
95% CI for proportion of subjects in corticosteroid-free clinical remission [e]	(8.9%, 53.2%)	(19.8%, 64.3%)	(18.6%, 52.2%)	(20.7%, 54.2%)	(35.1%, 72.1%)	(31.6%, 57.7%)
Week M-44						
N	12	15	27	28	24	52

	Ustekinumab SC					
	Baseline Weight					
	<40 kg			≥40 kg		
	q12w	q8w	Combined	q12w	q8w	Combined
Subjects in histologic-endoscopic mucosal improvement based on GS [a6],b,c,d	2 (16.7%)	6 (40.0%)	8 (29.6%)	9 (32.1%)	12 (50.0%)	21 (40.4%)
95% CI for proportion of subjects in histologic-endoscopic mucosal improvement based on GS [e]	(4.7%, 44.8%)	(19.8%, 64.3%)	(15.9%, 48.5%)	(17.9%, 50.7%)	(31.4%, 68.6%)	(28.2%, 53.9%)
Week M-44						
N	12	15	27	28	24	52
Subjects in histologic-endoscopic mucosal improvement based on RHI [a7],b,c,d	2 (16.7%)	6 (40.0%)	8 (29.6%)	7 (25.0%)	9 (37.5%)	16 (30.8%)
95% CI for proportion of subjects in histologic-endoscopic mucosal improvement based on RHI [e]	(4.7%, 44.8%)	(19.8%, 64.3%)	(15.9%, 48.5%)	(12.7%, 43.4%)	(21.2%, 57.3%)	(19.9%, 44.3%)
Subjects who are in clinical remission[a1] at Week I-8	6 (50.0%)	5 (33.3%)	11 (40.7%)	5 (17.9%)	11 (45.8%)	16 (30.8%)
Week M-44						
N	6	5	11	5	11	16
Number of subjects in clinical remission among subjects who are in clinical remission at Week I-8 [a1],b,c,d	3 (50.0%)	2 (40.0%)	5 (45.5%)	4 (80.0%)	7 (63.6%)	11 (68.8%)
95% CI for proportion of subjects in clinical remission among subjects who are in clinical remission at Week I-8 [e]	(18.8%, 81.2%)	(11.8%, 76.9%)	(21.3%, 72.0%)	(37.6%, 96.4%)	(35.4%, 84.8%)	(44.4%, 85.8%)
Subjects who received corticosteroid at Week I-0	3 (25.0%)	3 (20.0%)	6 (22.2%)	14 (50.0%)	13 (54.2%)	27 (51.9%)
Week M-44						
N	3	3	6	14	13	27
Number of subjects in corticosteroid-free clinical remission[a5],b,c,d	1 (33.3%)	1 (33.3%)	2 (33.3%)	6 (42.9%)	8 (61.5%)	14 (51.9%)
95% CI for proportion of subjects in corticosteroid-free clinical remission[e]	(6.1%, 79.2%)	(6.1%, 79.2%)	(9.7%, 70.0%)	(21.4%, 67.4%)	(35.5%, 82.3%)	(34.0%, 69.3%)

Efficacy Analyses for Participants who had a Dose Adjustment

A total of 7 (6.4%) of 109 randomised participants dose adjusted from ustekinumab through Week M-44 (5 participants who dose-adjusted to ustekinumab q8w and 2 participants who received a sham adjustment). Due to the small sample size, no conclusions can be drawn on the impact of dose adjustment.

Efficacy Analyses by Local Endoscopist

A local endoscopist also reviewed participant endoscopy data for the overall study population through Week I-8 and for the induction responders at Week M-44 and when compared to that of the central endoscopist readings, the central endoscopist was more conservative with improvement readings.

Exposure Optimisation Substudy Efficacy Analysis

Participants who experienced a LOR or were induction nonresponders with low 8-week steady state trough ustekinumab exposure of <1.4 μg/ml were eligible to enroll in the optional q4w EOS (assessed at Week M-8 or Week M-32).

A total of 22 participants (13 participants in the q12w treatment group and 9 participants in the q8w treatment group) entered the EOS. Of these, 1 participant who entered the EOS from the q12w treatment group did not receive treatment during the EOS and was therefore not considered to be part of the Substudy Analysis Set.

Of the 21 participants in the Substudy Analysis Set, 16 (76.2%) completed the EOS. A total of 6 (28.6%) of 21 participants discontinued treatment during the EOS. Only 13 participants completed the EOS up to Week 16.

Table 26: Number of Subjects in Clinical Response based on Partial Mayo Score Over Time up to 16 Weeks After Entering the Substudy; Substudy Analysis Set (CSR, Table 21)

	Ustekinumab SC		
	q12w→q4w	q8w→q4w	Combined
Analysis set: Substudy	12	9	21
Substudy Week 4			
N	11	7	18
Subjects in clinical response[a]	7 (63.6%)	4 (57.1%)	11 (61.1%)
95% CI for proportion of subjects in clinical response[b]	(35.4%, 84.8%)	(25.0%, 84.2%)	(38.6%, 79.7%)
Substudy Week 8			
N	9	6	15
Subjects in clinical response[a]	6 (66.7%)	5 (83.3%)	11 (73.3%)
95% CI for proportion of subjects in clinical response[b]	(35.4%, 87.9%)	(43.6%, 97.0%)	(48.0%, 89.1%)
Substudy Week 12			
N	9	7	16
Subjects in clinical response[a]	7 (77.8%)	5 (71.4%)	12 (75.0%)
95% CI for proportion of subjects in clinical response[b]	(45.3%, 93.7%)	(35.9%, 91.8%)	(50.5%, 89.8%)
	Ustekinumab SC		
	q12w→q4w	q8w→q4w	Combined
Substudy Week 16			
N	8	5	13
Subjects in clinical response[a]	6 (75.0%)	5 (100.0%)	11 (84.6%)
95% CI for proportion of subjects in clinical response[b]	(40.9%, 92.9%)	(56.6%, 100.0%)	(57.8%, 95.7%)

Note: Observed data are used.
[a] Clinical response is defined as decrease from induction baseline of ≥2 in the partial Mayo score.
[b] The confidence intervals are based on the Wilson statistic.

The overall observed efficacy results for EOS participants at 16 weeks after entering the substudy were the following:

- 84.6% of the EOS participants achieved clinical response based on the partial Mayo score.
- 56.3% of the EOS participants achieved clinical remission based on the PUCAI score.

- The mean (SD) and median changes from entry into the EOS in the partial Mayo score at Substudy Week 16 were -3.8 (2.39) and -4.5, respectively.
- The mean (SD) and median changes from entry into the EOS in the PUCAI score at Substudy Week 16 were -43.4 (18.32) and -47.5, respectively.

Ancillary analyses - Comparison with Ustekinumab Adult Studies

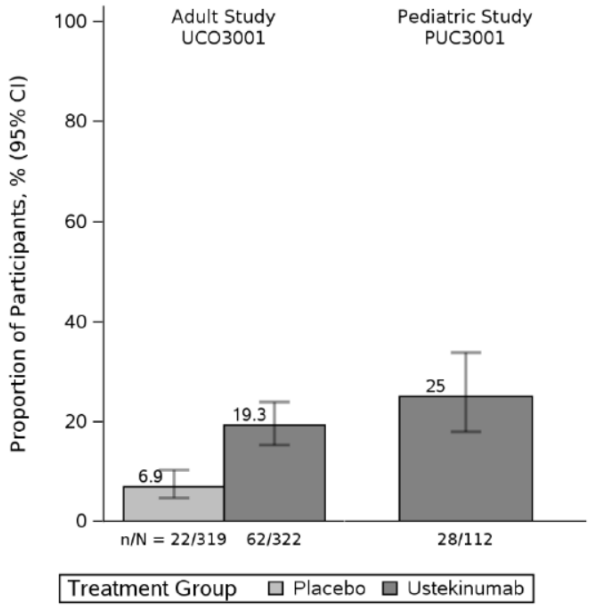
Extrapolation concept and plan provides data from the literature, real-world evidence, clinical studies, nonclinical data of a reference population of adults (18 years of age or older) with moderately to severely active UC against paediatric participants (2 to <18 years of age) with moderately to severely active UC. The key points of this comparison are summarised here:

- The pathogenic mechanisms mediating paediatric-onset UC are generally related to those in adult-onset UC, particularly in genetic and immune response mechanisms.
    - Most genes associated with the pathogenesis of adult UC are also associated with paediatric UC.
    - Both the innate and the adaptive immune systems are involved in the pathogenesis of UC across the age spectrum.
- Cytokine profiling in paediatric UC patients reveals similar patterns of IL-23 expression found in adults.
- Ulcerative colitis is defined in the same way in adults and children down to 2 years of age.
- Pancolitis in paediatric UC ranges from 32% to 66%, which overlaps the reported prevalence range in adults of 14% to 47%.
- There are rare phenotypic differences identified in paediatrics (macroscopic rectal sparing, relative lack of typical architectural distortion, cecal patch of inflammation, upper GI tract involvement, and occurrence of deep, fissuring ulcera) however, these are unlikely to affect therapeutic efficacy or extrapolation of adult data to paediatric patients.
- Probabilities for complicated disease course (undergoing colectomy, needing biologic drugs, or steroid dependency) can be twice as high in paediatric onset UC than in adult-onset.

As UC is similar in adults and paediatrics, the MAH has performed a direct comparison between the CNTO1275UCO3001 and UNIFI Jr studies. To note, the information below is purely descriptive and contains no formal statistical analysis. Efficacy is being determined by ratio comparisons between ustekinumab-treated paediatric participants to ustekinumab-treated adult participants.

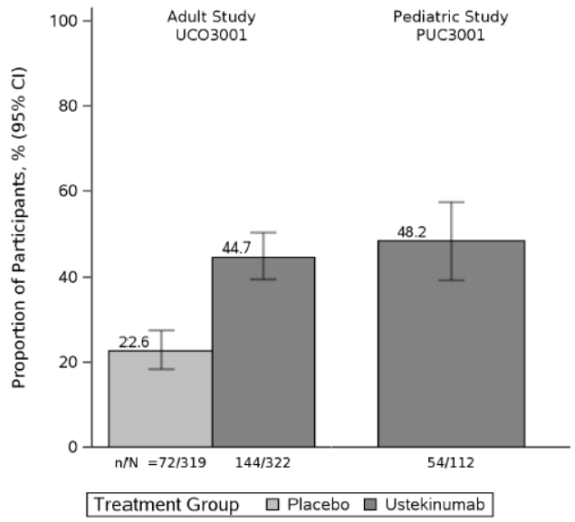
Primary Endpoint: At Week I-8, the proportion of ustekinumab-treated pediatric participants who achieved clinical remission (25.0%) was numerically higher than that of ustekinumab-treated adult participants (19.3%) in the Phase 3 study CNTO1275UCO3001 using the same paediatric definition of clinical remission from UNIFI Jr. The ratio of the proportion of ustekinumab-treated pediatric participants to ustekinumab-treated adult participants in clinical remission at Week I-8 was 1.30 (95%CI: 0.88, 1.92). This was nominally significant in the adult study.

Figure 32: Primary Endpoint Clinical Remission at Week I-8: Studies CNTO1275UCO3001 and CNTO1275PUC3001; Full Analysis Set (Study CNTO1275PUC3001) (CSR, Figure 3)



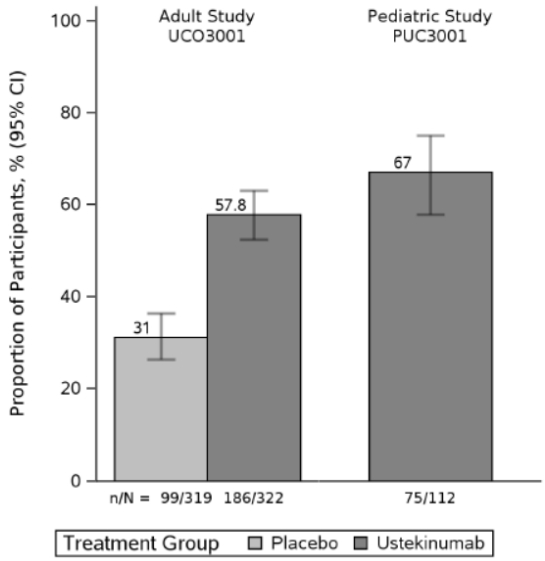
Induction Symptomatic Remission: At Week I-8, the proportion of ustekinumab-treated paediatric participants (48.2%) who achieved symptomatic remission was numerically higher than that of ustekinumab-treated adult participants (44.7%) in the Phase 3 study CNTO1275UCO3001. The ratio of the proportion of ustekinumab-treated paediatric participants to ustekinumab-treated adult participants in symptomatic remission at Week I-8 was 1.08 (95% CI: 0.86, 1.35). Symptomatic remission was nominally significant in the adult study.

Figure 33: Secondary Endpoint Symptomatic Remission at Week I-8: Studies CNTO1275UCO3001 and CNTO1275PUC3001; Full Analysis Set (Study CNTO1275PUC3001) (CSR, Figure 15)



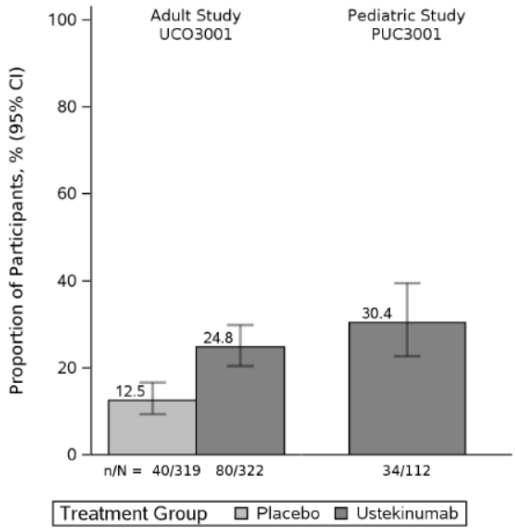
Induction Clinical Response: At Week I-8, the proportion of ustekinumab-treated paediatric participants (67.0%) who achieved clinical response was numerically higher than that of ustekinumab-treated adult participants (57.8%) in the Phase 3 study CNTO1275UCO3001. This was statistically significant in the adult study.

Figure 34: Secondary Endpoint Clinical Response at Week I-8: Studies CNTO1275UCO3001 and CNTO1275PUC3001; Full Analysis Set (Study CNTO1275PUC3001) (CSR, Figure 16)



Induction Endoscopic Improvement: At Week I-8, the proportion of ustekinumab-treated paediatric participants (30.4%) who achieved endoscopic improvement was numerically higher than that of ustekinumab-treated adult participants (24.8%) in the Phase 3 study CNTO1275UCO3001.

Figure 35: Secondary Endpoint Endoscopic Improvement at Week I-8: Studies CNTO1275UCO3001 and CNTO1275PUC3001; Full Analysis Set (Study CNTO1275PUC3001) (CSR, Figure 17)



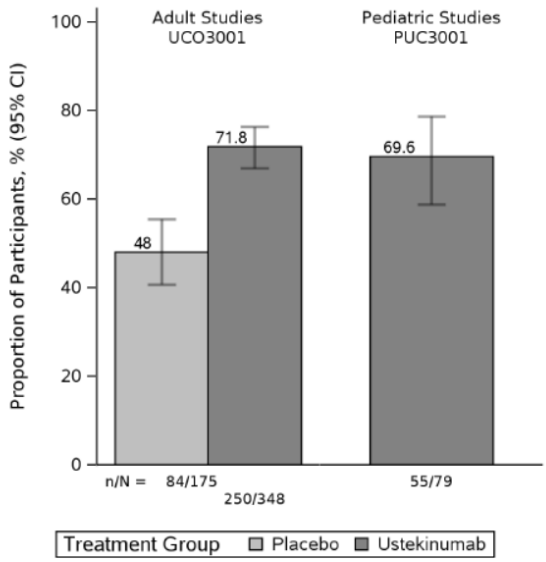
Maintenance Clinical Remission: At Week M-44, the proportion of ustekinumab-treated paediatric participants who achieved clinical remission was similar to that of ustekinumab-treated adult participants in the Phase 3 study CNTO1275UCO3001. The ratio of the proportion of ustekinumab-treated paediatric participants to ustekinumab-treated adult participants in clinical remission at Week M-44 was 0.97 (95% CI: 0.72, 1.31).

Maintenance Symptomatic Remission: At Week M-44, the proportion of ustekinumab-treated paediatric participants who achieved symptomatic remission was similar to that of ustekinumab-treated adult participants in the Phase 3 study CNTO1275UCO3001. The ratio of the proportion of ustekinumab-

treated paediatric participants to ustekinumab-treated adult participants in symptomatic remission at Week M-44 was 1.01 (95% CI: 0.85, 1.21).

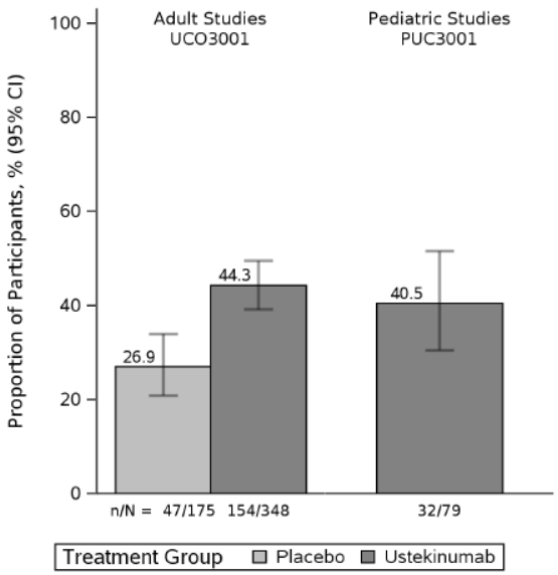
Maintenance Clinical Response: At Week M-44, the proportion of ustekinumab-treated paediatric participants who maintained clinical response (69.6%) was similar to that of ustekinumab-treated adult participants (71.8%).

Figure 36: Secondary Endpoint Clinical Response at Week M-44: Studies CNTO1275UCO3001 and CNTO1275PUC3001; Full Clinical Responder Analysis Set (Study CNTO1275PUC3001) (CSR, Figure 18)



Maintenance Endoscopic Improvement: At Week M-44, the proportion of ustekinumab-treated paediatric participants who achieved endoscopic improvement (40.5%) was similar to that of ustekinumab-treated adult participants (44.3%).

Figure 37: Secondary Endpoint Endoscopic improvement at Week M-44: Studies CNTO1275UCO3001 and CNTO1275PUC3001; Full Clinical Responder Analysis Set (Study CNTO1275PUC3001) (CSR, Figure 19)



Efficacy of endpoints based on serum ustekinumab concentrations: It should be noted that therapeutic efficacy seems to be partially linked with serum ustekinumab levels. Paediatric participants had a step-wise increase in the number of clinical remissions (Quartile <1 – ≥3) at week I-8 and the ≥3rd quartile having the highest proportion responders across all the tested endpoints at M-44. There was low numbers of participants across both adult and paediatric studies in clinical remission in the <1st quartile. Please see comparisons of efficacy based on serum ustekinumab concentrations in the below section.

Figure 38: Bar Chart of Pediatric vs Adult Clinical Remission at Week I-8 by Pediatric Serum Ustekinumab Concentrations Quartiles (micrograms/mL) at Week I-8; PK Analysis Set (Studies CNTO1275PUC3001 and CNTO1275UCO3001) (CSR, Figure 23)

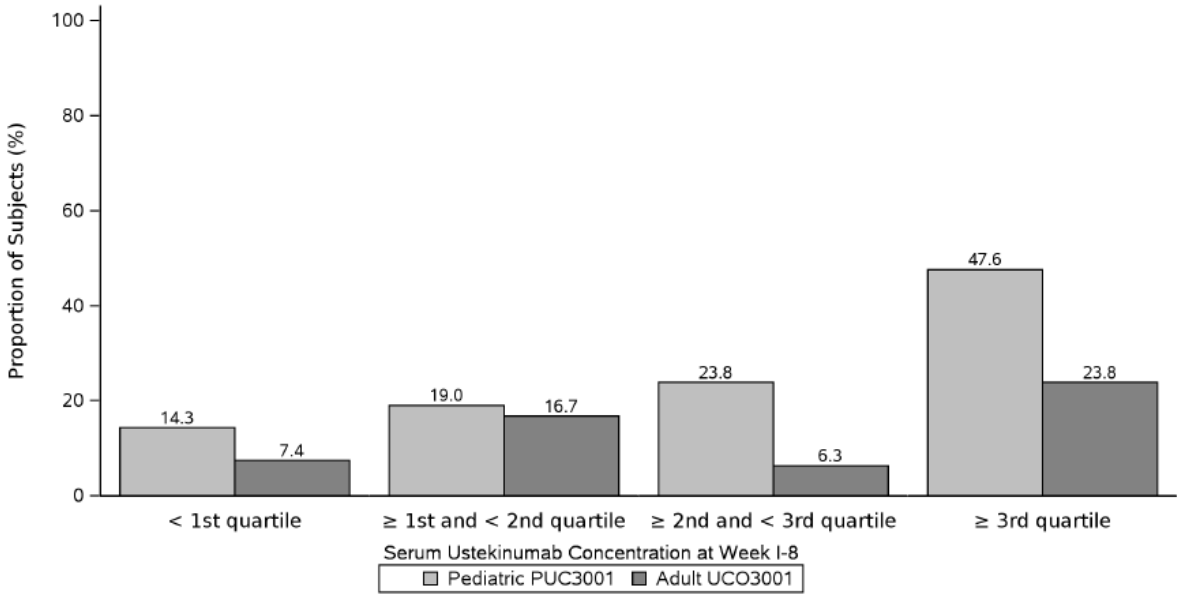


Figure 39: Bar Chart of Pediatric vs Adult Clinical Remission at Week M-44 by Pediatric Serum Ustekinumab Concentrations Quartiles (micrograms/mL) at Average Steady State Trough; PK Clinical Responder Analysis Set (Studies CNTO1275PUC3001 and CNTO1275UCO3001) (CSR, Figure 24)

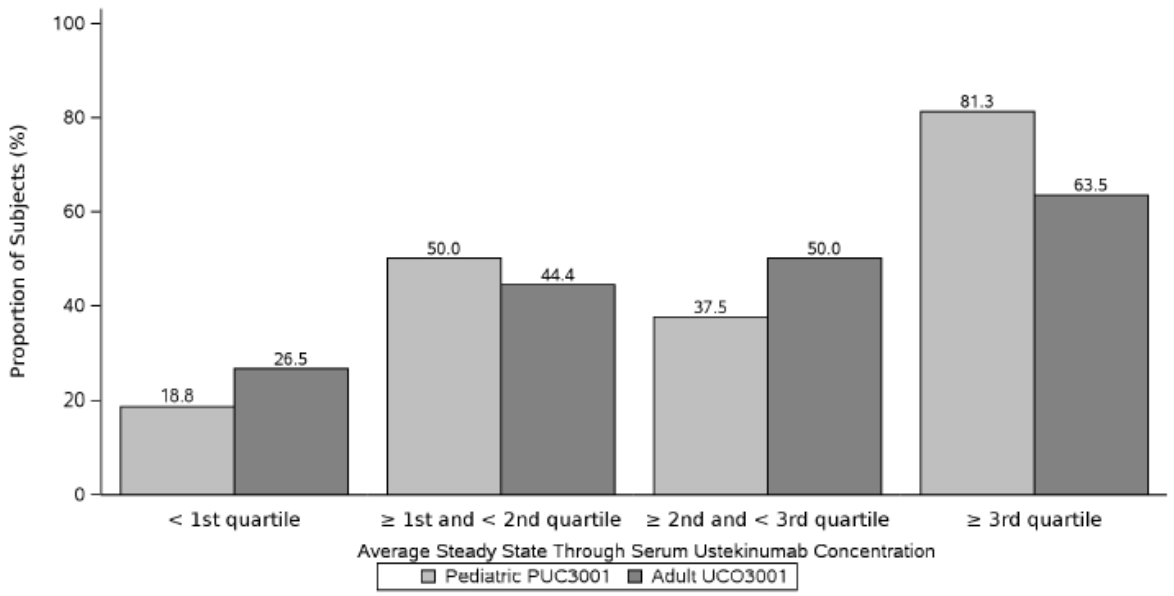
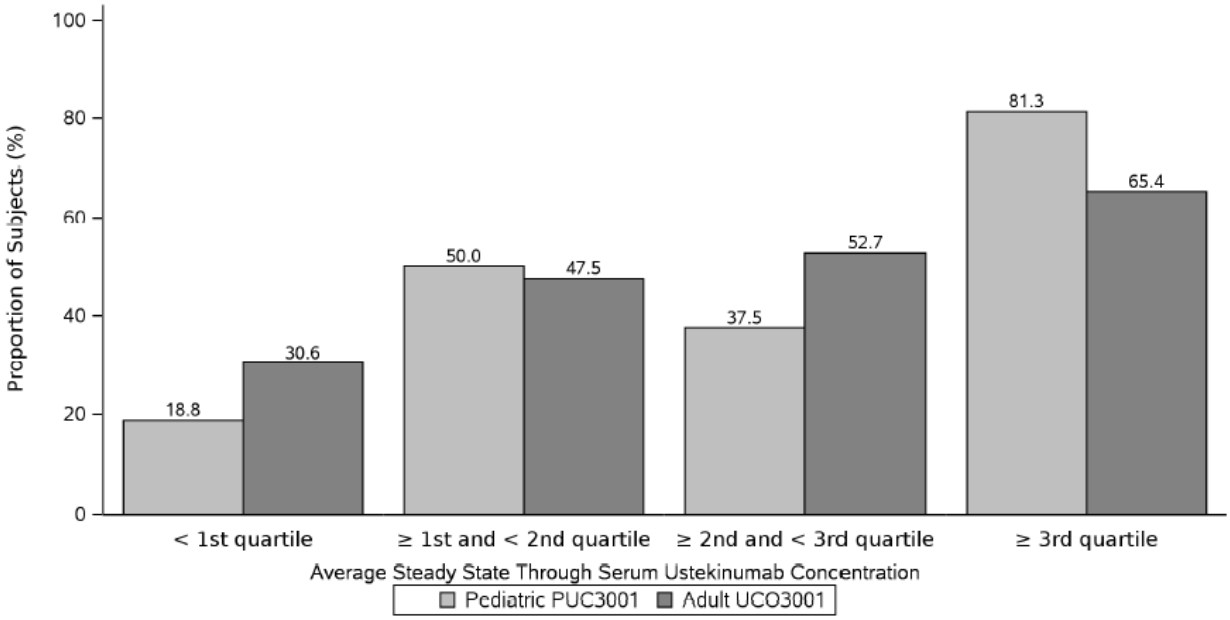


Figure 40: Bar Chart of Pediatric vs Adult Endoscopic Improvement at Week M-44 by Pediatric Serum Ustekinumab Concentrations Quartiles (micrograms/mL) at Average Steady State Trough; PK Clinical Responder Analysis Set (Studies CNTO1275PUC3001 and CNTO1275UCO3001) (CSR, Figure 25)



Analysis performed across trials (meta-analysis)

Meta-analysis was performed to support interpretation of data from the primary paediatric UC study (Study CNTO1275PUC3001/UNIFI Jr) as part of the ustekinumab UC submission.

The objective of the meta-analyses was to compute estimates of the proportions of adult placebo participants in clinical remission and symptomatic remission, and each corresponding 95% CI, at approximately 1 year after study start. The upper bound of the CI for the proportion of adult participants in clinical remission at approximately 1 year after study start was used as the threshold to evaluate the treatment effect.

No formal hypothesis testing was planned.

Methods

The meta-analysis was performed using selected studies from the UCCOD publication database that matched UNIFI Jr study design. The UCCOD fourth quarter 2024 version was used for the identification of studies eligible for selection for the meta-analyses.

A vendor conducted a systematic literature review using PRISMA and Cochrane standards to identify all randomised clinical studies with clinical study results in UC reported in PubMed, clinicaltrials.org, and other sources such as company registries, conference abstracts/posters/presentations, as well as regulatory reviews from FDA and EMA websites.

A second reviewer validated the search strategy against pre-identified references from meta-analyses, company studies, and major clinical studies. Any missed published studies were investigated, and relevant terms were added to the search strategy.

Inclusion Criteria

To estimate the proportion of adult placebo participants in clinical and symptomatic remission along with additional secondary endpoints at approximately 1 year after study start, studies were chosen that met the following hierarchical inclusion criteria:

- Phase 3 global clinical studies.
- Used a landmark endpoint approximately 1 year after study start.
- Randomised withdrawal study design.
- Approved study interventions for the treatment of moderately to severely active UC in adults.
- The placebo group at maintenance was based on responders at the end of the induction period.

AND

Clinical Remission

- The clinical remission endpoint was defined or could be derived based on data as a stool frequency sub score of 0 or 1, a rectal bleeding sub score of 0, and an endoscopy sub score of 0 or 1 with no friability present on the endoscopy, where the stool frequency sub score had not increased from induction baseline (without requiring sustained remission at multiple timepoints).

OR

Symptomatic Remission

- The symptomatic remission endpoint was defined or could be derived based on data as a stool frequency sub score of 0 or 1 and a rectal bleeding sub score of 0, where the stool frequency sub score had not increased from induction baseline.

OR

Secondary Endpoints

- The endpoints defined below were used or could be derived:

a. Clinical response: a decrease from baseline in the Modified Mayo score by ≥30% and ≥ 2 points, with either a decrease from baseline in the rectal bleeding sub score of ≥1 or a rectal bleeding sub score of 0 or 1.

b. Endoscopic improvement: a Mayo endoscopy sub score of 0 or 1 with no friability present on the endoscopy.

c. Corticosteroid-free clinical remission: a Mayo stool frequency sub score of 0 or 1, a rectal bleeding sub score of 0, and an endoscopy sub score of 0 or 1 with no friability present on the endoscopy, where the stool frequency sub score had not increased from induction baseline; and not receiving corticosteroids for at least 90 days prior to Week M-44.

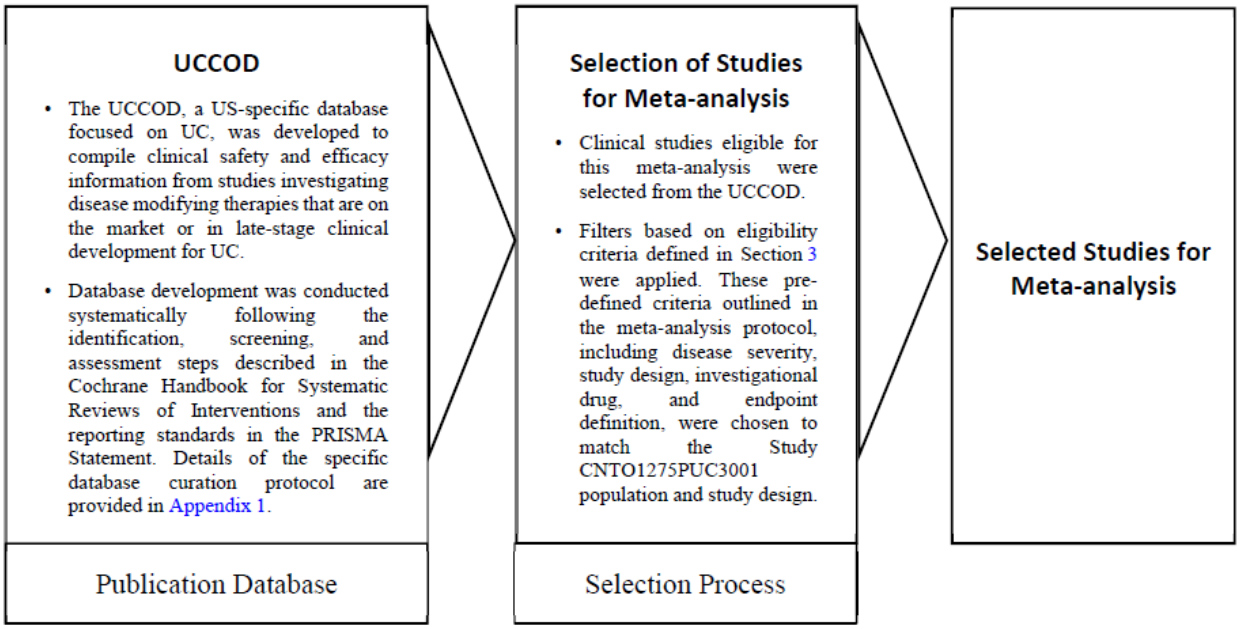
d. Clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44 among participants who received corticosteroids at Week I-0: a Mayo stool frequency sub score of 0 or 1, a rectal bleeding sub score of 0, and an endoscopy sub score of 0 or 1 with no friability present on the endoscopy, where the stool frequency sub score had not increased from induction baseline; and not

receiving corticosteroids for at least 90 days prior to Week M-44 among participants who received corticosteroids at Week I-0.

e. Sustained clinical remission: a Mayo stool frequency sub score of 0 or 1, a rectal bleeding sub score of 0, and an endoscopy sub score of 0 or 1 with no friability present on the endoscopy, where the stool frequency sub score had not increased from induction baseline at M-44 for participants who were in clinical remission at Week I-8.

f. Histologic-endoscopic mucosal improvement: achieving a combination of histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system) and endoscopic improvement (endoscopy sub score of 0 or 1 with no friability present on the endoscopy).

Figure 41: Flow Diagram of Study Selection for Inclusion in the Meta-analysis



Statistical Analysis

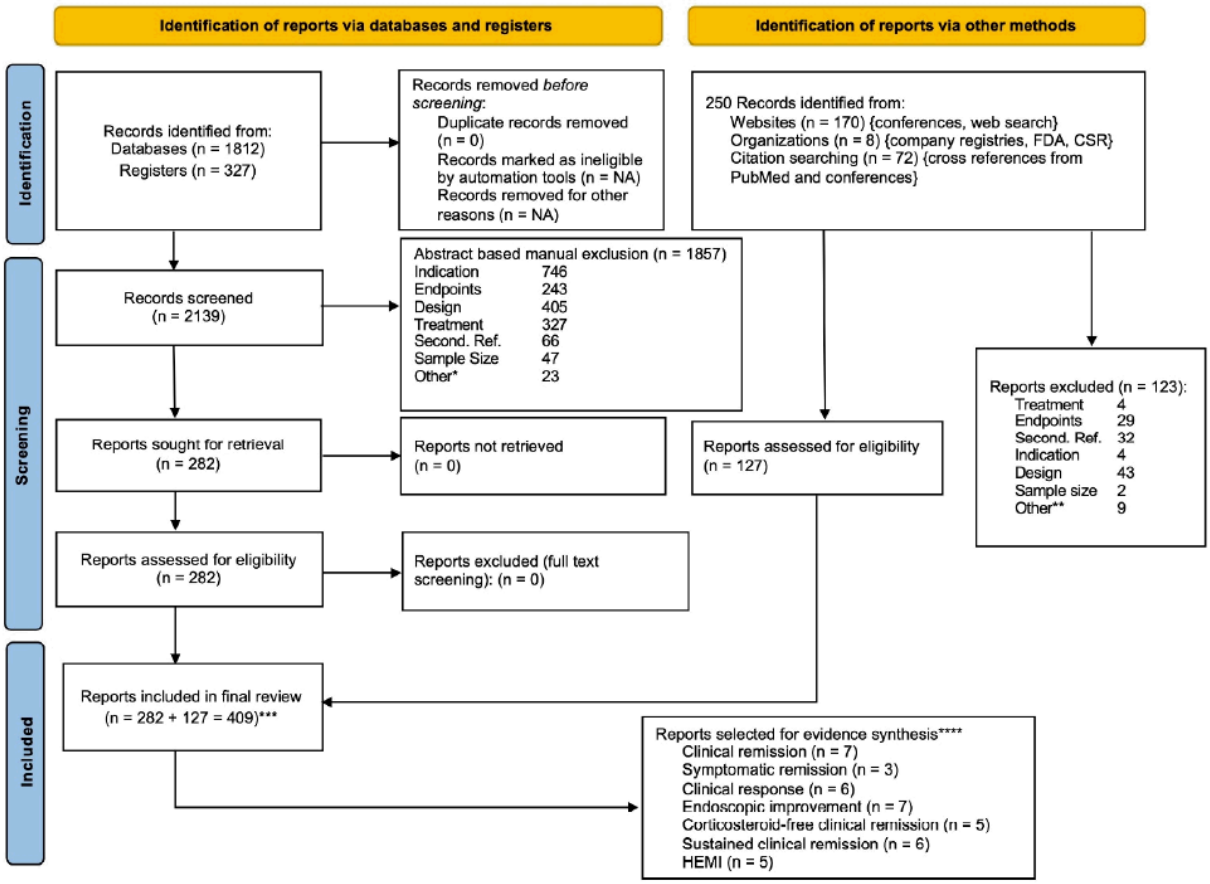
The main meta-analysis of the adult placebo response was based on a random effects model using study sample size as weight, and a supportive analysis using inverse variance as weight was also performed.

Meta-analysis Results

Population

A total of 2,139 records were identified based on the search criteria for studies in the UC indication from databases and clinical study registers, as well as 127 additional records from sources such as conferences and websites. 409 of these records corresponding to 237 unique clinical studies were included in the UCCOD. Out of the 237 studies in the UCCOD, 7 studies were eligible for the clinical remission meta-analysis and 3 for the symptomatic remission meta-analysis.

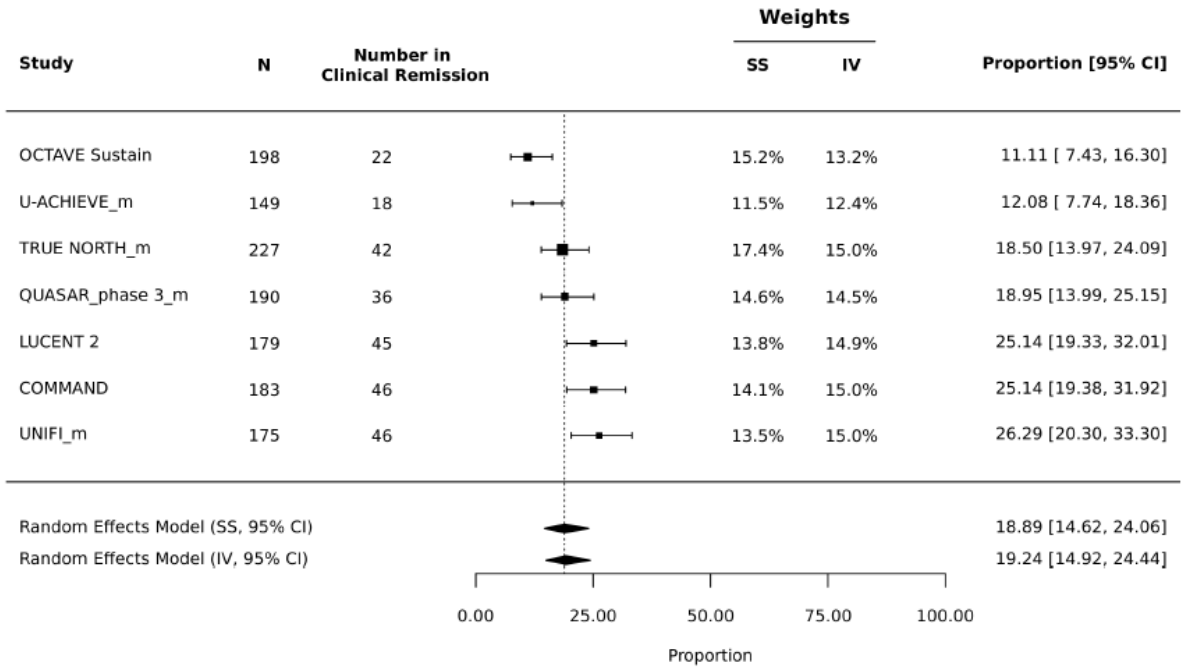
Figure 42: A PRISMA Chart Outlining the Curation Steps



Clinical Remission

The pooled proportion of participants receiving placebo in clinical remission at approximately 1 year after study start based on a random effects model using the REML method with sample size as weights was 18.89% (95% CI: 14.62%, 24.06%).

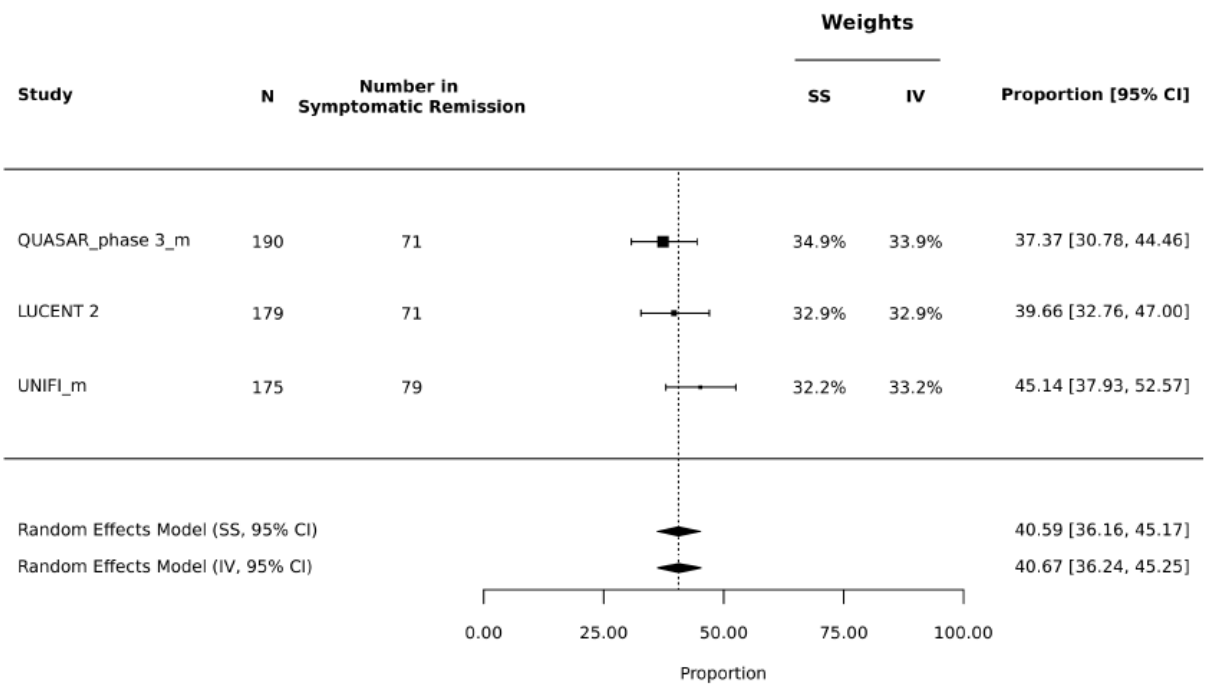
Table 27: Forest Plot of Number of Adult Participants Receiving Placebo in Clinical Remission at Approximately 1 Year After Study Start by Meta-analysis



Symptomatic Remission

The pooled proportion of participants receiving placebo in symptomatic remission at approximately 1 year after study start based on a random effects model using the REML method with sample size as weights was 40.59% (95% CI: 36.16%, 45.17%).

Table 28: Forest Plot of Number of Adult Participants Receiving Placebo in Symptomatic Remission at Approximately 1 Year After Study Start by Meta-analysis



Supplemental Analyses of Secondary Endpoints at Approximately 1 year After Study Start

Table 29: List of Phase 3 Studies Included in the Meta-analysis for the Remaining/Additional Secondary Endpoints at the End of Maintenance

Study (Reference)	Clinical Response	Endoscopic Improvement	Corticosteroid-free Remission	Sustained Clinical Remission	HEMI
OCTAVE Sustain (Sandborn 2017)		X			
U-ACHIEVE_m (Danese 2022)	X	X		X	X
TRUE NORTH_m (Sandborn 2021)	X[a]	X	X	X	
QUASAR_phase 3_m (Rubin 2024)	X	X	X	X	X
LUCENT 2 (Efficacy and safety [miri] 2022; D'Haens 2023)	X	X	X	X	X
COMMAND (Louis 2024)	X	X	X	X	X
UNIFI_m (Sands 2019)	X	X	X	X[b]	X
Number of studies selected	6	7	5	6	5

To note, there was insufficient data to perform the meta-analysis on the endpoint of clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44 among participants who received corticosteroids at Week I-0 was.

Table 30: Forest Plot of Number of Adult Participants Receiving Placebo in Clinical Response at Approximately 1 Year After Study Start by Meta-analysis

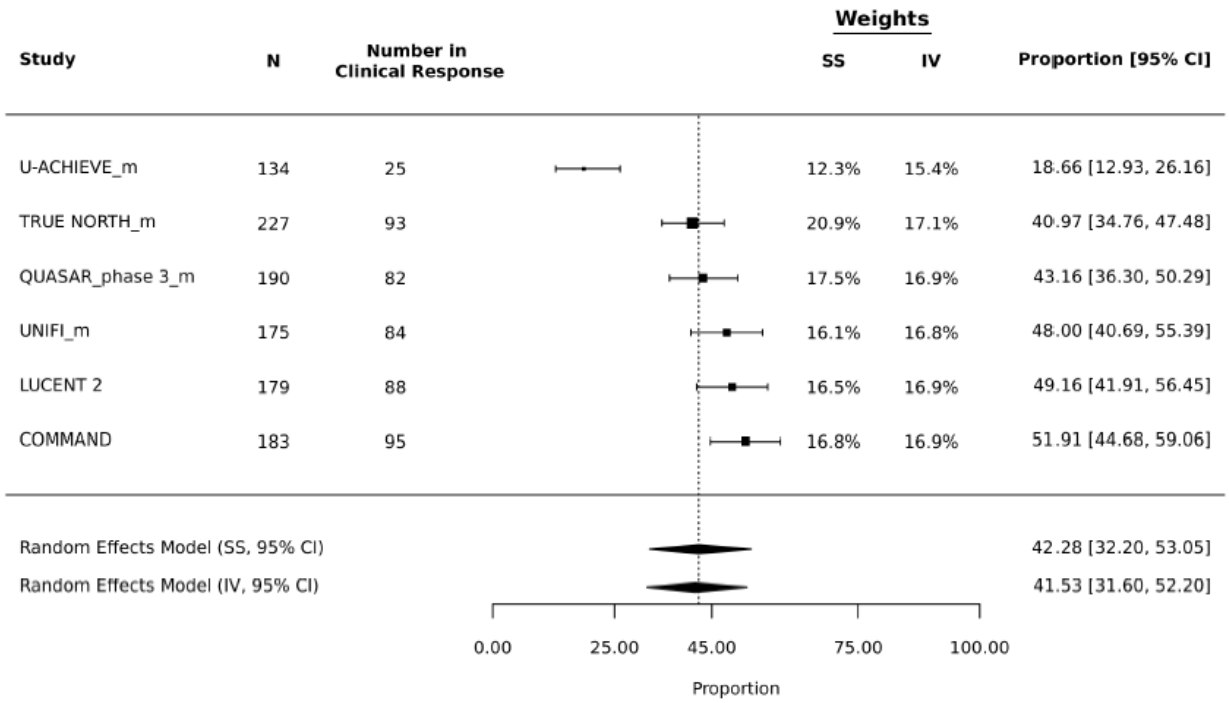


Table 31: Forest Plot of Number of Adult Participants Receiving Placebo in Endoscopic Improvement at Approximately 1 Year After Study Start by Meta-analysis

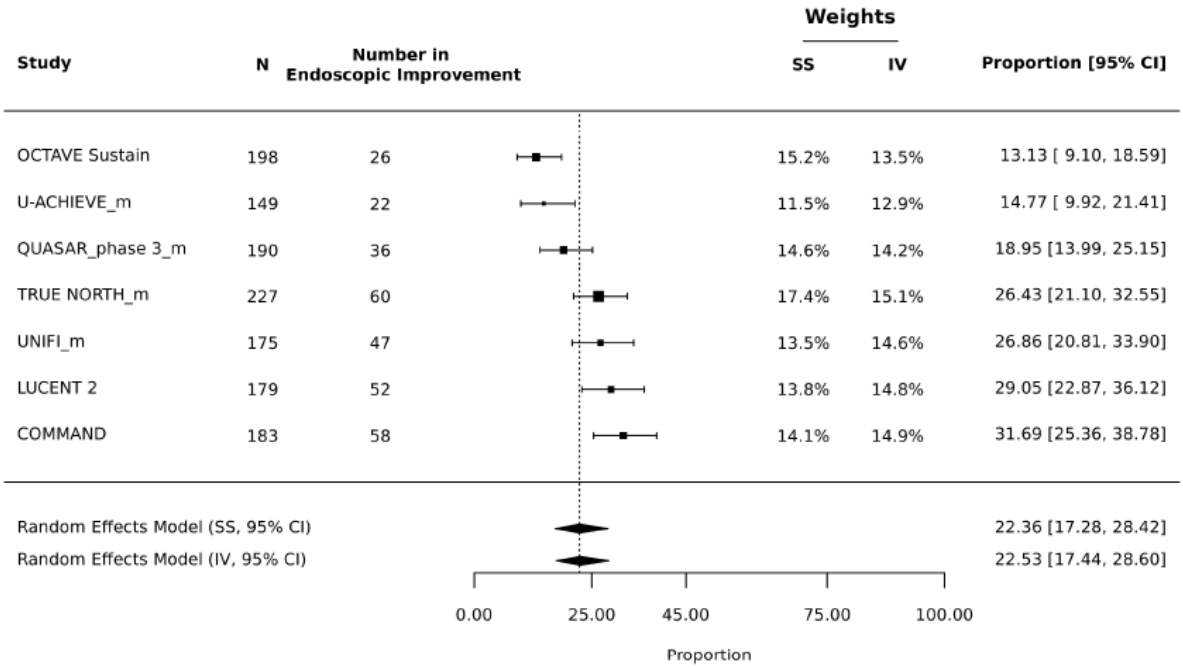


Table 32: Forest Plot of Number of Adult Participants Receiving Placebo in Corticosteroid-free Clinical Remission at Approximately 1 Year After Study Start by Meta-analysis

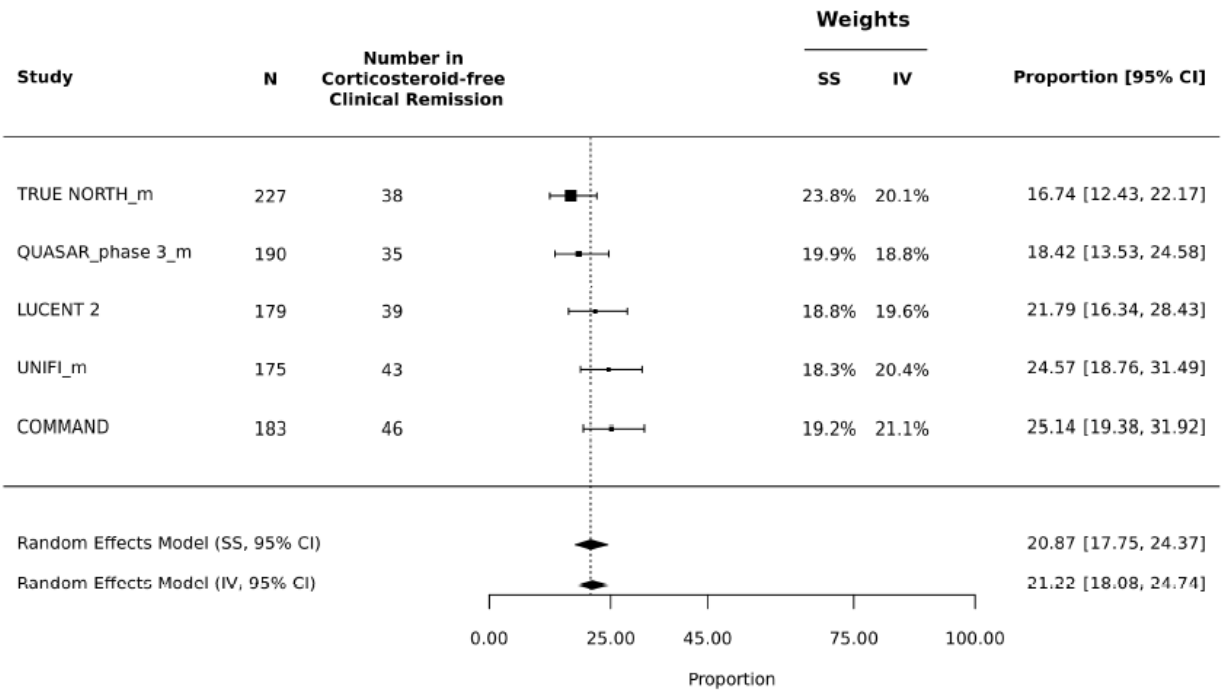


Table 33: Forest Plot of Number of Adult Participants Receiving Placebo in Sustained Clinical Remission at Approximately 1 Year After Study Start by Meta-analysis

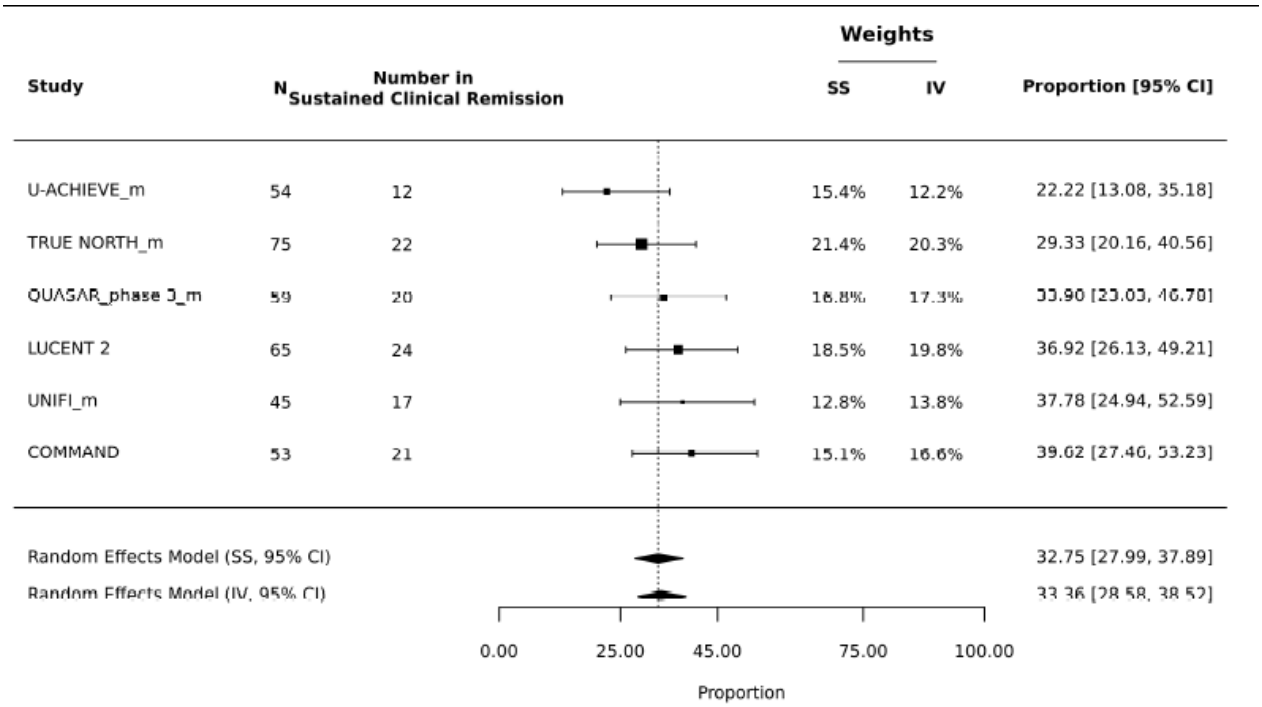
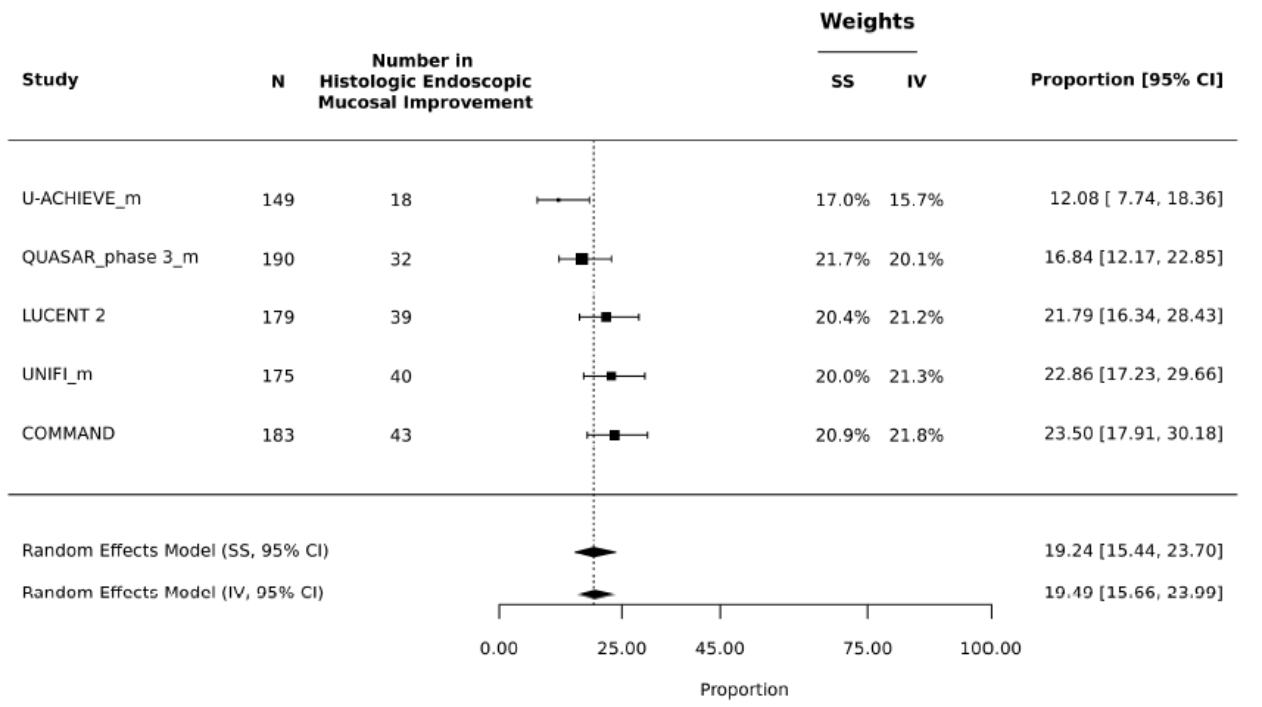


Table 34: Forest Plot of Number of Adult Participants Receiving Placebo in Histologic-Endoscopic Mucosal Improvement at Approximately 1 Year After Study Start by Meta-analysis



Comparison of Adult Placebo Response Rate from Meta-analysis with Paediatric Response Rate from Study UNIFI Jr

For each maintenance endpoint for which the meta-analysis of adult placebo responses was conducted, the upper bound of the 95% CI for the proportion of adult participants on placebo was below the lower

bound of the 95% CI for the proportion of paediatric participants treated with ustekinumab in study UNIFI Jr.

Table 35: Endpoint Comparison Between Adult Participants Receiving Placebo and Paediatric Participants Receiving Ustekinumab

	Proportion of Participants (%) (95% CI)	
Endpoint	**Adult Placebo Meta-analysis from SS Weights[a]**	**Pediatric UC Combined Treatment Group[b]**
Clinical remission	18.9 (14.6, 24.1)	40.5 (30.4, 51.5)
Symptomatic remission	40.6 (36.2, 45.2)	65.8 (54.8, 75.3)
Clinical response	42.3 (32.2, 53.1)	69.6 (58.8, 78.7)
Endoscopic improvement	22.4 (17.3, 28.4)	40.5 (30.4, 51.5)
Corticosteroid-free clinical remission	20.9 (17.8, 24.4)	40.5 (30.4, 51.5)
Sustained clinical remission	32.8 (28.0, 37.9)	59.3 (40.7, 75.5)
HEMI	19.2 (15.4, 23.7)	36.7 (26.9, 47.7)

Summary of main study

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 36. Summary of Efficacy for the clinical trial UNIFI Jr

Title: UNIFI Jr		
Study identifier	CNTO1275PUC3001	
Design	UNIFI Jr was a Phase 3, multicentre, interventional study consisting of an open-label induction period with a single IV ustekinumab 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.	
	Duration of main phase: Duration of run-in phase: Duration of Sub study:	8 weeks in the induction period and 40 weeks in the maintenance period. 6 weeks of screening At least 16 weeks in the optional exposure optimisation sub study (EOS).
Hypothesis	The global primary hypothesis is that ustekinumab is an effective therapy in paediatric participants with moderately to severely active UC. There is no placebo or comparator and so the study is exploratory.	
Treatment groups	Induction	Open-label, 8-weeks, 112 enrolled
	Maintenance	Q8w, 40 weeks, 54 randomised
	Maintenance	Q12w, 40 weeks, 55 randomised
Endpoints and definitions	Primary endpoint	The primary endpoint is clinical remission at Week I-8.

	Secondary endpoints I-8	Clinical response at Week I-8. Symptomatic remission at Week I-8. Clinical remission at Week I-8 as assessed by the PUCAI score. Endoscopic improvement at Week I-8. Histologic-endoscopic mucosal improvement at Week I-8.
	Secondary endpoint M-44	Clinical remission at Week M-44. Symptomatic remission at Week M-44. Clinical remission at Week M-44 as assessed by the PUCAI score. Endoscopic improvement at Week M-44. Corticosteroid-free clinical remission at Week M-44. Clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44 among participants who received corticosteroids at Week I-0. Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8. Histologic-endoscopic mucosal improvement at Week M-44.
Database lock	DBL 1: Occurred after the last participant either completed their Week M-44 visit or terminated study participation prior to Week M-44. DBL 2: Occurred after all participants, including those in the substudy, had completed their study participation.	
Results and analysis		
Analysis description	**Primary analysis**	
Week I-8	Full Analysis Set [FAS]; n=112	
Descriptive statistics and estimate variability	Treatment group	Open Label Induction
	Number of subjects	112
	Clinical remission at Week I-8.	28 participants (25.0%, 95% CI: 17.9%, 33.8%)
	Clinical response at Week I-8.	75 participants (67%, 95% CI: 57.8%, 75%)

	Symptomatic remission at Week I-8.	54 participants; 48.2%, 95% CI: 39.2%, 57.4%),		
	Clinical remission at Week I-8 as assessed by the PUCAI score.	43 participants (38.4%, 95% CI: 29.9%, 47.6%)		
	Endoscopic improvement at Week I-8.	34 participants (30.4%, 95% CI: 22.6%, 39.4%)		
	Histologic-endoscopic mucosal improvement at Week I-8 (GS).	22 participants (19.6%; 95% CI: 13.3%, 28%)		
Week M-44	Full Clinical Responder Analysis Set [FASCR]; n=79			
Descriptive statistics and estimate variability	Treatment group	Q12W	Q8W	Combined
	Number of subjects	40	39	79
	Clinical remission at Week M-44.	13 [32.5%]	19 [48.7%]	32 (40.5%; 95% CI: 30.4%, 51.5%)
	Symptomatic remission at Week M-44.	23 [57.5%]	29 [74.4%]	52 (65.8%; 95% CI: 54.8%, 75.3%)
	Clinical remission at Week M-44 as assessed by the PUCAI score.	23 [57.5%]	28 [71.8%]	43 (64.6%, 95% CI: 53.6%, 74.2%)
	Endoscopic improvement at Week M-44.	13 [32.5%]	19 [48.7%]	32 (40.5%; 95% CI: 30.4%, 51.5%)
	Corticosteroid-free clinical remission at Week M-44.	13 [32.5%]	19 [48.7%]	32 (40.5%; 95% CI: 30.4%, 51.5%)

	Clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44 among participants who received corticosteroids at Week I-0.	7 [41.2%] of 17 participants	9 [56.3%] of 16 participants	16 [48.5%] of 33 induction responders
	Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8.	7 [63.6%] of 11 participants	9 [56.3%] of 16 participants	16 [59.3%] of 27 induction responders
	Histologic-endoscopic mucosal improvement at Week M-44.	11 [27.5%] of 40 participants	18 [46.2%] of 39 participants	29 [36.7%] of 79 induction responders

2.4.3. Discussion on clinical efficacy

The MAH presents a pivotal phase 3 study of ustekinumab in paediatric moderate to severe Ulcerative Colitis patients (Mayo score of 6-12). UNIFI Jr was a multicentre, interventional study consisting of an open-label induction period with a single IV ustekinumab 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.

Design and conduct of clinical studies

The primary endpoint of the trial was clinical remission at week induction 8. Clinical remission was defined by Mayo sub scores as a stool frequency sub score of 0 or 1, a rectal bleeding sub score of 0, and an endoscopy sub score of 0 or 1 with no friability present on the endoscopy, where the stool frequency sub score had not increased from induction baseline. This differs from the adult definition of clinical remission presented in CNTO1275UCO3001 of "Mayo score ≤2 points, with no individual subscore > 1". These differences in the primary endpoint definition of clinical remission between CNTO1275UCO3001 and UNIFI Jr occurred due to updates to health authority guidance over time. The key difference in the UNIFI Jr definition is an explicit requirement of the absence of friability on endoscopy. This is considered acceptable. The MAH has provided a comparison between the CNTO1275UCO3001 definition of clinical remission and UNIFI Jr. This comparison provides evidence that paediatric Ulcerative clinical remission rates using the CNTO1275UCO3001 adult definition is in line with the UNIFI Jr study outcomes (Week I-8: UNIFI Jr 23.2% (16.4%, 31.8%), CNTO1275UCO3001 15.5% (12.0%, 19.9%); Week M-44: UNIFI Jr 39.2% (29.2%, 50.3%), CNTO1275UCO3001 41.1% (36.1%, 46.3%)). There is limited data in the dossier on the comparability of the Mayo-scores and PUCAI scores in the paediatric population, however the scores are found to be similar, with additional information available from the PUCAI score (abdominal pain, stool consistency, activity level, night symptoms) (Shields S, Gut, 2021; Shaoul R, Frontiers in

Pediatrics, 2021). It is agreed that the questions asked in the symptom scores are very similar, and the need to use an identical primary endpoint is generally supported.

This clinical trial is generally in line with the EMA guideline CHMP/EWP/18463/2006 Rev.1 'Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis'. While the MAH has not used the recommended co-primary endpoints targeting symptomatic remission and endoscopic mucosal healing, they have used the more conservative measure of efficacy of clinical remission encompassing both clinically important symptoms and the effect on the inflammatory process via endoscopy. This is in line with what was performed for the adult studies and, as it is a more conservative endpoint, it is therefore considered acceptable.

Endoscopic findings were assessed by the investigator (i.e., local endoscopist) during the endoscopy procedure and by the central reader reviewing a video of the endoscopy. If there was a discrepancy between the local endoscopist and the central reader subscores, the video endoscopy was submitted for adjudication. If a consensus was not reached, by the adjudicator scoring the same as either the central reader or local endoscopist, then the medium value was taken. This is acceptable as it ensures accuracy when evaluating participants.

The key secondary endpoints encompass clinical response, symptomatic remission, PUCAI clinical remission, endoscopic improvement, histologic-endoscopic mucosal improvement, corticosteroid-free clinical remission, and comparative assessments between induction and maintenance periods. All of these endpoints, bar PUCAI, are similar for both adults and paediatric patients.

The inclusion and exclusion criteria were effective to select moderate to severe UC paediatric patients and ensured exclusion of any potentially confounding comorbidities or other IBDs. The trial design included patients either naïve to biologic therapy or previously on biologics and corticosteroid therapy. This accurately represented the clinical setting and accounted for the severity of the disease in the paediatric population.

Regarding the phenotypic characteristics of inflammatory bowel disease in the paediatric population the disease is characterised by extensive intestinal involvement and rapid early progression (Limbergen J, Gastroenterology, 2008), which needs to be considered when using extrapolation between adults, adolescents and children in this population, but also impacts on the B/R including a greater unmet need in the paediatric population, due to a more limited option of treatments available. Extrapolation has also been applied in the application for the use of ustekinumab in the treatment of Crohn's disease in the paediatric population.

It is acknowledged that moderately to severely active ulcerative colitis in the youngest and lightest children is a rare condition, leading to feasibility issues when conducting clinical trials in this patient population. Thus, the presented study was designed as part of a paediatric extrapolation plan to evaluate efficacy, safety and PK.

No statistical comparisons were made as there was no placebo arm or comparator group, in line with EMA recommendations for UC trial design in paediatric populations (CHMP/EWP/18463/2006 Rev.1), and all the results were descriptive. The MAH has provided comparisons with adult populations to both placebo and ustekinumab intervention groups. ICEs are handled by a composite approach (not considered to have achieved clinical remission by I-8), except discontinuation due to COVID-19 which is handled by a hypothetical approach (missing data). Due to the descriptive nature of the statistical analysis, these are considered appropriate for handling ICEs.

Patients received placebo administrations to maintain the blind given the different frequencies of administration during the maintenance phase. Blinding and randomisation procedures were appropriate.

The doses proposed in the SmPC for paediatric patients are in line with the adult population for patients ≥40kg. For those below 40kg, an identical treatment plan to the extension of indication (EOI) for paediatric Crohn's Disease (EMA/VR/0000290099) has been proposed (mg/m^2 BSA). This dosing strategy was previously evaluated in a phase 1 clinical trial CNTO1275CRD1001 and is further assessed in both paediatric Crohn's Disease CNTO1275CRD3004 and in this pivotal trial UNIFI Jr.

While the sample size was small, this can be accepted as this is an EOI application and a lot of data is to be leveraged from the adult population who are known to have a similar disease profile. Although, it is to be noted that paediatric UC tends to be more aggressive than UC in adults.

Efficacy data and additional analyses

In the initial PIP (EMEA-000311-PIP05-17) it was decided that at least 90 subjects evaluable for the primary analysis, at least 24 subjects <40kg and at least 5 subjects <30kg should be included. This has been fulfilled (total n=112, here of n=33 <40kg and n=15 <30kg). Overall, the trial design is generally accepted, and the clinical trial has been performed broadly in line with that agreed in the PIP.

There was a total of 109 participants randomised to maintenance treatment, q12w (n=55) or q8w (n=54), at 32 study sites across 8 countries. 14 (12.8%) of 109 participants discontinued study due to Early escape and Lack of efficacy (3 participants each, 2.8%) with the remaining reasons accounting for <2% each. A higher proportion of participants discontinued study treatment in the q12w treatment group (9, 16.4%) compared to the q8w treatment group (5, 9.3%).

10 (9.2%) of 109 randomised participants terminated study participation due to withdrawal by parent or guardian (6, 5.5%), withdrawal by participant (3, 2.8%), and Other (1, 0.9%). More participants in the q12w treatment group (7, 12.7%) than the q8w treatment group (3, 5.6%) terminated study participation.

Of the 109 participants randomised to the maintenance treatment, 22 were enrolled into the exposure optimisation substudy (EOS) (4 [3.7%] participants who were induction nonresponders with low ustekinumab exposure levels who met the early escape criteria by Week M-8 and 18 [18.6%] participants who experienced a confirmed LOR and had low ustekinumab exposure levels) to receive q4w dosing. Only 21 participants entered the substudy analysis set and out of these, 6 (28.6%) discontinued treatment during the EOS (5 participants from the q12w treatment group and 1 participant from the q8w treatment group). The reasons for EOS treatment discontinuation included lack of efficacy (3 participants from q12w and 1 from q8w), AE of worsening UC, and Other.

A total of 20 (17.9%) of 112 study participants and 33 (30.3%) of 109 randomised participants had a major protocol deviation (MPD) during the induction and maintenance periods, respectively. The most common MPDs during both the induction and maintenance periods were classified as "other" (14.3% and 29.4%, respectively). Most of the "other" deviations were due to missing faecal samples, out of window visits, and insufficient diaries completed. Some of these deviations are accounted for in the sensitivity analysis of the primary endpoint, encompassing missing data. While out of window visits is not optimal, these are unlikely to affect the primary endpoint analysis as there is no comparator group.

During the maintenance period, 3 participants received a disallowed concomitant treatment. Two participants in the q12w treatment group initiated rescue therapy (1 participant received rectal budenofalk during induction and 1 participant received budenoside without meeting the LOR criteria), and 1 participant in the q8w treatment group failed to taper steroids after LOR as per protocol. This does not affect the final clinical assessment due to the ICE associated with prohibited changes in UC medications.

Baseline characteristics were generally balanced between the two arms of the study; however mean BMI z-scores (SD) were numerically lower in the q8w treatment group (-0.24 [0.692]) compared with the

q12w treatment group (-0.02 [0.985]). This difference does not have an impact on efficacy assessment as posology is based on body weight (≥40kg) or BSA (<40kg).

The sample size in the younger age groups (2 to <6 years of age (n=3)) and the <30 kg (n=13) and ≥30 to <40 kg (n=14) weight subgroups were too small for the induction responder population to draw any meaningful conclusions on efficacy outcomes. This limitation in the study has now been included in the SmPC.

There were too few participants who were delayed responders at Week M-8 (n=18) to draw any meaningful conclusions.

The median duration of disease was 1.2 years (0-11 years) with the majority of participants having extensive UC (67.0%) compared with UC being limited to the left side of the colon (33.0%). 91.7% of participants had moderate disease and 7.4% of participants had severe disease based on the Mayo score (Endoscopy subscore showing 54.1% being moderate while 45.9% being severe). This is below the estimated occurrence of severe UC in paediatrics of around 10% but is similar to another drug with a similar indication, adalimumab.

Nearly every participant had abnormal faecal lactoferrin (97.8%) and abnormal fecal calprotectin (96.7%) levels. Paediatric patients typically present with a more severe form of ulcerative colitis than adults and so this disease demographic representation is considered appropriate.

In general, the baseline UC disease characteristics for the q12w and q8w treatment groups were similar with no notable differences.

No participant missed an ustekinumab administration from Week I-0 through Week M-44.

A total of 108 (96.4%) of 112 participants had a complete Mayo score at Week I-0. Three participants each were missing subscores for stool frequency and rectal bleeding, while 1 participant was missing the PGA score because the score was entered after the visit and did not transfer correctly.

The majority (93.8%) of participants were receiving UC-related concomitant medications. The most frequently used concomitant medication across the combined q12w and q8w treatment groups was oral 5-ASA (74.1% of participants). Proportions were similar across the q12w and q8w treatment groups. Baseline UC-related concomitant medication use for all responders (both induction and delayed responders) was similar to those in the overall study population.

Primary Endpoint

Efficacy analyses were based on all study participants (Full Analysis Set [FAS]; n=112) for endpoints through Week I-8 and the induction responders (Full Clinical Responder Analysis Set [FASCR]; n=79) for endpoints from Week M-0 through Week M-44.

The global primary endpoint was clinical remission at Week I-8 in which 28 participants (25.0%, 95% CI: 17.9%, 33.8%) achieved clinical remission. Supplementary and sensitivity analyses performed for the global primary endpoint provided similar results as the primary analysis.

Consistency of treatment effect was evaluated in subgroups of demographics, UC disease characteristics, UC-related concomitant medication usage and UC-related medication history using the Global Primary Estimand. At Week I-8, clinical remission proportions were numerically higher among participants with weight <40 kg (11 [32.4%; 95% CI: 19.1%, 49.2%] of 34 participants) compared with participants with weight ≥ 40 kg (17 [21.8%; 95% CI: 14.1%, 32.2%) of 78 participants) and participants without biologic failure (20 [29.4%; 95% CI: 19.9%, 41.1%] of 68 participants) compared with participants with biologic failures (8 [18.2%; 95% CI: 9.5%, 32.0%) of 44 participants), although the CIs overlapped.

Secondary Endpoints

At Week I-8, the proportions of ustekinumab-treated paediatric participants who achieved clinical response was 75 participants; (67%, 95% CI: 57.8%, 75%), symptomatic remission occurred in 54 participants; (48.2%, 95% CI: 39.2%, 57.4%), and endoscopic improvement occurred in 34 participants; (30.4%, 95% CI: 22.6%, 39.4%).

At week I-8 the PUCAI score showed 43 participants attained clinical remission (38.4%, 95% CI: 29.9%, 47.6%), however, since there is no comparator, this is purely used to support the primary endpoint. Histologic-endoscopic mucosal improvement based on GS and RHI at week I-8 showed 22 participants (19.6%; 95% CI: 13.3%, 28%) and 20 participants (17.9%; 95% CI: 11.9%, 26%) had improvement respectively while 36.7% (95% CI: 26.9%, 47.7%) and 30.4% (95% CI: 21.3%, 41.2%) had improvement at week M-44 respectively.

Similar analyses were performed for the two treatment arms of the maintenance period to assess long-term treatment efficacy. At Week M-44, 32 (40.5%; 95% CI: 30.4%, 51.5%) of 79 induction responders in the combined treatment group (q12w: 13 [32.5%] of 40 participants; q8w: 19 [48.7%] of 39 participants) achieved clinical remission and 52 (65.8%; 95% CI: 54.8%, 75.3%) of 79 induction responders in the combined treatment group (q12w: 23 [57.5%] of 40 participants; q8w: 29 [74.4%] of 39 participants) achieved symptomatic remission. Numerically higher (>10%) response rates were observed for induction responders in the q8w treatment group compared with those in the q12w treatment group for most secondary endpoints.

At week M-44 the PUCAI score in the combined treatment showed 43 participants (64.6%, 95% CI: 53.6%, 74.2%) attained clinical remission (q12w: 23 [57.5%] of 40 participants; q8w: 28 [71.8%] of 39 participants). 90-day Corticosteroid-free Clinical Remission at Week M-44 was apparent in 32 participants (40.5%; 95% CI: 30.4%, 51.5%) (q12w: 13 [32.5%] of 40 participants; q8w: 19 [48.7%] of 39 participants). Endoscopic Improvement at Week M-44 was seen in 32 participants (40.5%; 95% CI: 30.4%, 51.5%) (q12w: 13 [32.5%] of 40 participants; q8w: 19 [48.7%] of 39 participants).

There was increased participant withdrawal in the q12w treatment group and, along with the improved treatment effect in the q8w treatment group compared to q12w, this would question why SmPC posology indicates patients' maintenance treatment aligns with q12w. However, this is considered justified in the paediatric population as it aligns with adult posology, there is a reduction in injection frequency, slightly reduced rates of SAEs, cost reduction to improve accessibility, and q12w has shown to be sufficiently effective in both paediatric and adults. Furthermore, there is a recommendation to increase dosing frequency should there be a lack of therapeutic efficacy (SmPC section 4.2).

Further Endpoints

As clinical remission is the primary endpoint, to show the robustness of the data the MAH assessed it using 3 alternative definitions at both week I-8 and M-44. This ranged from 19.6% - 25% for I-8 and 27.8% - 40.5% for M-44 (these lower values of 19.6% and 27.8% are due to the increased specificity for clinical remission, enhancing the requirements of the Mayo stool frequency subscore from 0 or 1 to 0).

The MAH also assessed the number of induction responders who were in clinical remission (16 of 79 participants, 20.3%) at both week I-8 and M-44. There was also a large proportion of induction responders who maintained symptomatic remission (36 of 51 participants, 70.6%%) and clinical remission by PUCAI score (32 of 41 participants, 78%) for the duration of the study.

There was a consistent reduction in mean and median Mayo score, modified Mayo score, partial Mayo score, and either a steady or improved reduction in Mayo subscores from baseline to week I-8 and through to week M-44.

At Week I-8, 10 (8.9%: 95% CI: 4.9%, 15.7%) of 112 participants in the study achieved endoscopic normalisation (an endoscopy subscore of 0). At Week M-44, 15 (19.0%; 95% CI:11.9%, 29.0%) of 79 induction responders in the combined treatment group achieved endoscopic normalisation.

The average daily prednisone-equivalent corticosteroid dose was decreased at Week I-8 and Week M-44, indicating a reduction in corticosteroid dependence. At Week I-8, the mean (SD) prednisone-equivalent corticosteroid dose was 2.9 (8.55) compared with 5.6 (12.54) at baseline. At Week M-44, the mean (SD) reduction in average daily corticosteroid use from baseline for the combined treatment group was -3.8 (9.7).

At Week M-44, change from baseline BMI z-scores showed an increase in both the q12w and q8w treatment groups. At Week M-44 in the combined treatment group, iron serum values shifted from low to normal for 21 of 58 participants, remained normal for 15 participants, and shifted from normal to low for 4 participants. At Week M-44 in the combined treatment group, 25-hydroxyvitamin D values shifted from low to normal for 7 of 56 participants, remained normal for 36 participants, and shifted from normal to low for 4 participants. At Week M-44 in the combined treatment group, MMA values stayed normal (0 to 378 nmol/L) for 55 of 57 participants and improved from high to normal for 1 participant.

As a measure of inflammation, the mean (SD) and median change from baseline in CRP concentrations was -2.75 (12.161) mg/L and -0.45 mg/L, respectively at week I-8. Additionally, among the 42 participants with elevated CRP levels (>3 mg/L) at Week I-0, 21 (50.0%) participants had normalised CRP levels (≤3 mg/L) at Week I-8. Similar trends occurred up to week M-44 with the mean (SD) and median change in CRP concentrations being -3.67 (13.911) mg/L and 0.00 mg/L, respectively. Among the 89 participants with abnormal faecal calprotectin levels (>250 mg/kg) at Week I-0, 20 (22.5%) participants had normalised faecal calprotectin levels (≤250 mg/kg) at Week I-8. At M-44, the mean (SD) and median change from Week I-0 in faecal calprotectin of -2427.6 (4593.26) mg/kg and -899.0 mg/kg, respectively.

The IMPACT III score is a health-related quality of life (HRQoL) measure specifically designed for paediatric patients with inflammatory bowel disease (IBD), assessing various aspects of their health and well-being. The IMPACT-III total score ranges from 35 to 175 with a higher score indicating that patients have a good overall health related quality of life (HRQoL). The MAH indicates that 0.5 SD as reasonable threshold for establishing clinically meaningful improvement in HRQoL concepts (Homco 2019; Norman 2003). Mean change scores for the combined treatment group (≥10 years of age) indicated that total score improvement from baseline in the IMPACT-III approached 1 SD at Week I-8 (21.6) and exceeded 1 SD at Week M-44 (26.3). To note, the Homco 2019 reference paper relates to the PROMIS-29 survey while the Norman 2003 reference encompasses a wide range of PROs. In lieu of a placebo or comparator group, this is an acceptable method of determining clinical relevance.

TUMMY-UC has been used as a surrogate PRO HRQoL for particpants aged ≥8 years to compensate for the lack of validated paediatric PROs in children aged ≤10 years. During induction, TUMMY-UC scores improved in participants ≥8 years at Week I-8 compared with baseline, with a mean (SD) change from baseline of -34.3 (28.98). This improvement in TUMMY-UC scores was maintained in induction responders ≥8 years old at Week M-44, with a mean (SD) change from baseline of -39.2 (25.90) for the combined treatment group. While this is not a validated PRO HRQoL, it is a sutiable alternative for the purposes of this study and is in line with the improvements in PRO HRQoL seen with IMPACT III. To note, baseline values were not recorded for participants <8 years (Observer TUMMY-UC), and there were too few participants <8 years with data at Week I-8 and Week M-44 (n=2 at both Week I-8 and Week M-44) to draw any meaningful conclusions for this age group.

Subgroup analysis

Subgroup analyses by baseline age and weight were performed to examine the consistency of the key efficacy endpoints of clinical remission, clinical response, symptomatic remission, clinical remission defined by PUCAI score, endoscopic improvement, and histologic-endoscopic mucosal improvement.

At Week I-8, clinical remission proportions were numerically higher among participants with weight <40 kg (11 [32.4%; 95% CI: 19.1%, 49.2%] of 34 participants) compared with participants with weight ≥ 40 kg (17 [21.8%; 95% CI: 14.1%, 32.2%) of 78 participants) and participants without biologic failure (20 [29.4%; 95% CI: 19.9%, 41.1%] of 68 participants) compared with participants with biologic failures (8 [18.2%; 95% CI: 9.5%, 32.0%) of 44 participants), although the CIs overlapped.

Across every assessed key endpoint, ustekinumab was less effective at M-44 in the 2-<12 age group (N=22) compared to the 12-<18 age group (N=57). For participants 2-<6 years, there was only an N of 3. For Week I-8, results were similar across key efficacy endpoints in the 2-<12 age group when compared to the 12-<18 age group.

Across every assessed key endpoint, ustekinumab was less effective at M-44 in participants weighing <30kg (N=13) compared to those weighing ≥30-<40kg (N=14) (same dosing strategy induction 250 mg/m^2 and maintenance 60 mg/m^2). A similar trend occurred for participants weighing <40kg (N=27) compared to those weighing ≥40kg (N=52) bar "Subjects in clinical remission as assessed by the PUCAI score".

Similar to the previous OC in regards to low sample size in the younger age groups, the <30 kg (n=13) and ≥30 to <40 kg (n=14) weight subgroups were too small for the induction responder population to draw any meaningful conclusions on efficacy outcomes, the MAH has included information in the SmPC section 5.1 for the low numbers within these subgroups and this is considered acceptable.

A total of 7 (6.4%) of 109 randomised participants had a dose adjustment (5 participants who dose-adjusted to ustekinumab q8w and 2 participants who received a sham adjustment). Due to the small sample size, no conclusions can be drawn on the impact of dose adjustment. However, based on the improved efficacy seen in the q8w cohort, and in line with adult posology at maintenance, a dose adjustment of q12w to q8w is deemed to be appropriate for LOR in paediatric patients. These low numbers are reflected in the SmPC section 5.1 already.

Exposure Optimisation Substudy

Participants who experienced a LOR or were induction nonresponders with low 8-week steady state trough ustekinumab exposure of <1.4 μg/ml were eligible to enroll in the optional q4w EOS (assessed at Week M-8 or Week M-32).

Of the 21 participants in the Substudy Analysis Set, 16 (76.2%) completed the EOS. A total of 6 (28.6%) of 21 participants discontinued treatment during the EOS. Only 13 participants completed the EOS up to Week 16.

Unfortunately, data is limited in this population and the primary endpoint was not tested. Based on the limited information, 84.6% achieved clinical response based on the partial Mayo score, 56.3% achieved clinical remission based on the PUCAI score; mean (SD) and median changes from entry in the partial Mayo score at Substudy Week 16 were -3.8 (2.39) and -4.5, respectively, and the mean (SD) and median changes from entry into the EOS in the PUCAI score at Substudy Week 16 were -43.4 (18.32) and -47.5, respectively.

It should be noted that therapeutic efficacy seems to be partially linked with serum ustekinumab levels. Paediatric participants had a step-wise increase in the number of clinical remissions (Quartile <1 – ≥3) at week I-8 and the ≥3rd quartile having the highest proportion of participants in clinical remission at M-44.

There was low numbers of participants across both adult and paediatric studies in clinical remission in the <1st quartile. Please see comparisons of efficacy based on serum ustekinumab concentrations in the below section.

There is limited information available for the change in dosing frequency to q4w as it was not performed in an adult population, however, this is in line with paediatric Chrons' Disease indication and is considered acceptable.

Extrapolation Plan

The MAH presented an extrapolation plan with their submission of this extension of indication to leverage the adult results, along with the paediatric studies, to determine clinical efficacy. The MAH provided a comparison between baseline UC disease characteristics between adult and paediatric populations from CNTO1275UCO3001 and UNIFI Jr. It identified that the median UC disease duration was 6.03 years in adults and 1.22 years in pediatrics while the baseline Mayo scores were 9.0 in adults and 8.0 in pediatrics. Extensive UC was observed in a lower proportion of adults than in pediatrics (47.8% vs 67.0%), consistent with the tendency for pediatric UC to be more extensive than adult-onset UC. Corticosteroid use was increased in adults (51.8%) when compared to pediatrics (43.8%), however, immunomodulatory drug use was lower in adults (28.2%) when compared to pediatrics (39.3%). These baseline disease characteristics indicate an acceptable level of comparability between the adult and pediatric population.

As UC is similar in adults and paediatrics, the MAH has performed an indirect comparison between the CNTO1275UCO3001 and UNIFI Jr studies. To note, the information is purely descriptive and contains no formal statistical analysis. Comparative efficacy is being described by ratio comparisons between ustekinumab-treated paediatric participants and ustekinumab-treated adult participants.

The ratio of the proportion of ustekinumab-treated paediatric participants to ustekinumab-treated adult participants in clinical remission at Week I-8 was 1.30 (95% CI: 0.88, 1.92).

The ratio of the proportion of ustekinumab-treated paediatric participants to ustekinumab-treated adult participants in symptomatic remission at Week I-8 was 1.08 (95% CI: 0.86, 1.35).

The ratio of the proportion of ustekinumab-treated paediatric participants to ustekinumab-treated adult participants in clinical remission at Week M-44 was 0.97 (95% CI: 0.72, 1.31).

The ratio of the proportion of ustekinumab-treated paediatric participants to ustekinumab-treated adult participants in symptomatic remission at Week M-44 was 1.01 (95% CI: 0.85, 1.21).

Clinical response and endoscopic improvement was numerically higher in paediatrics than adults at I-8 (9.2% and 6.6% increase over adults respectively). The inverse was true at M-44 with clinical response and endoscopic improvement being numerically lower in paediatrics than adults (-2.2% and -3.8% respectively).

Considering the similarities in responsiveness to ustekinumab between paediatrics and adults, the extrapolation of data is acceptable.

Meta-analysis

Meta-analysis was performed to support interpretation of data from the primary paediatric UC study.

The objective of the meta-analyses was to compute estimates of the proportions of adult placebo participants in clinical remission and symptomatic remission, and each corresponding 95% CI, at approximately 1 year after study start. The upper bound of the CI for the proportion of adult participants in clinical remission at approximately 1 year after study start was used as the threshold to evaluate the treatment effect.

The meta-analysis was performed using selected studies from the UCCOD publication database that matched UNIFI Jr study design.

Studies were chosen that met the following hierarchical inclusion criteria:

- Phase 3 global clinical studies.
- Used a landmark endpoint approximately 1 year after study start.
- Randomised withdrawal study design.
- Approved study interventions for the treatment of moderately to severely active UC in adults.
- The placebo group at maintenance was based on responders at the end of the induction period.

There were also specific inclusion criteria for each of the following key study endpoints of clinical remission, symptomatic remission, clinical response, endoscopic improvement, corticosteroid-free clinical remission, clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44, sustained clinical remission, and histologic-endoscopic mucosal improvement which followed the definitions of each as outlined in UNIFI Jr.

The main meta-analysis of the adult placebo response was based on a random effects model using study sample size as weight, and a supportive analysis using inverse variance as weight was also performed. 237 unique clinical studies were included in the UCCOD. Out of the 237 studies in the UCCOD, 7 studies were eligible for the clinical remission meta-analysis and 3 for the symptomatic remission meta-analysis.

There was insufficient data to perform the meta-analysis on the endpoint of "clinical remission at Week M-44 and not receiving corticosteroids for at least 90 days prior to Week M-44 among participants who received corticosteroids at Week I-0".

For each maintenance endpoint for which the meta-analysis of adult placebo responses was conducted, the upper bound of the 95% CI for the proportion of adult participants on placebo was below the lower bound of the 95% CI for the proportion of paediatric participants treated with ustekinumab in study UNIFI Jr.

It should be noted that there is no information on the spontaneous rate of paediatric clinical remission, symptomatic remission, and the aforementioned secondary endpoints. This limits the ability to directly compare as it is not known if these are similar between the adult and paediatric populations. The MAH was requested to provide comment on the lack of information on spontaneous rate of paediatric clinical remission, symptomatic remission, and secondary endpoints in the context of the meta-analysis comparison between treated pediatric participants from UNIFI Jr and placebo adult control from selected clinical trials. They identified a lack of placebo-controlled data due to ethical challenges in clinical trial design for pediatric participants and that the only identified clinical trial, ENVISION 1 for Ulcerative Colitis in pediatrics, terminated the placebo group early due to lack of enrolment. This is considered acceptable and the issue is not pursued further.

2.4.4. Conclusions on the clinical efficacy

The extension of indication variation application to include paediatric patients can accommodate an unmet need for the treatment of moderately to severely active ulcerative colitis inpatients from the age of 2 years and older, who have had an inadequate response to, or were intolerant to either conventional therapy or a biologic. The study is designed as part of a paediatric extrapolation plan to evaluate efficacy, safety and PK. For the efficacy the primary endpoint 'clinical remission at Week I-8' and secondary endpoint 'clinical remission at week M44' it is found that generally the response rates are similar to the

outcomes in the adult population. The occasional divergent outcomes in the youngest and lightest children are expected to be due to the limited number of patients.

Thus, the claimed indication is supported by the presented evidence. Overall, the efficacy of ustekinumab in paediatric patients aged 2 to < 18 years of age is positive.

2.5. Clinical safety

Introduction

Design of the paediatric ulcerative colitis studies, as relevant for safety assessment

Table 37: Overview of Paediatric UC Clinical Studies (Ref table 1, Summary of clinical safety)

Study Number/ Description/Status	Study Population	Dosing Information	Number of Participants Enrolled/Treated Participants
Pediatric UC Studies			
CNTO1275PUC3001 (UNIFI Jr.) Phase 3, multicenter, open-label induction period with a single IV ustekinumab induction dose followed by a maintenance period with randomized, double-blind, parallel-group, 2-arm regimens Participants who had an LOR and low exposure were eligible to enroll in an optional open-label EOS. Completed	Pediatric participants aged 2 to <18 years with moderately to severely active UC (defined by a Mayo score of 6 through 12, inclusive, with an endoscopy subscore of ≥2) who had an inadequate response or intolerance to conventional therapies and/or biologic therapy or had corticosteroid dependence.	Induction (Week I-0 through Week I-8)- Single open-label IV dose at Week I-0 based on body weight: • 250 mg/m^2 for participants with body weight <40 kg • 260 mg for participants with body weight ≥40 kg to ≤55 kg • 390 mg for participants with body weight >55 kg to ≤85 kg body weight • 520 mg for participants with body weight >85 kg Maintenance (Week M-0 through Week M-44)- Participants were randomized in a blinded fashion in a 1:1 ratio to 1 of the following SC treatments, stratified by response status at Week I-8 (induction responders, induction nonresponders) and weight (<40 kg, ≥40 kg): • Ustekinumab q8w: 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight. • Ustekinumab q12w: 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight. Participants randomized to receive ustekinumab q8w received ustekinumab at Weeks M-0, M-8, M-16, M-24, M-32, and M-40 and matching placebo at Weeks M-12 and M-36 to maintain the blind. Participants randomized to receive ustekinumab q12w received ustekinumab at Weeks M-0, M-12, M-24, and M-36 and matching placebo at Weeks M-8, M-16, M-32, and M-40 to maintain the blind. Beginning at Week M-8 for induction responders and Week M-16 for delayed responders (induction responders who were in clinical response at Week M-8), participants who experienced LOR were eligible for a dose adjustment as follows: • Participants who were randomized to ustekinumab q12w were dose adjusted to q8w. • Participants who were randomized to ustekinumab q8w received a sham adjustment (q8w → q8w).	Induction: 112 enrolled Maintenance:109 randomized • q12w (n=55) • q8w (n=54) q12w or q8w → q4w optional substudy (n=22) All participants who received study intervention (n=112) at Week I-0 were included in the SCS safety analyses (Table 4).
CNTO1275ISD3001 (UNITED) Phase 3, multicenter, open-label, basket LTE study of SC ustekinumab Ongoing	Pediatric participants (2 to <18 years of age) who had participated in a pediatric ustekinumab clinical study	*LTE regimen:* *Dose:* 90 mg SC for ≥40 kg body weight or 60 mg/m^2 SC for <40 kg body weight *Frequency:* Previously blinded: q8w Previously unblinded: q4w or q8w	As of 28 April 2025, participants included in the SCS analyses: CNTO1275PUC3001: 66 in individual pooled analyses (66 in the All Enrolled Analysis Set; 65 in the Safety Analysis Set) CNTO1275CRD3004: 20 in a pooled safety analysis No participants from CNTO1275CRD1001 or CNTO1275JPA3001 were included in this analysis.

Patient exposure and baseline demographics

Overall paediatric exposure to ustekinumab across all indications:

In the ustekinumab clinical development program, paediatric participants have been exposed to ustekinumab in clinical studies across three disease indications: UC participants from PUC3001 and ISD3001; CD participants from CRD3004; and participants with PsO in PSO3006 and PSO3013 (Table 38).

There are two additional observational PASSs conducted in paediatric patients exposed to ustekinumab. These PASSs are the ongoing DEVELOP IBD registry which includes the 51 paediatric patients (>2 and <18 years of age) with UC who were enrolled as part of the overall study of paediatric patients with IBD, and the ongoing PSO4056 study in 125 adolescent patients with PsO.

Table 38: Overall summary of treatment exposure with ustekinumab in clinical studies (Ref table 5, Summary of clinical safety)

	Number of Treated Subjects	Median (Q1, Q3) Cumulative/Total Dose (mg)	Median (Q1, Q3) Total Duration of Ustekinumab Exposure (Weeks)
PUC3001[a,b]			
q12w	55	620.0 (449.5; 750.0)	44.0 (20.4; 45.0)
q8w	54	800.0 (660.0; 865.0)	48.1 (47.1; 48.9)
CRD3004[a,b]			
q12w	49	620.0 (468.5; 620.0)	44.1 (32.1; 45.1)
q8w	48	800.0 (660.0; 847.5)	48.1 (31.9; 49.1)
Exposure Optimization Substudy (q4w)			
PUC3001	21	450.0 (261.0; 540.0)	18.1 (12.9; 24.1)
CRD3004	26	450.0 (360.0; 603.0)	17.2 (16.3; 25.1)
ISD3001			
PUC3001[c]			
q8w	55	630.0 (450.0; 900.0)	48.6 (29.6; 80.1)
q4w	10	405.0 (288.0; 810.0)	16.1 (12.1; 34.1)
CRD3004[d]			
q8w	48	630.0 (411.8; 900.0)	48.8 (32.8; 79.6)
q4w	18	810.0 (360.0; 1260.0)	41.1 (12.1; 60.0)
UCO3001[e]			
q12w	172	620.0 (490.0; 750.0)	44.1 (43.9; 44.7)
q8w	176	800.0 (670.0; 930.0)	48.2 (48.0; 49.0)
PSO3006[f]	73	143.1 (109.8; 225.0)	40.1 (40.1; 40.6)
PSO3013[g]	44	125.6 (106.7; 179.6)	40.1 (40.1; 40.4)

PUC3001 exposure

The primary evidence of safety of ustekinumab in paediatric patients with UC comes from the pivotal Phase 3 PUC3001 study.

A total of 112 participants were enrolled, and 109 participants were randomised in the study. A total of 109 participants were treated with ustekinumab in the maintenance period, 55 participants in the q12w treatment group and 54 participants in the q8w treatment group:

- All participants received one IV induction dose.
- Median total duration of exposure (weeks) through the end of the maintenance period in the q12w and q8w treatment groups were 44.0 weeks and 48.1 weeks, respectively.

- The median total number of IV infusions and SC injections received was 5.0 (5.0 in the q12w treatment group [n=55] and 7.0 in the q8w treatment group [n=54]).
- The median total dose (mg) of ustekinumab (IV induction and SC maintenance) in the q12w and q8w treatment groups were 620.0 mg and 800.0 mg, respectively.

Table 39: Number of subjects who received scheduled SC study agent by time point from Week M-0 through Week M-44; Safety Randomised Analysis Set (Study CNTO1275PUC3001) (Ref table TSIEX04b, CNTO1275PUC3001 CSR)

TSIEX04b: Number of Subjects Who Received Scheduled SC Study Agent by Time Point From Week M-0 Through Week M-44; Safety Randomized Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: Safety Randomized	55	54	109
Subjects receiving a scheduled study agent			
Week M-0	55 (100.0%)	54 (100.0%)	109 (100.0%)
Week M-8	0	53 (98.1%)	53 (48.6%)
Week M-12	47 (85.5%)	1 (1.9%)	48 (44.0%)
Week M-16	0	46 (85.2%)	46 (42.2%)
Week M-24	38 (69.1%)	44 (81.5%)	82 (75.2%)
Week M-32	2 (3.6%)	42 (77.8%)	44 (40.4%)
Week M-36	35 (63.6%)	0	35 (32.1%)
Week M-40	2 (3.6%)	41 (75.9%)	43 (39.4%)

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

ISD3001 exposure

In the ISD3001 LTE study, participants rolling over from PUC3001 who were on q12w or q8w dosing received ustekinumab q8w dosing. Participants in the PUC3001 EOS on q4w dosing remained on this dose unless they had high exposure, in which case they were adjusted to q8w. A total of 65 participants with UC were treated with ustekinumab: 55 participants in the q8w treatment group and 10 participants in the q4w treatment group:

- Median total duration of exposure (weeks) in the LTE was 48.6 and 16.1 weeks in q8w and q4w treatment groups, respectively.
- The median total number of SC injections in the LTE was 7.0 in the q8w treatment group and 5.0 in the q4w treatment group.

Table 40: Summary of exposure for subjects who received ustekinumab during LTE through 28 April 2025; Safety analysis set (Ref table TSIEX01, CNTO1275ISD3001 Summary of Safety data*)*

TSIEX01: Summary of Exposure for Subjects Who Received Ustekinumab During LTE Through 28 April 2025; Safety Analysis Set (Study CNTO1275ISD3001)			
	Ustekinumab SC		
	PUC3001		
	q8w	q4w	Combined
Analysis set: Safety	55	10	65
Total duration of Ustekinumab exposure (weeks)[a]			
N	55	10	65
Mean (SD)	54.7 (36.70)	31.2 (41.19)	51.1 (38.06)
Median	48.6	16.1	48.1
Range	(0; 145)	(0; 140)	(0; 145)
Total number of Ustekinumab injections received			
N	55	10	65
Mean (SD)	8.7 (6.01)	8.9 (10.88)	8.8 (6.86)
Median	7.0	5.0	7.0
Range	(1; 26)	(1; 38)	(1; 38)
Total dose of Ustekinumab administrations (mg)			
N	55	10	65
Mean (SD)	671.2 (396.50)	741.6 (859.86)	682.0 (487.11)
Median	630.0	405.0	630.0
Range	(41; 1620)	(90; 2988)	(41; 2988)

[a]Total duration of treatment is defined as [(date of last dose of Ustekinumab – date of first dose of Ustekinumab in LTE) +1]/7.

UCO3001 exposure

Safety findings in the Phase 3 paediatric UC study PUC3001 are compared descriptively with those in the Phase 3 adult UC study UCO3001 as part of this application. Participants in the primary population who were randomised to ustekinumab received study intervention as follows (up to the point of meeting LOR criteria for dose adjustment):

- **90 mg q12w**: 172 participants received a median cumulative dose of 360.0 mg.
- **90 mg q8w**: 176 participants received a median cumulative dose of 540.0 mg.

Safety Analysis Sets

Table 41: Number of subjects in each analysis set; safety analysis set (Ref table 4, Summary of clinical safety)

	Ustekinumab						
	Pediatric Studies						
			ISD3001				Adult Study
	PUC3001	CRD3004	PUC3001	CRD3004	PSO3013	PSO3006	UCO3001
Induction Period							
Safety Analysis Set	112	101					320
Maintenance Period							
Safety Randomized Analysis Set	109	97					348
Through Approximately One Year							
Safety Analysis Set	112	101			44	73	825
Long-term Extension Period							
Enrolled Analysis Set			66	20			
Safety Analysis Set			65	18			
Exposure Optimization Substudy							
Safety Analysis Set	21	26					

1) The Safety Analysis Set in Induction Period:
- Studies CNTO1275PUC3001 and CNTO1275CRD3004: Includes all subjects who received an administration of ustekinumab in induction period at Week I-0.
- Study CNTO1275UCO3001: Includes all subjects who received an administration of ustekinumab 6 mg/kg in induction period at Week I-0.
2) The Safety Randomized Analysis Set in Maintenance Period:
- Studies CNTO1275PUC3001 and CNTO1275CRD3004: Includes all subjects who were randomized (induction responders and nonresponders) into the maintenance period (Week M-0) and received at least one dose of ustekinumab during maintenance period.
- Study CNTO1275UCO3001: Includes all subjects who were randomized (induction responders regardless of the treatment group randomized at Week I-0) into the maintenance period at Week M-0 and received at least one dose of ustekinumab during maintenance period.
3) The Safety Analysis Set Through Approximately One Year:
- Studies CNTO1275PUC3001 and CNTO1275CRD3004: Includes all subjects who received at least one dose of ustekinumab from Week I-0 through Week M-44.
- Study CNTO1275PSO3006: Includes all subjects who were randomized to the ustekinumab half-standard and standard dosage groups and received at least one dose of ustekinumab from Week 0 through Week 60.
- Study CNTO1275PSO3013: Includes all subjects who received at least one dose of ustekinumab from Week 0 through Week 56.
- Study CNTO1275UCO3001: Includes subjects who received an administration of ustekinumab 6 mg/kg or 130 mg/kg in induction period at Week I-0, and subjects who received placebo in induction period at Week I-0 and crossed over to receive ustekinumab.
4) The Analysis Sets in Long-term Extension Period:
- Enrolled Analysis Set: Includes all subjects from study CNTO1275PUC3001 who signed the ICF and entered the long-term extension study. Includes all subjects from study CNTO1275CRD3004 exposure optimization substudy and who signed the ICF and entered the long-term extension study.
- Safety Analysis Set: Includes all subjects from study CNTO1275PUC3001 who entered the long-term extension period and received at least one dose of ustekinumab during long-term extension study. Includes all subjects from study CNTO1275CRD3004 exposure optimization substudy who entered the long-term extension period and received at least one dose of ustekinumab during long-term extension study.
5) The Safety Analysis Set in Exposure Optimization Substudy:
- Studies CNTO1275PUC3001 and CNTO1275CRD3004: Includes all subjects who entered the exposure optimization substudy and received at least one dose of ustekinumab during the exposure optimization substudy.

Demographics and disease characteristics of the paediatric UC safety analysis set

Demographic characteristics of the paediatric clinical study participants are as follows:

Table 42: Summary of demographics at baseline; safety analysis set (Adapted from Summary of clinical safety)

TSIDEM01a: Summary of Demographics at Baseline; Safety Analysis Set (Studies CNTO1275PUC3001 and CNTO1275ISD3001)							
	Ustekinumab						
	PUC3001				ISD3001		
	Not randomized[a]	q12w[a]	q8w[a]	Total	q8w	q4w	Total
Analysis set: Safety[b] or Enrolled[c]	3	55	54	112	56	10	66
Age, years							
N	3	55	54	112	56	10	66
Mean (SD)	11.3 (3.06)	13.2 (3.37)	13.3 (2.80)	13.2 (3.09)	13.9 (2.88)	13.4 (3.03)	13.8 (2.89)
Median	12.0	14.0	14.0	14.0	15.0	15.0	15.0
Range	(8; 14)	(3; 17)	(4; 17)	(3; 17)	(4; 17)	(6; 16)	(4; 17)
IQ range	(8.0; 14.0)	(11.0; 16.0)	(12.0; 15.0)	(11.0; 15.5)	(12.0; 16.0)	(12.0; 15.0)	(12.0; 16.0)
2-<12 years	1 (33.3%)	16 (29.1%)	13 (24.1%)	30 (26.8%)	10 (17.9%)	2 (20.0%)	12 (18.2%)
2-<6 years	0	2 (3.6%)	1 (1.9%)	3 (2.7%)	1 (1.8%)	0	1 (1.5%)
6-<12 years	1 (33.3%)	14 (25.5%)	12 (22.2%)	27 (24.1%)	9 (16.1%)	2 (20.0%)	11 (16.7%)
12-<18 years	2 (66.7%)	39 (70.9%)	41 (75.9%)	82 (73.2%)	46 (82.1%)	8 (80.0%)	54 (81.8%)
Sex							
N	3	55	54	112	56	10	66
Female	3 (100.0%)	28 (50.9%)	30 (55.6%)	61 (54.5%)	30 (53.6%)	5 (50.0%)	35 (53.0%)
Male	0	27 (49.1%)	24 (44.4%)	51 (45.5%)	26 (46.4%)	5 (50.0%)	31 (47.0%)
Race							
N	3	55	54	112	56	10	66
American Indian or Alaska Native	0	0	0	0	0	0	0
Asian	0	7 (12.7%)	6 (11.1%)	13 (11.6%)	8 (14.3%)	1 (10.0%)	9 (13.6%)
Black or African American	0	1 (1.8%)	1 (1.9%)	2 (1.8%)	1 (1.8%)	0	1 (1.5%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
White	2 (66.7%)	46 (83.6%)	46 (85.2%)	94 (83.9%)	46 (82.1%)	9 (90.0%)	55 (83.3%)
Multiple	0	0	0	0	0	0	0
Not reported	0	0	1 (1.9%)	1 (0.9%)	1 (1.8%)	0	1 (1.5%)
Unknown	1 (33.3%)	1 (1.8%)	0	2 (1.8%)	0	0	0
Ethnicity							
N	3	55	54	112	56	10	66
Hispanic or Latino	0	0	1 (1.9%)	1 (0.9%)	1 (1.8%)	0	1 (1.5%)
Not Hispanic or Latino	2 (66.7%)	54 (98.2%)	52 (96.3%)	108 (96.4%)	55 (98.2%)	10 (100.0%)	65 (98.5%)
Not Reported	0	0	1 (1.9%)	1 (0.9%)	0	0	0
Weight, kg							
N	3	55	54	112	56	10	66
Mean (SD)	38.4 (8.07)	47.9 (15.86)	46.6 (13.49)	47.0 (14.59)	51.6 (14.71)	56.5 (18.44)	52.4 (15.27)
Median	40.0	47.0	47.2	46.9	53.2	57.2	53.6
Range	(30; 46)	(14; 80)	(14; 76)	(14; 80)	(17; 90)	(25; 82)	(17; 90)
IQ range	(29.6; 45.5)	(37.2; 57.7)	(36.0; 57.4)	(36.1; 57.2)	(41.8; 59.9)	(44.5; 66.2)	(41.9; 60.8)
<40 kg	1 (33.3%)	15 (27.3%)	18 (33.3%)	34 (30.4%)	13 (23.2%)	2 (20.0%)	15 (22.7%)
<30 kg	1 (33.3%)	8 (14.5%)	7 (13.0%)	16 (14.3%)	5 (8.9%)	1 (10.0%)	6 (9.1%)
≥30 - <40 kg	0	7 (12.7%)	11 (20.4%)	18 (16.1%)	8 (14.3%)	1 (10.0%)	9 (13.6%)
≥40 kg	2 (66.7%)	40 (72.7%)	36 (66.7%)	78 (69.6%)	43 (76.8%)	8 (80.0%)	51 (77.3%)
≥40 - ≤55 kg	2 (66.7%)	22 (40.0%)	18 (33.3%)	42 (37.5%)	19 (33.9%)	3 (30.0%)	22 (33.3%)
>55 - ≤85 kg	0	18 (32.7%)	18 (33.3%)	36 (32.1%)	23 (41.1%)	5 (50.0%)	28 (42.4%)
>85 kg	0	0	0	0	1 (1.8%)	0	1 (1.5%)
Height, cm							
N	3	55	54	112	56	10	66
Mean (SD)	141.8 (7.65)	157.2 (18.73)	158.4 (16.08)	157.4 (17.39)	160.7 (15.08)	160.5 (18.25)	160.7 (15.45)
Median	139.0	163.9	161.0	161.5	163.7	166.7	164.0
Range	(136; 151)	(96; 178)	(99; 183)	(96; 183)	(107; 182)	(121; 177)	(107; 182)
IQ range	(136.0; 150.5)	(152.0; 172.0)	(149.6; 170.0)	(149.6; 170.0)	(153.6; 170.8)	(155.0; 175.0)	(155.0; 171.0)
Body mass index, kg/m^2							
N	3	55	54	112	56	10	66
Mean (SD)	18.9 (2.55)	18.8 (3.67)	18.1 (2.79)	18.5 (3.24)	19.5 (3.28)	21.5 (5.00)	19.8 (3.61)
Median	20.1	18.4	18.3	18.3	19.1	20.1	19.3
Range	(16; 21)	(13; 28)	(14; 26)	(13; 28)	(14; 29)	(17; 32)	(14; 32)
IQ range	(16.0; 20.7)	(16.1; 20.7)	(15.4; 19.8)	(16.0; 20.2)	(17.2; 21.7)	(18.5; 21.2)	(17.3; 21.7)
Underweight <18.5	1 (33.3%)	31 (56.4%)	29 (53.7%)	61 (54.5%)	24 (42.9%)	2 (20.0%)	26 (39.4%)
Normal 18.5-<25	2 (66.7%)	18 (32.7%)	24 (44.4%)	44 (39.3%)	28 (50.0%)	6 (60.0%)	34 (51.5%)
Overweight 25-<30	0	6 (10.9%)	1 (1.9%)	7 (6.3%)	4 (7.1%)	1 (10.0%)	5 (7.6%)
Obese ≥30	0	0	0	0	0	1 (10.0%)	1 (1.5%)

Baseline UC disease characteristics of the paediatric clinical study participants are as follows:

Table 43: Summary of baseline UC disease characteristics; safety analysis set (Adapted from Summary of clinical safety)

TSIDEM02a: Summary of Baseline UC Disease Characteristics; Safety Analysis Set (Studies CNTO1275PUC3001 and CNTO1275ISD3001)							
	Ustekinumab						
	PUC3001				ISD3001		
	Not randomized[a]	q12w[a]	q8w[a]	Total	q8w	q4w	Total
Analysis set: Safety[b] or Enrolled[c]	3	55	54	112	56	10	66
Age at diagnosis, years							
N	3	55	54	112	56	10	66
Mean (SD)	8.2 (4.49)	11.0 (3.75)	11.6 (3.09)	11.2 (3.48)	10.9 (2.96)	10.1 (3.49)	10.8 (3.04)
Median	7.0	12.1	11.8	11.8	11.6	11.0	11.5
Range	(4; 13)	(2; 17)	(2; 17)	(2; 17)	(2; 16)	(4; 14)	(2; 16)
IQ range	(4.4; 13.2)	(7.6; 13.7)	(9.9; 14.3)	(9.1; 13.7)	(9.8; 13.1)	(7.4; 12.3)	(9.7; 13.0)
Ulcerative colitis disease duration, years							
N	3	55	54	112	56	10	66
Mean (SD)	3.23 (3.874)	2.28 (2.182)	1.75 (1.638)	2.05 (1.994)	2.00 (1.947)	2.31 (2.050)	2.05 (1.950)
Median	1.03	1.52	1.17	1.22	1.28	1.30	1.28
Range	(1.0; 7.7)	(0.3; 11.4)	(0.1; 8.8)	(0.1; 11.4)	(0.1; 11.4)	(0.7; 6.7)	(0.1; 11.4)
IQ range	(0.96; 7.71)	(0.75; 3.26)	(0.67; 2.48)	(0.75; 2.76)	(0.76; 2.74)	(0.81; 3.67)	(0.77; 2.77)
Extent of ulcerative colitis disease							
N	3	55	54	112	56	10	66
Limited to left side of colon	1 (33.3%)	19 (34.5%)	17 (31.5%)	37 (33.0%)	22 (39.3%)	1 (10.0%)	23 (34.8%)
Extensive	2 (66.7%)	36 (65.5%)	37 (68.5%)	75 (67.0%)	34 (60.7%)	9 (90.0%)	43 (65.2%)
PUCAI Score							
N	3	55	54	112	56	10	66
Mean (SD)	66.7 (17.56)	53.5 (12.97)	51.5 (16.10)	52.9 (14.74)	51.5 (11.75)	46.0 (12.43)	50.7 (11.93)
Median	65.0	55.0	55.0	55.0	52.5	47.5	50.0
Range	(50; 85)	(25; 85)	(5; 80)	(5; 85)	(20; 80)	(25; 60)	(20; 80)
IQ range	(50.0; 85.0)	(45.0; 60.0)	(40.0; 60.0)	(45.0; 60.0)	(45.0; 60.0)	(40.0; 60.0)	(45.0; 60.0)
Mayo Score[d]							
N	2	54	52	108	56	9	65
Mean (SD)	8.0 (0.00)	8.4 (1.44)	8.4 (1.50)	8.4 (1.45)	8.1 (1.35)	8.0 (1.00)	8.1 (1.31)
Median	8.0	8.5	8.0	8.0	8.0	8.0	8.0
Range	(8; 8)	(6; 11)	(4; 12)	(4; 12)	(6; 12)	(6; 9)	(6; 12)
IQ range	(8.0; 8.0)	(7.0; 9.0)	(7.5; 9.0)	(7.0; 9.0)	(7.0; 9.0)	(8.0; 9.0)	(7.0; 9.0)
Modified Mayo Score							
N	2	55	52	109	56	9	65
Mean (SD)	6.0 (0.00)	6.1 (1.26)	6.3 (1.30)	6.2 (1.27)	6.0 (1.24)	6.0 (1.00)	6.0 (1.21)
Median	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Range	(6; 6)	(4; 8)	(3; 9)	(3; 9)	(3; 9)	(4; 7)	(3; 9)
IQ range	(6.0; 6.0)	(5.0; 7.0)	(5.5; 7.0)	(5.0; 7.0)	(5.0; 7.0)	(6.0; 7.0)	(5.0; 7.0)

Concomitant Medications and Medication History of the paediatric UC safety analysis set

A majority (105 [93.8%] of 112 participants in PUC3001 and 56 [84.8%] of 66 participants in ISD3001 [at ISD3001 baseline]) were taking at least one UC-related concomitant medication at baseline:

- 49 (43.8%) participants in PUC3001 and no participants in ISD3001 received corticosteroids.
- 44 (39.3%) participants in PUC3001 and 25 (37.9%) participants in ISD3001 received immunomodulatory drugs (including 6-MP/AZA and MTX).
- 83 (74.1%) participants in PUC3001 and 48 (72.7%) participants in ISD3001 received 5-ASA.

Less than half (44 [39.3%] of 112 participants in PUC3001 and 18 [27.3%] of 66 participants in ISD3001) had a history of biologic failure. In PUC3001, proportions were numerically greater in the q12w treatment group compared with the q8w treatment group (47.3% vs 31.5%). In ISD3001, proportions were numerically greater in the q4w treatment group compared with the q8w treatment group (40.0% vs 25.0%).

Table 44: Summary of UC-related concomitant medications at baseline; safety analysis set (Studies CNTO1275PUC3001 and CNTO1275ISD3001) (Ref table TSICM01a, Summary of clinical safety)

TSICM01a: Summary of UC-related Concomitant Medications at Baseline; Safety Analysis Set (Studies CNTO1275PUC3001 and CNTO1275ISD3001)

	Ustekinumab						
	PUC3001				ISD3001		
	Not randomized*	q12w[a]	q8w[a]	Total	q8w	q4w	Total
Analysis set: Safety[b] or Enrolled[c]	3	55	54	112	56	10	66
Subjects who received any of the following UC medications	2 (66.7%)	50 (90.9%)	53 (98.1%)	105 (93.8%)	47 (83.9%)	9 (90.0%)	56 (84.8%)
Any Antibiotic use	0	0	0	0	0	0	0
Corticosteroid use	1 (33.3%)	25 (45.5%)	23 (42.6%)	49 (43.8%)	0	0	0
Oral/Rectal Corticosteroid use (excluding budesonide and beclomethasone dipropionate)	1 (33.3%)	15 (27.3%)	12 (22.2%)	28 (25.0%)	0	0	0
Budesonide[d]	0	10 (18.2%)	10 (18.5%)	20 (17.9%)	0	0	0
Beclomethasone dipropionate[d]	0	0	1 (1.9%)	1 (0.9%)	0	0	0
Immunomodulatory drugs	0	18 (32.7%)	26 (48.1%)	44 (39.3%)	22 (39.3%)	3 (30.0%)	25 (37.9%)
6-mercaptopurine/azathioprine	0	18 (32.7%)	25 (46.3%)	43 (38.4%)	22 (39.3%)	2 (20.0%)	24 (36.4%)
Methotrexate	0	0	1 (1.9%)	1 (0.9%)	0	1 (10.0%)	1 (1.5%)
Colchicine	0	0	0	0	1 (1.8%)	0	1 (1.5%)
Oral 5-Aminosalicylate	1 (33.3%)	39 (70.9%)	43 (79.6%)	83 (74.1%)	40 (71.4%)	8 (80.0%)	48 (72.7%)

* Subjects received ustekinumab at Week I-0 in induction but not randomized at Week M-0 in maintenance.
[a] Subjects are counted in the treatment group they were randomized at Week M-0.
[b] Study CNTO1275PUC3001: Includes all subjects who received an administration of ustekinumab in induction at Week I-0.
[c] Study CNTO1275ISD3001: Includes all subjects from study CNTO1275PUC3001 who signed the ICF and entered the long-term extension study.
[d] Including oral or rectal
Note: Subjects may appear in more than one category.
Note: UC-related Concomitant medication at induction baseline was summarized in study CNTO1275PUC3001. UC-related Concomitant medication at long-term extension baseline was summarized in study CNTO1275ISD3001.

Table 45: Summary of UC-related biologic medication history; safety analysis set (Studies CNTO1275PUC3001 and CNTO1275ISD3001) (Adapted from ref table TSICM11a, Summary of clinical safety)

TSICM11a: Summary of UC-related Biologic Medication History; Safety Analysis Set (Studies CNTO1275PUC3001 and CNTO1275ISD3001)

	Ustekinumab						
	PUC3001				ISD3001		
	Not randomized*	q12w[a]	q8w[a]	Total	q8w	q4w	Total
Analysis set: Safety[b] or Enrolled[c]	3	55	54	112	56	10	66
Subjects without a history of biological failure	2 (66.7%)	29 (52.7%)	37 (68.5%)	68 (60.7%)	42 (75.0%)	6 (60.0%)	48 (72.7%)
Biologic-naive	2 (66.7%)	29 (52.7%)	37 (68.5%)	68 (60.7%)	42 (75.0%)	6 (60.0%)	48 (72.7%)
Biologic-experienced, but not documented failure	0	0	0	0	0	0	0

Adverse events

Safety data are presented from the 8-week induction period, the 44-week maintenance period, and the subsequent 20-week safety follow-up period following the last study intervention (either at Week M-40 in the main study or at the end of participation in the EOS).

Induction Period; AE Overview, Safety Analysis Set (PUC3001)

Table 46: Overall summary of treatment-emergent adverse events through Week I-8; safety analysis set (Study CNTO1275PUC3001) (Ref table 23, CNTO1275PUC3001 CSR)

	Ustekinumab IV
Analysis set: Safety	112
Avg duration of follow-up (weeks)	8.2
Avg exposure (number of administrations)	1.0
Subjects with 1 or more:	
AEs	59 (52.7%)
Serious AEs	6 (5.4%)
AEs leading to death	0
AEs leading to discontinuation of study intervention	2 (1.8%)
AEs reasonably related to study intervention	6 (5.4%)
AEs of severe intensity	5 (4.5%)
Infections	26 (23.2%)
Serious infections	1 (0.9%)
Infection requiring oral and/or parenteral antimicrobial treatment	4 (3.6%)
Malignancy	0
Active tuberculous infections	0
Opportunistic infections	0
AEs temporally associated with the infusion of study intervention at Week I-0	3 (2.7%)

Key: AE = adverse event, Avg = average
Note: Infections as assessed by the investigator.

Induction Period: AE Breakdown, Safety Analysis Set (PUC3001)

A total of 59 (52.7%) of 112 participants had one or more AEs through Week I-8. AEs were most frequently reported in the following SOCs and PTs:

- Infections and infestations (25 [22.3%] participants); COVID-19 (7 [6.3%]) and upper respiratory tract infection (4 [3.6%] participants) were the most frequently reported PTs.
- Blood and lymphatic system disorders (15 [13.4%] participants); anaemia (12 [10.7%] participants) was the most frequently reported PT.
- Gastrointestinal disorders (13 [11.6%] participants); colitis ulcerative (5 [4.5%] participants) and vomiting (3 [2.7%] participants) were the most frequently reported PTs.
- Skin and subcutaneous tissue disorders (9 [8.0%] participants); acne and urticaria (3 [2.7%] participants each) were the most frequently reported PTs.

Table 47: Number of subjects with treatment-emergent adverse events through Week I-8 by system organ class and preferred term; safety analysis set (Study CNTO1275PUC3001) (Ref table TSFAE03a CNTO1275PUC3001 CSR)

TSFAE03a: Number of Subjects With Treatment-emergent Adverse Events Through Week I-8 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab IV
Analysis set: Safety	112
Avg duration of follow-up (weeks)	8.2
Avg exposure (number of administrations)	1.0
Subjects with 1 or more AEs	59 (52.7%)
System organ class Preferred term	
Infections and infestations	25 (22.3%)
COVID-19	7 (6.3%)
Upper respiratory tract infection	4 (3.6%)
Bronchitis	2 (1.8%)
Fungal foot infection	2 (1.8%)
Gastroenteritis	2 (1.8%)
Nasopharyngitis	2 (1.8%)
Conjunctivitis	1 (0.9%)
Fungal skin infection	1 (0.9%)
Infectious mononucleosis	1 (0.9%)
Paronychia	1 (0.9%)
Pharyngitis	1 (0.9%)
Rhinitis	1 (0.9%)
Subcutaneous abscess	1 (0.9%)
Blood and lymphatic system disorders	15 (13.4%)
Anaemia	12 (10.7%)
Iron deficiency anaemia	2 (1.8%)
Lymphopenia	1 (0.9%)

Gastrointestinal disorders	13 (11.6%)
Colitis ulcerative	5 (4.5%)
Vomiting	3 (2.7%)
Abdominal pain	2 (1.8%)
Nausea	2 (1.8%)
Angular cheilitis	1 (0.9%)
Constipation	1 (0.9%)
Diarrhoea haemorrhagic	1 (0.9%)
Flatulence	1 (0.9%)
Haematochezia	1 (0.9%)
Skin and subcutaneous tissue disorders	9 (8.0%)
Acne	3 (2.7%)
Urticaria	3 (2.7%)
Dry skin	1 (0.9%)
Erythema	1 (0.9%)
Skin lesion	1 (0.9%)
Skin striae	1 (0.9%)
Metabolism and nutrition disorders	7 (6.3%)
Vitamin D deficiency	5 (4.5%)
Decreased appetite	1 (0.9%)
Hypokalaemia	1 (0.9%)
Nervous system disorders	7 (6.3%)
Headache	5 (4.5%)
Migraine	1 (0.9%)
Nerve compression	1 (0.9%)
Tremor	1 (0.9%)
Injury, poisoning and procedural complications	6 (5.4%)
Anaesthetic complication	1 (0.9%)
Contusion	1 (0.9%)
Infusion related reaction	1 (0.9%)
Ligament sprain	1 (0.9%)
Procedural nausea	1 (0.9%)
Vaccination complication	1 (0.9%)
General disorders and administration site conditions	5 (4.5%)
Fatigue	2 (1.8%)
Catheter site phlebitis	1 (0.9%)
Non-cardiac chest pain	1 (0.9%)
Pain	1 (0.9%)
Pyrexia	1 (0.9%)
Endocrine disorders	3 (2.7%)
Cushingoid	2 (1.8%)
Cushing's syndrome	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	3 (2.7%)
Dyspnoea	1 (0.9%)
Pleural effusion	1 (0.9%)
Rhinorrhoea	1 (0.9%)
Eye disorders	1 (0.9%)
Cataract subcapsular	1 (0.9%)

Investigations	1 (0.9%)
Blood iron decreased	1 (0.9%)
Faecal calprotectin increased	1 (0.9%)
White blood cell count increased	1 (0.9%)
Musculoskeletal and connective tissue disorders	1 (0.9%)
Arthralgia	1 (0.9%)
Vascular disorders	1 (0.9%)
Hypotension	1 (0.9%)

Key: AE = adverse event, Avg = average
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 28.0

A reasonably related AE was defined as any event, in the opinion of the investigator, with a relationship to study intervention of "related" on the AE eCRF page or if the relationship to study intervention was missing. A total of 6 (5.4%) of 112 participants had at least one related AE through Week I-8. Individual AEs considered by the investigator to be reasonably related to study intervention were:

- Urticaria (n=2 [1.8%])
- Headache (n=1 [0.9%])
- Migraine (n=1 [0.9%])
- Vomiting (n=1 [0.9%])
- Non-cardiac chest pain (n=1 [0.9%])
- Infusion related reaction (n=1 [0.9%])
- Dyspnea (n=1 [0.9%])

A total of 5 (4.5%) of 112 participants in the study had at least one AE of severe intensity through Week I-8. Individual AEs of severe intensity were:

- Anaemia (n=2 [1.8%])
- Colitis ulcerative (n=2 [1.8%])
- Urticaria (n=1 [0.9%])

Maintenance Period; AE Overview, Safety Analysis Set (PUC3001)

Table 48: Overall summary of treatment-emergent adverse events from Week M-0 through Week M-44; safety randomised analysis set (Study CNTO1275PUC3001) (CNTO1275PUC3001 CSR)

	Ustekinumab SC						
	q12w[a]			q8w[a]			
	q12w[b]	q12w→q8w[c]	Combined	q8w[b]	q8w→q8w[c]	Combined	Total
Analysis set: Safety Randomized	55	5	55	54	2	54	109
Avg duration of follow-up (weeks)	36.0	11.7	37.0	38.1	21.5	38.9	38.0
Avg exposure (number of administrations)	7.6	2.4	7.8	8.1	3.5	8.2	8.0
Subjects with 1 or more:							
AEs	52 (94.5%)	3 (60.0%)	52 (94.5%)	48 (88.9%)	2 (100.0%)	48 (88.9%)	100 (91.7%)
Serious AEs	2 (3.6%)	0	2 (3.6%)	5 (9.3%)	0	5 (9.3%)	7 (6.4%)
AEs leading to death	0	0	0	0	0	0	0
AEs leading to discontinuation of study intervention	3 (5.5%)	0	3 (5.5%)	2 (3.7%)	0	2 (3.7%)	5 (4.6%)
AEs reasonably related to study intervention	2 (3.6%)	0	2 (3.6%)	4 (7.4%)	0	4 (7.4%)	6 (5.5%)
AEs of severe intensity	1 (1.8%)	0	1 (1.8%)	6 (11.1%)	0	6 (11.1%)	7 (6.4%)
Infections	35 (63.6%)	2 (40.0%)	37 (67.3%)	32 (59.3%)	0	32 (59.3%)	69 (63.3%)
Serious infections	0	0	0	1 (1.9%)	0	1 (1.9%)	1 (0.9%)
Infection requiring oral and/or parenteral antimicrobial treatment	10 (18.2%)	1 (20.0%)	11 (20.0%)	7 (13.0%)	0	7 (13.0%)	18 (16.5%)
Malignancy	0	0	0	0	0	0	0
Active tuberculous infections	0	0	0	0	0	0	0
Opportunistic infections	1 (1.8%)	0	1 (1.8%)	0	0	0	1 (0.9%)
Injection site-reactions[d]	0	0	0	1 (1.9%)	0	1 (1.9%)	1 (0.9%)

Key: AE = adverse event, Avg = average
Note: Infections as assessed by the investigator.
Note: Data from the time of substudy onward are not included.
[a] Subjects are counted in the treatment group they were randomized at Week M-0.
[b] Includes data through Week M-44 or up to the time of dose adjustment.
[c] Includes data from the time of dose adjustment onward.
[d] 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.

Maintenance Period; AE Breakdown, Safety Analysis Set (PUC3001)

From Week M-0 through Week M-44, the proportion of participants with one or more AEs was similar in the q12w treatment group (52 [94.5%] of 55 participants) and the q8w treatment group (48 [88.9%] of 54 participants). AEs were most frequently reported in the following SOCs and PTs based on the combined treatment group (n=109):

- Infections and infestations (68 [62.4%] participants); upper respiratory tract infection (27 [24.8%] participants) and nasopharyngitis (17 [15.6%] participants) were the most frequently reported PTs.
- Gastrointestinal disorders (50 [45.9%] participants); colitis ulcerative was the most frequently reported PT (34 [31.2%] participants).
- Blood and lymphatic system disorders (18 [16.5%] participants); anaemia was the most frequently reported PT (13 [11.9%] participants.

Table 49: Number of subjects with treatment-emergent adverse events with a frequency of at least 5% in the combined treatment group from Week M-0 through Week M-44 or up to the time of dose adjustment by preferred term; safety randomised analysis set (Study CNTO1275PUC3001) (CNTO1275PUC3001 CSR)

TSFAE25b: Number of Subjects With Treatment-emergent Adverse Events With Frequency of at Least 5% in the Combined Treatment Group From Week M-0 Through Week M-44 or Up to the Time of Dose Adjustment by Preferred Term; Safety Randomized Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab SC		
	Randomized at Week M-0		
	q12w	q8w	Combined
Analysis set: Safety Randomized	55	54	109
Avg duration of follow-up (weeks)	36.0	38.1	37.0
Avg exposure (number of administrations)	7.6	8.1	7.8
Subjects with 1 or more AEs with frequency of at least 5%	42 (76.4%)	35 (64.8%)	77 (70.6%)
Preferred term			
Colitis ulcerative	21 (38.2%)	13 (24.1%)	34 (31.2%)
Upper respiratory tract infection	13 (23.6%)	14 (25.9%)	27 (24.8%)
Nasopharyngitis	7 (12.7%)	10 (18.5%)	17 (15.6%)
Anaemia	5 (9.1%)	8 (14.8%)	13 (11.9%)
Headache	7 (12.7%)	3 (5.6%)	10 (9.2%)
COVID-19	5 (9.1%)	2 (3.7%)	7 (6.4%)
Respiratory tract infection	4 (7.3%)	2 (3.7%)	6 (5.5%)

Key: AE = adverse event, Avg = average
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 28.0
Note: Data from the time of dose adjustment onward are not included.

From Week M-0 through Week M-44, 2 (3.6%) of 55 participants in the q12w treatment group and four (7.4%) of 54 participants in the q8w treatment group had at least one related AE.

- Individual AEs considered by the investigator to be reasonably related to study intervention (clostridium difficile infection and rash) occurred in one participant each in the q12w treatment group.
- Individual AEs considered by the investigator to be reasonably related to study intervention (bronchitis, injection-site erythema, injection-site swelling, hepatic enzyme increased, and headache) occurred in one participant each in the q8w treatment group.

A total of 7 (6.4%) of the 109 participants had at least one AE of severe intensity. Most were reported in the q8w treatment group. Individual AEs of severe intensity were:

- Colitis ulcerative (n=3 [2.8%])
- Anaemia (n=2 [1.8%])
- Salmonellosis (n=1 [0.9%])
- Suicidal ideation (n=1 [0.9%])

Long-term extension Period: i.e. ISD3001 in Paediatric UC; AE Overview, Safety Analysis Set

Table 50: Overall summary of treatment-emergent adverse events in the LTE through 28 April 2025; safety analysis set (Study CNTO1275ISD3001) (Ref table 7, CNTO1275ISD3001 Summary of Safety Data)

	Ustekinumab SC		
	PUC3001		
	q8w	q4w	Combined
Analysis set: Safety	55	10	65
Avg duration of follow-up (weeks)	61.6	34.7	57.5
Avg exposure (number of administrations)	8.7	8.9	8.8
Subjects with 1 or more:			
AEs	43 (78.2%)	7 (70.0%)	50 (76.9%)
Serious AEs	5 (9.1%)	0	5 (7.7%)
AEs leading to death	1 (1.8%)	0	1 (1.5%)
AEs leading to discontinuation of study intervention	5 (9.1%)	1 (10.0%)	6 (9.2%)
AEs related to study intervention	1 (1.8%)	0	1 (1.5%)
AEs of severe intensity	3 (5.5%)	0	3 (4.6%)
Infections	32 (58.2%)	6 (60.0%)	38 (58.5%)
Serious infections	1 (1.8%)	0	1 (1.5%)
Infection requiring oral and/or parenteral antimicrobial treatment	15 (27.3%)	3 (30.0%)	18 (27.7%)
Malignancy	0	0	0
Active Tuberculous infections	0	0	0
Opportunistic infections	0	0	0
Possible anaphylactic or serum-sickness like reactions	0	0	0
Injection site reactions	0	0	0

Key: AE = adverse event, Avg = average

Long-term extension Period: i.e. ISD3001 in Paediatric UC; AE Breakdown, Safety Analysis Set

A total of 50 (76.9%) participants reported one or more AEs in the Safety Analysis Set. AEs were most frequently reported in the following SOCs and PTs:

- AEs within the Infections and infestations SOC were reported in 37 [56.9%] of 65 participants; the most frequently reported PTs (>5%) included upper respiratory tract infection (12 [18.5%] participants), influenza (9 [13.8%] participants), nasopharyngitis (5 [7.7%] participants), and gastroenteritis (4 [6.2%] participants).
- AEs within the Gastrointestinal disorders SOC were reported in 26 [40.0%] of 65 participants (40% each of the q8w and q4w treatment groups); the most frequently reported PT (>5%) was colitis ulcerative (15 [23.1%]), which was similarly reported in 12 (21.8%) of 55 participants in the q8w treatment group and 3 (30.0%) of 10 participants in the q4w treatment group.

Table 51: Number of subjects with treatment-emergent adverse events with a frequency of at least 5% in the treatment group by preferred term in the LTE through 28 April 2025; safety analysis set (Study CNTO1275ISD3001) (Ref table TSFAE12, CNTO1275ISD3001 Summary of Safety Data)

TSFAE12: Number of Subjects With Treatment-emergent Adverse Events With Frequency of at Least 5% in the Treatment Group by Preferred Term in the LTE Through 28 April 2025; Safety Analysis Set (Study CNTO1275ISD3001)

	Ustekinumab SC PUC3001		
	q8w	q4w	Combined
Analysis set: Safety	55	10	65
Avg duration of follow-up (weeks)	61.6	34.7	57.5
Avg exposure (number of administrations)	8.7	8.9	8.8
Subjects with 1 or more AEs	43 (78.2%)	7 (70.0%)	50 (76.9%)
Preferred term			
Colitis ulcerative	12 (21.8%)	3 (30.0%)	15 (23.1%)
Upper respiratory tract infection	10 (18.2%)	2 (20.0%)	12 (18.5%)
Influenza	7 (12.7%)	2 (20.0%)	9 (13.8%)
Anaemia	4 (7.3%)	1 (10.0%)	5 (7.7%)
Nasopharyngitis	4 (7.3%)	1 (10.0%)	5 (7.7%)
Vitamin D deficiency	3 (5.5%)	2 (20.0%)	5 (7.7%)
Gastroenteritis	4 (7.3%)	0	4 (6.2%)
Pyrexia	4 (7.3%)	0	4 (6.2%)

Key: AE = adverse event, Avg = average
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA version 27.1.

There was a single AE reported as related to ustekinumab, in the q8w treatment group. This AE, PT of neuropathy peripheral, was an SAE, mild in severity, and led to discontinuation of ustekinumab. The patient was a responder to ustekinumab IV induction dosing and randomised to receive SC ustekinumab in the maintenance phase. The dosing regimen was blinded q8w and no SAEs were reported during the PUC3001 parent study.

- On LTE Study Day -96 (during the parent study), a nonserious AE of nerve compression (ulnar nerve compression of the left elbow) was reported and considered as moderate in intensity. No treatment was reported and the AE was assessed as not related to ustekinumab.
- On LTE Study Day -13, an electromyogram showed mild new sensory neuropathy in the lower limbs and a nonserious AE of neuropathy peripheral was reported. No treatment was reported and the AE was assessed as not related to ustekinumab.

In the LTE study, the participant received one dose of ustekinumab (90 mg SC q8w) on Study Day 31 prior to the SAE of neuropathy peripheral.

- On LTE Study Day 53, the participant experienced a sudden onset of symptoms, including a loss of sensation on the lateral aspects of both lower limbs, some difficulty walking, and was hospitalised due to an SAE of neuropathy peripheral. The event was considered mild in intensity and no treatment was reported. Treatment with ustekinumab was permanently discontinued due to the event. The investigator assessed the event of neuropathy peripheral as related to ustekinumab. The participant was continuing in the safety follow-up phase of the LTE study and the events of neuropathy peripheral and nerve compression were reported as not resolved at the clinical cut-off date 28 April 2025 (Study Day 127).

Three (4.6%) of the 66 participants reported at least one AE of severe intensity. Each of these severe AEs were serious. Individual AEs of severe intensity were reported in the following SOCs:

- Gastrointestinal disorders (colitis ulcerative) (n=1 [1.5%])
- Infections and infestations (cholangitis infective and endoscopic retrograde cholangiopancreatography – both in one participant) (n=1 [1.5%] each)
- Psychiatric disorders (completed suicide) (n=1 [1.5%])

Safety Data during the Induction and Maintenance Periods and LTE; AE Overview, Safety Analysis Set (PUC3001 and ISD3001)

Table 52: Incidence of key safety events per 100 person-years of follow-up from Week I-0 through End of Study and during Long-term Extension Period; safety analysis set (Studies CNTO1275PUC3001 and CNTO1275ISD3001) (Ref table 6, Summary of Clinical Safety)

	Ustekinumab							
	From Week I-0 Through End of Study					Long-term Extension		
	PUC3001					ISD3001		
	Not randomized*	q12w[a, b]	q8w[a, b]	q4w[c]	Total	q8w	q4w	Total
Analysis set: Safety[d] or Enrolled[e] Analysis Set	3	55	54	21	112	56	10	66
Avg duration of follow-up (weeks)	14.3	48.1	49.2	23.5	52.1	60.7	34.7	56.8
Avg exposure (number of administrations)	1.0	8.8	9.2	6.7	10.0	8.6	8.9	8.6
Total person-year of follow-up	0.82	50.68	50.94	9.47	111.91	65.19	6.65	71.84
Events per 100 person-years (n/incidence rate (95% CI))								
AEs	11/1339.3 (668.5, 2396.3)	254/501.2 (441.4, 566.7)	209/410.3 (356.6, 469.9)	51/538.5 (401.0, 708.1)	525/469.1 (429.8, 511.0)	179/274.6 (235.8, 317.9)	31/466.1 (316.7, 661.7)	210/292.3 (254.1, 334.6)
AEs by intensity								
Mild	6/730.5 (268.1, 1590.0)	188/370.9 (319.8, 427.9)	155/304.3 (258.3, 356.1)	35/369.6 (257.4, 514.0)	384/343.1 (309.7, 379.2)	129/197.9 (165.2, 235.1)	23/345.9 (219.2, 518.9)	152/211.6 (179.3, 248.0)
Moderate	2/243.5 (29.5, 879.6)	63/124.3 (95.5, 159.0)	46/90.3 (66.1, 120.5)	13/137.3 (73.1, 234.7)	124/110.8 (92.2, 132.1)	46/70.6 (51.7, 94.1)	8/120.3 (51.9, 237.0)	54/75.2 (56.5, 98.1)
Severe	3/365.3 (75.3, 1067.4)	3/5.9 (1.2, 17.3)	8/15.7 (6.8, 30.9)	3/31.7 (6.5, 92.6)	17/15.2 (8.8, 24.3)	4/6.1 (1.7, 15.7)	0/0.0 (0, 45.0)	4/5.6 (1.5, 14.3)
Serious AEs	3/365.3 (75.3, 1067.4)	6/11.8 (4.3, 25.8)	6/11.8 (4.3, 25.6)	3/31.7 (6.5, 92.6)	18/16.1 (9.5, 25.4)	9/13.8 (6.3, 26.2)	0/0.0 (0, 45.0)	9/12.5 (5.7, 23.8)
AEs leading to discontinuation of study intervention	2/243.5 (29.5, 879.6)	3/5.9 (1.2, 17.3)	2/3.9 (0.5, 14.2)	1/10.6 (0.3, 58.8)	8/7.1 (3.1, 14.1)	6/9.2 (3.4, 20.0)	1/15.0 (0.4, 83.8)	7/9.7 (3.9, 20.1)
Infections[f]	0/0.0 (0, 364.7)	94/185.5 (149.9, 227.0)	79/155.1 (122.8, 193.3)	21/221.7 (137.3, 339.0)	194/173.3 (149.8, 199.5)	69/105.8 (82.4, 134.0)	15/225.6 (126.2, 372.0)	84/116.9 (93.3, 144.8)
Serious infections[f]	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	1/2.0 (0.0, 10.9)	0/0.0 (0, 31.6)	2/1.8 (0.2, 6.5)	3/4.6 (0.9, 13.4)	0/0.0 (0, 45.0)	3/4.2 (0.9, 12.2)
Opportunistic infections	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	0/0.0 (0, 5.9)	1/10.6 (0.3, 58.8)	2/1.8 (0.2, 6.5)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Death	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)

Key: AE = adverse event, Avg = average, CI = confidence interval, n = number of events
* Subjects received ustekinumab at Week I-0 in induction but not randomized at Week M-0 in maintenance.
[a] Subjects are counted in the treatment group they were randomized at Week M-0.
[b] Includes data through end of study or up to the time of exposure optimization substudy.
[c] Includes data from the time of exposure optimization substudy onward.
[d] Study CNTO1275PUC3001: Includes all subjects who received an administration of ustekinumab in induction at Week I-0.
[e] Study CNTO1275ISD3001: Includes all subjects from study CNTO1275PUC3001 who signed the ICF and entered the long-term extension study. Includes data from the date of informed consent for long-term extension study up to 28Apr2025.
[f] Infections as assessed by the investigator.
Note: Person-year of follow-up for a subject is calculated as (days of follow-up)/365.25. Incidence rate is calculated per 100 person-year and equals to 100 × (number of events) / (sum of person-year of follow-up).
Note: The 95% CI is computed using an exact Poisson approach.

Serious adverse event/deaths/other significant events

Serious adverse events

Serious AEs (SAEs) were infrequently reported during the induction period. A generally similar proportion of participants experienced at least one or more SAEs during the maintenance period. No PT was reported as an SAE more than once during the LTE. A majority of the reported PTs were consistent with the underlying disease under study. Additionally, most events resolved and were considered by the investigator to be not related to study intervention.

Induction Period: SAEs, Safety Analysis Set (PUC3001)

A total of 6 (5.4%) of 112 participants experienced at least one SAE during the induction period. All SAEs occurred in no more than two participants without any notable patterns with regard to SOC or type of event. Events included:

- Anaemia (SOC Blood and lymphatic system disorders) (n=2 [1.8%])
- Colitis ulcerative, (SOC Gastrointestinal disorders) (n=2 [1.8%])
- Infusion-related reaction (SOC Injury, poisoning and procedural complications) (n=1 [0.9%])
- Subcutaneous abscess (SOC Infections and infestations) (n=1 [0.9%])

Maintenance Period: SAEs, Safety Analysis Set (PUC3001)

During the maintenance period, 7 (6.4%) of 109 participants experienced one or more SAEs. Two (3.6%) of 55 participants in the q12w treatment group and 5 (9.3%) of 54 participants in the q8w treatment group reported an SAE. Events included:

- Colitis ulcerative, (SOC Gastrointestinal disorders) (n=2 [1.8%])
- Anaemia, (SOC Blood and lymphatic system disorders) (n=1 [0.9%])
- Salmonellosis, (SOC Infections and infestations) (n=1 [0.9%])
- Malnutrition, (SOC Metabolism and nutrition disorders) (n=1 [0.9%])
- Suicidal ideation, (SOC Psychiatric disorders) (n=1 [0.9%])
- Asthma, (SOC Respiratory, thoracic and mediastinal disorders) (n=1 [0.9%])

One SAE was a suicidal ideation in a participant who did not have a history of depression but was diagnosed at admission.

Long-term extension Period: i.e. ISD3001 in Paediatric UC; SAEs, Safety Analysis Set

In the LTE through the end of the reporting period, a total of 6 (9.1%) of 66 participants experienced at least one or more SAEs (

Table 53). Six (10.7%) of 56 participants in the q8w treatment group and 0 of 10 participants in the q4w treatment group reported an SAE. SAE event incidence was 12.5 per 100 PY across both treatment groups combined (71.84 total PY follow-up). Events included:

- Colitis ulcerative, (SOC Gastrointestinal disorders) (n=1 [1.5%])
- Bacterial colitis, (SOC Infections and infestations) (n=1 [1.5%])
- Cholangitis infective, (SOC Infections and infestations) (n=1 [1.5%])
- Cytomegalovirus colitis, (SOC Infections and infestations) (n=1 [1.5%])
- Incision site abscess, (SOC Infections and infestations) (n=1 [1.5%])
- Completed suicide, (SOC Psychiatric disorders) (n=1 [1.5%])
- Gender dysphoria, (SOC Psychiatric disorders) (n=1 [1.5%])
- Endoscopic retrograde cholangiopancreatography (SOC Investigations) (n=1 [1.5%])
- Neuropathy peripheral (SOC Nervous system disorders) (n=1 [1.5%])

Safety Data during the Induction and Maintenance Periods and LTE; SAEs, Safety Analysis Set (PUC3001 and ISD3001)

In the induction and maintenance periods through the end of the study (PUC3001), a total of 13 (11.6%) of 112 participants experienced at least one or more SAEs. Five (9.1%) of the 55 participants in the q12w treatment group, 6 (11.1%) of the 54 participants in the q8w treatment group, 2 (9.5%) of 21 participants in the q4w treatment group, and 1 (33.3%) of 3 participants in the not randomised group. SAE incidence was 16.1 per 100 PY (111.91 total PY of follow-up) across all treatment groups.

SAE incidence rates were comparable in the q12w and q8w treatment groups, higher in the q4w treatment group, and highest in the nonrandomised group.

Table 53: Incidence of treatment-emergent serious adverse events per 100 person-years from Week I-0 through End of Study and during Long-term Extension Period by system organ class and preferred term; safety analysis set (Studies CNTO1275PUC3001 and CNTO1275ISD3001) (Ref table TSFAEPED04, Summary of Clinical Safety)

TSFAEPED04: Incidence of Treatment-emergent Serious Adverse Events per 100 Person-years From Week I-0 Through End of Study and During Long-term Extension Period by System Organ Class and Preferred Term; Safety Analysis Set (Studies CNTO1275PUC3001 and CNTO1275ISD3001)

	Ustekinumab							
	From Week I-0 Through End of Study					Long-term Extension		
	PUC3001					ISD3001		
	Not randomized*	q12w[a, b]	q8w[a, b]	q4w[c]	Total	q8w	q4w	Total
Analysis set: Safety[d] or Enrolled[e] Analysis Set	3	55	54	21	112	56	10	66
Avg duration of follow-up (weeks)	14.3	48.1	49.2	23.5	52.1	60.7	34.7	56.8
Avg exposure (number of administrations)	1.0	8.8	9.2	6.7	10.0	8.6	8.9	8.6
Total person-year of follow-up	0.82	50.68	50.94	9.47	111.91	65.19	6.65	71.84
Number of subjects with 1 or more serious AEs	1	5	6	2	13	6	0	6
Any serious AEs (n/incidence rate (95% CI))	3/365.3 (75.3, 1067.4)	6/11.8 (4.3, 25.8)	6/11.8 (4.3, 25.6)	3/31.7 (6.5, 92.6)	18/16.1 (9.5, 25.4)	9/13.8 (6.3, 26.2)	0/0.0 (0, 45.0)	9/12.5 (5.7, 23.8)
System organ class/preferred term (n/incidence rate (95% CI))								
Gastrointestinal disorders	2/243.5 (29.5, 879.6)	1/2.0 (0.0, 11.0)	2/3.9 (0.5, 14.2)	1/10.6 (0.3, 58.8)	6/5.4 (2.0, 11.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Colitis ulcerative	2/243.5 (29.5, 879.6)	1/2.0 (0.0, 11.0)	2/3.9 (0.5, 14.2)	1/10.6 (0.3, 58.8)	6/5.4 (2.0, 11.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Blood and lymphatic system disorders	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	2/3.9 (0.5, 14.2)	1/10.6 (0.3, 58.8)	4/3.6 (1.0, 9.2)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Anaemia	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	2/3.9 (0.5, 14.2)	0/0.0 (0, 31.6)	3/2.7 (0.6, 7.8)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Iron deficiency anaemia	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	1/10.6 (0.3, 58.8)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Infections and infestations	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	1/2.0 (0.0, 10.9)	0/0.0 (0, 31.6)	2/1.8 (0.2, 6.5)	4/6.1 (1.7, 15.7)	0/0.0 (0, 45.0)	4/5.6 (1.5, 14.3)
Salmonellosis	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	1/2.0 (0.0, 10.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Subcutaneous abscess	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Bacterial colitis	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Cholangitis infective	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Cytomegalovirus colitis	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Incision site abscess	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Injury, poisoning and procedural complications	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Infusion related reaction	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Metabolism and nutrition disorders	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Malnutrition	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Psychiatric disorders	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	1/2.0 (0.0, 10.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	2/3.1 (0.4, 11.1)	0/0.0 (0, 45.0)	2/2.8 (0.3, 10.1)
Suicidal ideation	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	1/2.0 (0.0, 10.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Completed suicide	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Gender dysphoria	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Renal and urinary disorders	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	1/10.6 (0.3, 58.8)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)

Acute kidney injury	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	1/10.6 (0.3, 58.8)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Respiratory, thoracic and mediastinal disorders	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Asthma	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Surgical and medical procedures	1/121.8 (3.1, 678.3)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Stoma closure	1/121.8 (3.1, 678.3)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Investigations	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Endoscopic retrograde cholangiopancreatography	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Nervous system disorders	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Neuropathy peripheral	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)

Key: AE = adverse event, Avg = average, CI = confidence interval, n = number of events
* Subjects received ustekinumab at Week I-0 in induction but not randomized at Week M-0 in maintenance.
[a] Subjects are counted in the treatment group they were randomized at Week M-0.
[b] Includes data through end of study or up to the time of exposure optimization substudy.
[c] Includes data from the time of exposure optimization substudy onward.
[d] Study CNTO1275PUC3001: Includes all subjects who received an administration of ustekinumab in induction at Week I-0.
[e] Study CNTO1275ISD3001: Includes all subjects from study CNTO1275PUC3001 who signed the ICF and entered the long-term extension study. Includes data from the date of informed consent for long-term extension study up to 28Apr2025.
Note: Person-year of follow-up for a subject is calculated as (days of follow-up)/365.25. Incidence rate is calculated per 100 person-year and equals to 100 × (number of events) / (sum of person-year of follow-up).
Note: The 95% CI is computed using an exact Poisson approach.
Note: Adverse events are coded using MedDRA Version 28.0.

Deaths

Safety Data during the Induction and Maintenance Periods and LTE; Deaths, Safety Analysis Set (PUC3001 and ISD3001)

No deaths were reported through the end of study in PUC3001. One death was reported during the LTE (ISD3001). A PT of completed suicide was reported, which was considered serious and severe. The investigator assessed the event of suicide as not related to ustekinumab.

The patient was a delayed responder to ustekinumab IV induction dosing and randomised to receive ustekinumab SC in the maintenance phase. The dosing regimen was blinded q8w and no SAEs were reported during the PUC3001 parent study.

- The participant did not have a history of depression or suicidal ideation at study entry or during PUC3001 study. Within the PUC3001 protocol specified IMPACT-III evaluations, the participant's response regarding "How do you feel during the past 2 weeks?" and "Are you happy with your life?" improved from a 3 (not good or bad/not happy or unhappy) at I-0, to a 4 (good/happy) or 5 (great/very happy) at I-8 and M-44. Clinically, the participant improved from a PUCAI score of 40 at screening to achieving and maintaining a score of 0 from M-12 through the end of the parent study. Similarly, the partial Mayo score improved from a 3 at I-0 to a 0 from M-16 through the end of the parent study.

In the LTE study, the participant received treatment with ustekinumab (90 mg SC q8w) on Study Day 31. The participant received the last dose of ustekinumab 90 mg SC on Study Day 80.

- On LTE Study Day 115 a serious AE of completed suicide (reported term: suicide) was reported, which was considered as severe in intensity. The investigator assessed the event of suicide as not related to ustekinumab.

Targeted adverse events of special interest

Targeted events are rare events that were selected for evaluation based on mechanistic plausibility (eg, serious infections, active TB, malignancies), or potential safety or population risks. Targeted AESIs are classified into the following categories:

- Serious infections
- Malignancies
- Opportunistic infection
- Active TB

Safety data for targeted AESIs include data through one year of induction and maintenance, i.e., through Week M-44 (including any final safety visit data for participants who discontinued study intervention prior to Week M-44) for PUC3001 and during LTE for ISD3001.

Table 54*:* Incidence of treatment-emergent serious infections per 100 person-years from Week I-0 through End of Study and during Long-term Extension Period by system organ class and preferred term; safety analysis set (Studies CNTO1275PUC3001 and CNTO1275ISD3001) (Ref table TSFAEPED06, Summary of Clinical Safety)

TSFAEPED06: Incidence of Treatment-emergent Serious Infections per 100 Person-years From Week I-0 Through End of Study and During Long-term Extension Period by System Organ Class and Preferred Term; Safety Analysis Set (Studies CNTO1275PUC3001 and CNTO1275ISD3001)

	Ustekinumab							
	From Week I-0 Through End of Study					Long-term Extension		
	PUC3001					ISD3001		
	Not randomized*	q12w[a, b]	q8w[a, b]	q4w[c]	Total	q8w	q4w	Total
Analysis set: Safety[d] or Enrolled[e] Analysis Set	3	55	54	21	112	56	10	66
Avg duration of follow-up (weeks)	14.3	48.1	49.2	23.5	52.1	60.7	34.7	56.8
Avg exposure (number of administrations)	1.0	8.8	9.2	6.7	10.0	8.6	8.9	8.6
Total person-year of follow-up	0.82	50.68	50.94	9.47	111.91	65.19	6.65	71.84
Number of subjects with 1 or more serious infections[f]	0	1	1	0	2	2	0	2
Any serious infections[f] (n/incidence rate (95% CI))	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	1/2.0 (0.0, 10.9)	0/0.0 (0, 31.6)	2/1.8 (0.2, 6.5)	3/4.6 (0.9, 13.4)	0/0.0 (0, 45.0)	3/4.2 (0.9, 12.2)
System organ class/preferred term (n/incidence rate (95% CI))								
Infections and infestations	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	1/2.0 (0.0, 10.9)	0/0.0 (0, 31.6)	2/1.8 (0.2, 6.5)	3/4.6 (0.9, 13.4)	0/0.0 (0, 45.0)	3/4.2 (0.9, 12.2)
Salmonellosis	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	1/2.0 (0.0, 10.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Subcutaneous abscess	0/0.0 (0, 364.7)	1/2.0 (0.0, 11.0)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	1/0.9 (0.0, 5.0)	0/0.0 (0, 4.6)	0/0.0 (0, 45.0)	0/0.0 (0, 4.2)
Bacterial colitis	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Cholangitis infective	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)
Cytomegalovirus colitis	0/0.0 (0, 364.7)	0/0.0 (0, 5.9)	0/0.0 (0, 5.9)	0/0.0 (0, 31.6)	0/0.0 (0, 2.7)	1/1.5 (0.0, 8.5)	0/0.0 (0, 45.0)	1/1.4 (0.0, 7.8)

Key: AE = adverse event, Avg = average, CI = confidence interval, n = number of events
* Subjects received ustekinumab at Week I-0 in induction but not randomized at Week M-0 in maintenance.
[a] Subjects are counted in the treatment group they were randomized at Week M-0.
[b] Includes data through end of study or up to the time of exposure optimization substudy.
[c] Includes data from the time of exposure optimization substudy onward.
[d] Study CNTO1275PUC3001: Includes all subjects who received an administration of ustekinumab in induction at Week I-0.
[e] Study CNTO1275ISD3001: Includes all subjects from study CNTO1275PUC3001 who signed the ICF and entered the long-term extension study. Includes data from the date of informed consent for long-term extension study up to 28Apr2025.
[f] Infections as assessed by the investigator.
Note: Person-year of follow-up for a subject is calculated as (days of follow-up)/365.25. Incidence rate is calculated per 100 person-year and equals to 100 × (number of events) / (sum of person-year of follow-up).
Note: The 95% CI is computed using an exact Poisson approach.
Note: Adverse events are coded using MedDRA Version 28.0.

Serious infections: The incidence rate of serious infections in PUC3001 was 1.8 per 100 PY (111.91 total PY of follow-up). In ISD3001, the incidence rate of serious infections was 4.2 per 100 PY (71.84 total PY of follow-up).

In PUC3001, 1 (0.9%) of 112 participants reported a serious infection during the induction phase. The participant had subcutaneous abscesses of the left lower abdomen and inter-scapular region that were judged not related to study drug injection but due to underlying disease. The abscesses required hospitalisation for incision, drainage, and oral antibiotics, and did not lead to discontinuation of ustekinumab.

In PUC3001, 1 (1.9%) of 54 participants in the q8w treatment group reported a serious infection of salmonellosis during the maintenance period. The event was considered by the investigator to be not related to study intervention, was severe, and did not lead to discontinuation of ustekinumab.

In the LTE ISD3001 study, 3 (4.5%) of the 66 participants had serious infections: bacterial colitis, cholangitis infective, and cytomegalovirus colitis. Cholangitis infective was reported by one participant in the q8w treatment group. The onset date of this AE was Study Day 50 and was 16 days duration. The event was considered by the investigator to be not related to study intervention and did not lead to discontinuation of ustekinumab.

In ISD3001, the serious infections bacterial colitis and cytomegalovirus colitis were reported in a participant that did not receive ustekinumab during the LTE. The SAE of cytomegalovirus colitis was reported on Study Day 8 and considered moderate in intensity. The event was resolved on Study Day 29, and the investigator assessed the event as not related to ustekinumab. The participant continued in the LTE safety follow-up period. On Study Day 98 (162 days after the last dose of ustekinumab), an SAE of bacterial colitis was reported and considered moderate in intensity. The investigator assessed the event as not related to ustekinumab.

Opportunistic infections: In PUC3001, one participant in the q12w group had an opportunistic infection (PT fungal esophagitis) during the maintenance period. The investigator reported this as a nonserious AE of mycotic oesophagitis of moderate intensity on Study Day 56 and assessed the event as not related to ustekinumab. The participant was treated with Fluconazole, and the AE was deemed resolved. No action was taken with ustekinumab due to this event.

In PUC3001, one participant in the Exposure Optimisation Substudy had an opportunistic infection (PT cytomegalovirus infection). The participant was first randomised to the q12w treatment group in the maintenance period and then enrolled in the q4w group of the EOS following a loss of response to ustekinumab on Study Day 141. On Study Day 260, the participant received a dose of ustekinumab 90 mg SC q4w prior to SAE of prerenal acute renal failure due to CMV on Study Day 274. The CMV infection was limited to the GI tract and required hospitalisation for antiviral therapy and rehydration. The event was considered resolved and the participant resumed study drug (ustekinumab 90 mg SC q4w) on Study Day 302. The investigator assessed the event as not related to ustekinumab.

In ISD3001, one participant had an opportunistic infection (PT cytomegalovirus colitis) reported on Study Day 8. The patient had completed the parent PUC3001 study in the q12w treatment arm. Treatment was interrupted due to the event and later permanently discontinued. Consequently, the participant did not receive any study treatment during the LTE ISD3001 study. On Study Day 29, the SAE of CMV colitis was reported as resolved. The investigator assessed the event as not related to ustekinumab.

Malignancy: No cases of malignancy were reported in the paediatric UC Safety Analysis Set of either PUC3001 or ISD3001 studies.

Active TB infections: No cases of active TB infections were reported in the paediatric UC Safety Analysis Set of either PUC3001 or ISD3001 studies.

Other significant events

A total of 3 (2.7%) of 112 participants had one or more 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). Events included:

- Non-cardiac chest pain, (SOC General disorders) (n=1 [0.9%]).
- Infusion related reaction, (SOC Injury, poisoning and procedural complications) (n=1 [0.9%]).
- Dyspnoea, (SOC Respiratory, thoracic and mediastinal disorders) (n=1 [0.9%]).
- Urticaria, (SOC Skin and subcutaneous tissue disorders) (n=1 [0.9%]).

One participant had mild dyspnoea and non-cardiac chest pain that resolved within 3 minutes of treatment and did not lead to discontinuation of study treatment. One participant had a serious infusion-related reaction with an elevated body temperature that resolved within one day and did not lead to discontinuation of study treatment. One participant had a nonserious case of urticaria that resolved within one hour of treatment. This event led to discontinuation of study treatment.

During the maintenance period of PUC3001, no participants in the q12w treatment group and one (1.9%) of 54 participants in the q8w treatment group had at least one AE of injection-site reaction. The participant had nonserious AEs of injection-site erythema and injection-site swelling. The events were mild in severity, did not lead to discontinuation of study intervention, and were considered resolved on the same day. No injection-site reaction events were reported during the LTE ISD3001 study.

There were no reports of anaphylaxis or delayed hypersensitivity (serum sickness-like) reactions in the ustekinumab groups for PUC3001 and ISD3001

Laboratory findings

Haematology & Chemistry

Haematology laboratory parameters included, but were not limited to, haemoglobin, haematocrit, platelet count, and WBC count with differential. Clinical chemistry parameters included, but were not limited to, sodium, potassium, chloride, blood urea nitrogen, creatinine, ALT, AST, GGT, total and direct bilirubin, alkaline phosphatase, calcium, phosphate, albumin, total protein, and CRP.

In general, the proportions of participants experiencing markedly abnormal values in haematology and chemistry laboratory test results were low, were similar between the q12w and q8w treatment groups, and there were no consistent trends observed that suggested an association of ustekinumab with changes in routine laboratory parameters.

Induction Period: Haematology & Chemistry, Safety Analysis Set (PUC3001)

Table 55: Summary of chemistry and haematology worst US NCI-CTCAE grade through Week I-8; safety analysis set (Study CNTO1275PUC3001) (Ref table TSFLAB02a, CNTO1275PUC3001 CSR)

TSFLAB02a:Summary of Chemistry and Hematology Worst US NCI-CTCAE Grade Through Week I-8; Safety Analysis Set (Study CNTO1275PUC3001)

		Ustekinumab IV				
		Worst US NCI-CTCAE Grade[a] Through Week I-8				
	N	0	1	2	3	4
Analysis set: Safety	112					
Chemistry						
Alanine Aminotransferase Increased	107	107 (100.0%)	0	0	0	0
Aspartate Aminotransferase Increased	105	105 (100.0%)	0	0	0	0
Hypoalbuminemia	107	106 (99.1%)	1 (0.9%)	0	0	0
Alkaline Phosphatase Increased	107	105 (98.1%)	2 (1.9%)	0	0	0
Blood Bilirubin Increased	107	102 (95.3%)	0	5 (4.7%)	0	0
Creatinine Increased	107	103 (96.3%)	4 (3.7%)	0	0	0
GGT Increased	107	107 (100.0%)	0	0	0	0
Hyperkalemia	107	106 (99.1%)	1 (0.9%)	0	0	0
Hypokalemia	107	106 (99.1%)	0	1 (0.9%)	0	0
Hypernatremia	107	107 (100.0%)	0	0	0	0
Hyponatremia	107	107 (100.0%)	0	0	0	0
Hematology						
Hemoglobin Increased	102	102 (100.0%)	0	0	0	0
Anemia	102	57 (55.9%)	27 (26.5%)	16 (15.7%)	2 (2.0%)	0
Lymphocyte Count Increased	101	100 (99.0%)	0	1 (1.0%)	0	0
Lymphocyte Count Decreased	101	96 (95.0%)	3 (3.0%)	1 (1.0%)	1 (1.0%)	0
Platelet Count Decreased	100	100 (100.0%)	0	0	0	0
Leukocytosis	102	102 (100.0%)	0	0	0	0
White Blood Cell Decreased	102	94 (92.2%)	6 (5.9%)	2 (2.0%)	0	0

Key: NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events
Note: N is the number of subjects with at least 1 postbaseline assessment for the specific lab test within the time period.
[a] Grades 1-4 are based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Haematology: During the induction period of PUC3001 study, no Grade 4 abnormalities were observed. Two (2.0%) of 102 participants had Grade 3 anaemia and 1 (1.0%) of 101 participants had Grade 3 lymphocyte count decreased. Grade 2 abnormalities of anaemia (16 [15.7%] of 102 participants), lymphocyte count decreased and lymphocyte count increased (1 [1.0%] of 101 participants each), and WBC decreased (2 [2.0%] of 102 participants) were observed during the induction period.

Chemistry: During the induction period of PUC3001 study, there were no Grade 4 or Grade 3 clinical chemistry parameter abnormalities observed. Chemistry parameter abnormalities of Grade 2 were sporadic in nature, reported in only 5 (4.7%) of 107 participants who had blood bilirubin increased and 1 (0.9%) of 107 participants who had hypokalemia.

Maintenance Period: Haematology & Chemistry, Safety Analysis Set (PUC3001)

Table 56: Summary of chemistry and haematology worst US NCI-CTCAE grade from Week M-0 through Week M-44; safety randomised analysis set (Study CNTO1275PUC3001) (Ref table TSFLAB02b, CNTO1275PUC3001 CSR)

TSFLAB02b: Summary of Chemistry and Hematology Worst US NCI-CTCAE Grade From Week M-0 Through Week M-44; Safety Randomized Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab SC q12w[a]						Ustekinumab SC q8w[a]						Combined					
		Worst US NCI-CTCAE Grade[b]						Worst US NCI-CTCAE Grade[b]						Worst US NCI-CTCAE Grade[b]				
	N	0	1	2	3	4	N	0	1	2	3	4	N	0	1	2	3	4
Analysis set: Safety Randomized	55						54						109					
Chemistry																		
Alanine Aminotransferase Increased	54	52 (96.3%)	2 (3.7%)	0	0	0	53	47 (88.7%)	4 (7.5%)	1 (1.9%)	1 (1.9%)	0	107	99 (92.5%)	6 (5.6%)	1 (0.9%)	1 (0.9%)	0
Aspartate Aminotransferase Increased	54	53 (98.1%)	1 (1.9%)	0	0	0	53	47 (88.7%)	5 (9.4%)	1 (1.9%)	0	0	107	100 (93.5%)	6 (5.6%)	1 (0.9%)	0	0
Hypoalbuminemia	54	54 (100.0%)	0	0	0	0	53	53 (100.0%)	0	0	0	0	107	107 (100.0%)	0	0	0	0
Alkaline Phosphatase Increased	54	48 (88.9%)	6 (11.1%)	0	0	0	53	44 (83.0%)	8 (15.1%)	1 (1.9%)	0	0	107	92 (86.0%)	14 (13.1%)	1 (0.9%)	0	0
Blood Bilirubin Increased	54	51 (94.4%)	2 (3.7%)	1 (1.9%)	0	0	53	48 (90.6%)	2 (3.8%)	3 (5.7%)	0	0	107	99 (92.5%)	4 (3.7%)	4 (3.7%)	0	0
Creatinine Increased	54	51 (94.4%)	3 (5.6%)	0	0	0	53	46 (86.8%)	6 (11.3%)	1 (1.9%)	0	0	107	97 (90.7%)	9 (8.4%)	1 (0.9%)	0	0
GGT Increased	54	53 (98.1%)	0	1 (1.9%)	0	0	53	50 (94.3%)	0	1 (1.9%)	2 (3.8%)	0	107	103 (96.3%)	0	2 (1.9%)	2 (1.9%)	0
Hyperkalemia	54	50 (92.6%)	3 (5.6%)	1 (1.9%)	0	0	53	49 (92.5%)	3 (5.7%)	1 (1.9%)	0	0	107	99 (92.5%)	6 (5.6%)	2 (1.9%)	0	0
Hypokalemia	54	53 (98.1%)	0	1 (1.9%)	0	0	53	52 (98.1%)	0	1 (1.9%)	0	0	107	105 (98.1%)	0	2 (1.9%)	0	0
Hypernatremia	54	53 (98.1%)	1 (1.9%)	0	0	0	53	53 (100.0%)	0	0	0	0	107	106 (99.1%)	1 (0.9%)	0	0	0
Hyponatremia	54	54 (100.0%)	0	0	0	0	53	53 (100.0%)	0	0	0	0	107	107 (100.0%)	0	0	0	0
Hematology																		
Hemoglobin Increased	54	54 (100.0%)	0	0	0	0	53	53 (100.0%)	0	0	0	0	107	107 (100.0%)	0	0	0	0
Anemia	54	20 (37.0%)	24 (44.4%)	7 (13.0%)	3 (5.6%)	0	53	20 (37.7%)	25 (47.2%)	7 (13.2%)	1 (1.9%)	0	107	40 (37.4%)	49 (45.8%)	14 (13.1%)	4 (3.7%)	0
Lymphocyte Count Increased	54	52 (96.3%)	0	2 (3.7%)	0	0	53	53 (100.0%)	0	0	0	0	107	105 (98.1%)	0	2 (1.9%)	0	0
Lymphocyte Count Decreased	54	47 (87.0%)	4 (7.4%)	2 (3.7%)	1 (1.9%)	0	53	44 (83.0%)	7 (13.2%)	1 (1.9%)	1 (1.9%)	0	107	91 (85.0%)	11 (10.3%)	3 (2.8%)	2 (1.9%)	0
Platelet Count Decreased	54	54 (100.0%)	0	0	0	0	53	52 (98.1%)	1 (1.9%)	0	0	0	107	106 (99.1%)	1 (0.9%)	0	0	0
Leukocytosis	54	54 (100.0%)	0	0	0	0	53	53 (100.0%)	0	0	0	0	107	107 (100.0%)	0	0	0	0
White Blood Cell Decreased	54	43 (79.6%)	11 (20.4%)	0	0	0	53	38 (71.7%)	11 (20.8%)	4 (7.5%)	0	0	107	81 (75.7%)	22 (20.6%)	4 (3.7%)	0	0

Key: NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events.
Note: N is the number of subjects with at least 1 postbaseline assessment for the specific lab test within the time period.
Note: Data from the time of substudy onward are not included and are summarized separately.
[a] Subjects who dose adjust will be counted in the treatment group they were randomized to at Week M-0.
[b] Grades 1-4 are based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Haematology: During the maintenance period of PUC3001 study, no Grade 4 abnormalities were observed. Of 107 participants, 2 (1.9%) had Grade 3 lymphocyte count decreased and 4 (3.7%) had Grade 3 anaemia. Grade 2 abnormalities of anaemia (14 [13.1%]), lymphocyte count increased (2

[1.9%]), lymphocyte count decreased (3 [2.8%]), and WBC decreased (4 [3.7%]) were observed during the maintenance period.

A large proportion of all participants (62.6%) had anaemia Grade ≥1. Although over 50% of all participants had Grade 1 or Grade 2 values, this is not uncommon for paediatric UC. The proportions of participants who had markedly abnormal values were consistent between the q12w and q8w treatment groups.

Chemistry: During the maintenance period of PUC3001 study, there were no Grade 4 clinical chemistry parameter abnormalities were observed in either treatment group. There were three participants in the q8w treatment group had Grade 3 chemistry abnormalities (1 ALT increased and 2 GGT increased); none of these Grade 3 events were associated with clinically relevant AEs (eg, infections). These events were considered not serious and did not lead to study intervention discontinuation.

Few Grade 2 clinical chemistry parameter abnormalities of ALT increased, AST increased, alkaline phosphatase increased, blood bilirubin increased, GGT increased, creatinine increased, hyperkalemia, and hypokalemia were observed, mostly reported in the q8w treatment group.

Long-term extension Period: i.e. ISD3001 in Paediatric UC; Haematology & Chemistry, Safety Analysis Set

Haematology: During the LTE ISD3001 study, no Grade 4 abnormalities were observed. One participant in the q8w treatment group had a Grade 3 abnormality of anaemia. Grade 2 abnormalities of anaemia (2 [3.7%] of 54 participants) and lymphocyte count decreased (2 [3.8%] of 53 participants) were observed.

Chemistry: In the LTE (ISD3001) through the end of the reporting period, there were no Grade 4 chemistry abnormalities observed in either treatment group (q8w or q4w). One participant in the q8w treatment group with a known diagnosis of primary sclerosing cholangitis had a Grade 3 chemistry laboratory abnormality (blood bilirubin increased). Grade 2 abnormalities of blood bilirubin increased (1 [1.9%] of 53 participants) and creatinine increased (2 [3.8%] of 52 participants) were observed, both in the q8w treatment group.

Few clinical chemistry parameter-related abnormalities have been reported as AEs (PTs ALT increased, CRP increased, transferrin saturation decreased, and serum ferritin decreased). These occurred in 1 (1.8%) of 55 participants each and only in the q8w treatment group. None of these AEs resulted in discontinuation of study intervention and none were considered serious by the investigator.

Liver function (Maximum ALT, AST, and Bilirubin)

During the induction period, all participants who had liver enzyme values ≤ ULN at baseline had maximum postbaseline ALT and AST levels that were within the reference range (≤1×ULN), and 102 (92%) of 106 participants had maximum postbaseline total bilirubin levels that were within the reference range. There were no observations of ALT or AST >5×ULN.

One participant, who was diagnosed with Gilbert's syndrome prior to the study, had total bilirubin values of 21 µmol/L at screening and 16 µmol/L at Week I-0 (both ≤1×ULN of 21 µmoL/L); the bilirubin value increased to >2×ULN (>42 µmoL/L) at Week I-8 and fluctuated between a high of 57 µmoL/L and normal throughout the study, with no concomitant elevations in ALT/AST. This event at Week I-8 was considered nonserious, moderate in severity, not related, and did not lead to study intervention discontinuation.

Table 57: Summary of worst postbaseline NCI-CTCAE toxicity grades for chemistry laboratory values from Week I-0 through Week I-8; safety analysis set (Ref table TSFLAB01a, Summary of Clinical Safety)

TSFLAB01a: Summary of Worst Postbaseline NCI-CTCAE Toxicity Grades for Chemistry Laboratory Value From Week I-0 Through Week I-8; Safety Analysis Set (Studies Summary of Clinical Safety)

	Ustekinumab IV	
	Pediatric UC (2-<18 Years)	Adult UC (≥18 Years)
	PUC3001	UCO3001 6 mg/kg
Analysis set: Safety[a]	112	320
Alanine Aminotransferase Increased		
N	107	318
Grade 0	107 (100.0%)	292 (91.8%)
Grade 1	0	23 (7.2%)
Grade 2	0	3 (0.9%)
Grade 3	0	0
Grade 4	0	0
Aspartate Aminotransferase Increased		
N	105	318
Grade 0	105 (100.0%)	298 (93.7%)
Grade 1	0	16 (5.0%)
Grade 2	0	3 (0.9%)
Grade 3	0	1 (0.3%)
Grade 4	0	0

During the maintenance period, most participants (≥92.3%) who had liver enzyme values ≤ULN at baseline, had maximum post baseline ALT, AST, and total bilirubin levels that were within the reference range (≤1×ULN).

Several participants had maximum postbaseline ALT, AST, and/or total bilirubin abnormalities through the maintenance period:

- 2 (3.8%) of 53 participants in the q12w treatment group and 4 (7.8%) of 51 participants in the q8w treatment group had a postbaseline maximum measurement of ALT >1 and ≤3×ULN.
- 1 (2.0%) participant in the q8w treatment group had a postbaseline maximum measurement of ALT >3 and ≤5×ULN, and 1 (2.0%) participant had ALT >5 and ≤20×ULN. Both participants had no concomitant elevations of bilirubin to ≥2×ULN.
- 1 (1.9%) of 53 participants in the q12w treatment group and 5 (9.6%) of 52 participants in the q8w treatment group had a postbaseline maximum measurement of AST >1 and ≤3×ULN.
- 1 (1.9%) participant in the q8w treatment group had a postbaseline maximum measurement AST value of >3 and ≤5×ULN.
- 2 (3.8%) of 53 participants in the q12w treatment group and 4 (7.5%) of 53 participants in the q8w treatment group had a postbaseline total bilirubin maximum measurement of >1 and ≤2×ULN (>21 and ≤42 µmoL/L).
- 1 (1.9%) participant in the q8w treatment group, who was diagnosed with Gilbert's syndrome prior to the study as mentioned in Section 3.1.2.2.1, had a postbaseline total bilirubin maximum measurement of 57 µmoL/L, which was >2×ULN (>42 µmoL/L) at Week M-44; other bilirubin

values during the maintenance period were normal except for an elevation to >1 and ≤2×ULN (>21 and ≤42 µmoL/L) at Week M-24.

One paediatric participant had a postbaseline maximum measurement of ALT >3 and ≤5×ULN at Weeks M-24 and M-44 and was later diagnosed with primary sclerosing cholangitis not related to ustekinumab. One paediatric participant had a postbaseline ALT value >5×ULN and ≤20×ULN at Week M-4, with all ALT values returning to normal from Week M-8 to Week M-44.

Table 58: Summary of worst postbaseline NCI-CTCAE toxicity grades for chemistry laboratory values from Week M-0 through Week M-44; safety randomised analysis set (Ref table TSFLAB01b, Summary of Clinical Safety)

TSFLAB01b: Summary of Worst Postbaseline NCI-CTCAE Toxicity Grades for Chemistry Laboratory Value From Week M-0 Through Week M-44; Safety Randomized Analysis Set (Studies Summary of Clinical Safety)

	Ustekinumab	
	Pediatric UC (2-<18 Years)	Adult UC (≥18 Years)
	PUC3001	UCO3001
Analysis set: Safety Randomized[a]	109	348
Alanine Aminotransferase Increased		
N	107	347
Grade 0	99 (92.5%)	292 (84.1%)
Grade 1	6 (5.6%)	51 (14.7%)
Grade 2	1 (0.9%)	4 (1.2%)
Grade 3	1 (0.9%)	0
Grade 4	0	0
Aspartate Aminotransferase Increased		
N	107	347
Grade 0	100 (93.5%)	294 (84.7%)
Grade 1	6 (5.6%)	49 (14.1%)
Grade 2	1 (0.9%)	3 (0.9%)
Grade 3	0	1 (0.3%)
Grade 4	0	0

In the LTE through the end of the reporting period:

- 49 (75.4%) of 65 participants each had ALT or AST ≤ULN at baseline. Of these, 1 participant each had a maximum postbaseline measurement of >1 and ≤3×ULN in the q8w treatment group only; all other participants had maximum postbaseline values within the reference range.
- 49 (75.4%) of 65 participants had total bilirubin ≤ULN at baseline. Of these, 2 participants in the q8w treatment group and 1 participant in the q4w treatment group had maximum postbaseline measurements of >1 and ≤2×ULN; all other participants with a total bilirubin ≤ULN at baseline had maximum postbaseline values within the reference range.

Few participants who had values within reference range (≤ULN) at baseline had maximum postbaseline ALT, AST, and/or total bilirubin abnormalities through the reporting period. Additionally, there were no observations of AST or ALT values >5×ULN. All other participants had baseline and maximum postbaseline values within the reference range.

Physical Findings and Growth

No meaningful trends related to physical findings and growth were observed in PUC3001 or ISD3001, and the changes were consistent with a normal pattern of growth.

Safety in special populations

No distinct trends were observed in the safety profile for ustekinumab across subgroups based on prior biologic failure status, age, weight, and sex. It is noted that a history of biologic failure was not assessed in the LTE study ISD3001.

Age

The age range of the enrolled participants in PUC3001 and ISD3001 was 4 to 17 years. Due to the low number of participants ≥2 to <12 years of age (n=30 and n=12, respectively) compared with participants ≥12 to <18 years of age (n=82 and n=53), no meaningful comparisons can be made between the two age groups.

Induction Period; Weight Subgroup Analysis Set (PUC3001)

In the induction period of the pivotal PUC3001 study, AEs by age category were generally consistent between the younger (2 to <12 years of age) and older (12 to <18 years of age) subgroups through Week I-8 and from Week M-0 through Week M-44, with the exception of the following:

- Through Week I-8, a numerically higher proportion of participants 2 to <12 years of age compared with participants 12 to <18 years of age had 1 or more AEs (18 [60.0%] of 30 participants versus 41 [50.0%] of 82 participants) and infections (9 [30.0%] of 30 participants versus 17 [20.7%] of 82 participants.

Table 59: Overall summary of treatment-emergent adverse events through Week I-8 by baseline age; safety analysis set (Study CNTO1275PUC3001) (Ref table TSFAE01b, CNTO1275PUC3001 CSR)

TSFAE01b: Overall Summary of Treatment-emergent Adverse Events Through Week I-8 by Baseline Age; Safety Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab IV				
	Baseline Age				
	2-<12 years				
	2-<6 years	6-<12 years	Combined	12-<18 years	Total
Analysis set: Safety	3	27	30	82	112
Avg duration of follow-up (weeks)	8.5	8.3	8.3	8.2	8.2
Avg exposure (number of administrations)	1.0	1.0	1.0	1.0	1.0
Subjects with 1 or more:					
AEs	1 (33.3%)	17 (63.0%)	18 (60.0%)	41 (50.0%)	59 (52.7%)
Serious AEs	0	2 (7.4%)	2 (6.7%)	4 (4.9%)	6 (5.4%)
AEs leading to death	0	0	0	0	0
AEs leading to discontinuation of study intervention	0	0	0	2 (2.4%)	2 (1.8%)
AEs reasonably related to study intervention	0	1 (3.7%)	1 (3.3%)	5 (6.1%)	6 (5.4%)
AEs of severe intensity	0	2 (7.4%)	2 (6.7%)	3 (3.7%)	5 (4.5%)
Infections	1 (33.3%)	8 (29.6%)	9 (30.0%)	17 (20.7%)	26 (23.2%)
Serious infections	0	0	0	1 (1.2%)	1 (0.9%)
Infection requiring oral and/or parenteral antimicrobial treatment	0	1 (3.7%)	1 (3.3%)	3 (3.7%)	4 (3.6%)
Malignancy	0	0	0	0	0
Active tuberculous infections	0	0	0	0	0
Opportunistic infections	0	0	0	0	0
AEs temporally associated with the infusion of study intervention at Week I-0	0	0	0	3 (3.7%)	3 (2.7%)

Key: AE = adverse event, Avg = average
Note: Infections as assessed by the investigator.

Maintenance Period; Age Subgroup Analysis Set (PUC3001)

Table 60*:* Overall summary of treatment-emergent adverse events from Week M-0 through Week M-44 by baseline age; randomised analysis set (Study CNTO1275PUC3001) (Ref table TSFAE02f, CNTO1275PUC3001 CSR)

TSFAE02f: Overall Summary of Treatment-emergent Adverse Events From Week M-0 Through Week M-44 by Baseline Age; Safety Randomized Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab SC					
	Baseline Age					
	2-<12 years			12-<18 years		
	q12w[a]	q8w[a]	Combined	q12w[a]	q8w[a]	Combined
Analysis set: Safety Randomized	16	13	29	39	41	80
Avg duration of follow-up (weeks)	35.5	38.4	36.8	37.6	39.1	38.4
Avg exposure (number of administrations)	10.8	11.8	11.2	6.6	7.0	6.8
Subjects with 1 or more:						
AEs	15 (93.8%)	11 (84.6%)	26 (89.7%)	37 (94.9%)	37 (90.2%)	74 (92.5%)
Serious AEs	0	2 (15.4%)	2 (6.9%)	2 (5.1%)	3 (7.3%)	5 (6.3%)
AEs leading to death	0	0	0	0	0	0
AEs leading to discontinuation of study intervention	1 (6.3%)	0	1 (3.4%)	2 (5.1%)	2 (4.9%)	4 (5.0%)
AEs reasonably related to study intervention	0	0	0	2 (5.1%)	4 (9.8%)	6 (7.5%)
AEs of severe intensity	1 (6.3%)	1 (7.7%)	2 (6.9%)	0	5 (12.2%)	5 (6.3%)
Infections	13 (81.3%)	7 (53.8%)	20 (69.0%)	24 (61.5%)	25 (61.0%)	49 (61.3%)
Serious infections	0	0	0	0	1 (2.4%)	1 (1.3%)
Infection requiring oral and/or parenteral antimicrobial treatment	3 (18.8%)	1 (7.7%)	4 (13.8%)	8 (20.5%)	6 (14.6%)	14 (17.5%)
Malignancy	0	0	0	0	0	0
Active tuberculous infections	0	0	0	0	0	0
Opportunistic infections	1 (6.3%)	0	1 (3.4%)	0	0	0
Injection site-reactions[b]	0	0	0	0	1 (2.4%)	1 (1.3%)

Key: AE = adverse event, Avg = average
Note: Infections as assessed by the investigator.
Note: Data from the time of substudy onward are not included.
[a] Subjects who dose adjust will be counted in the treatment group they were randomized to at Week M-0.
[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.

LTE; Age Subgroup Analysis Set (ISD3001)

In the LTE, overall AEs by age category were generally consistent, with participants 2 to 11 years of age (10 [83.3%] of 12 participants) compared with participants 12 to 17 years of age (40 [75.5%] of 53 participants) reporting at least one AE. A few exceptions include SAEs, AEs of severe intensity, and serious infections, which were only reported among participants 12 to 17 years of age. One AE of completed suicide, not related to ustekinumab, led to death in the 12- to 17-year age group.

Table 61: Overall summary of adverse events in the LTE by LTE baseline age through 28 April 2025; all enrolled analysis set (Study CNTO1275ISD3001) (Ref table TSFAE14a, Summary of Clinical Safety)

TSFAE14a: Overall Summary of Adverse Events in the LTE by LTE Baseline Age Through 28 April 2025; All Enrolled Analysis Set (Study CNTO1275ISD3001)

	Ustekinumab SC PUC3001 Baseline Age				
	2-11 years				
	2-5 years	6-11 years	Combined	12-17 years	Total
Analysis set: All enrolled	1	11	12	54	66
Avg duration of follow-up (weeks)	4.3	87.3	80.4	51.6	56.8
Avg exposure (number of administrations)	1.0	17.1	15.8	7.1	8.6
Subjects with 1 or more:					
AEs	0	11 (100.0%)	11 (91.7%)	42 (77.8%)	53 (80.3%)
Serious AEs	0	0	0	6 (11.1%)	6 (9.1%)
AEs leading to death	0	0	0	1 (1.9%)	1 (1.5%)
AEs leading to discontinuation of study intervention	0	1 (9.1%)	1 (8.3%)	6 (11.1%)	7 (10.6%)
AEs related to study intervention	0	0	0	1 (1.9%)	1 (1.5%)
AEs of severe intensity	0	0	0	3 (5.6%)	3 (4.5%)
Infections	0	9 (81.8%)	9 (75.0%)	31 (57.4%)	40 (60.6%)
Serious infections	0	0	0	2 (3.7%)	2 (3.0%)
Infection requiring oral and/or parenteral antimicrobial treatment	0	6 (54.5%)	6 (50.0%)	14 (25.9%)	20 (30.3%)
Malignancy	0	0	0	0	0
Active Tuberculous infections	0	0	0	0	0
Opportunistic infections	0	0	0	1 (1.9%)	1 (1.5%)
Possible anaphylactic or serum-sickness like reactions	0	0	0	0	0
Injection site reactions	0	0	0	0	0

Key: AE = adverse event, Avg = average

Weight

Overall AEs by weight category were generally consistent between participants <40 kg and participants ≥40 kg through Week I-8 and from Week M-0 through Week M-44. In the LTE through the end of the reporting period, overall AEs were generally consistent between weight categories with the exception of SAEs, which were numerically higher in the ≥40 kg subgroup.

Induction Period; Weight Subgroup Analysis Set (PUC3001)

When evaluating the impact of baseline weight (<40 kg [n=34] vs ≥40 kg [n=78]) on the overall summary of AEs in the induction period, a similar proportion of participants reported one or more AE in each weight subgroup (52.9% of participants <40 kg and 52.6% of participants ≥40 kg).

Through Week I-8, a numerically higher proportion of participants <30 kg had 1 or more AEs (11 [68.8%] of 16 participants) compared with participants ≥30 to <40 kg (7 [38.9%] of 18 participants) or those in the ≥40 kg subgroup (41 [52.6%] of 78 participants).

Infections and infection requiring oral and/or parenteral antimicrobial treatment were similar in the <40 kg subgroup and the ≥40 kg subgroup. However, a numerically higher proportion of participants <30 kg had 1 or more infections (7 [43.8%] of 16 participants) compared with participants ≥30 to <40 kg (3 [16.7%] of 18 participants) or those in the ≥40 kg subgroup (16 [20.5%] of 78 participants).

SAEs were reported in 1 (2.9%) participant with baseline weight <40 kg and 5 (6.4%) participants with baseline weight ≥40 kg. AEs leading to discontinuation of study intervention were reported in no participants in the <40 kg subgroup and 2 (2.6%) participants in the ≥40 kg subgroup.

Table 62: Overall summary of treatment-emergent adverse events through Week I-8 by baseline weight; safety analysis set (Study CNTO1275PUC3001) (Ref table TSFAE01b, CNTO1275PUC3001 CSR)

TSFAE01c: Overall Summary of Treatment-emergent Adverse Events Through Week I-8 by Baseline Weight; Safety Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab IV				
	Baseline Weight				
	<40 kg				
	<30 kg	≥30 - <40 kg	Combined	≥ 40 kg	Total
Analysis set: Safety	16	18	34	78	112
Avg duration of follow-up (weeks)	8.5	8.1	8.3	8.2	8.2
Avg exposure (number of administrations)	1.0	1.0	1.0	1.0	1.0
Subjects with 1 or more:					
AEs	11 (68.8%)	7 (38.9%)	18 (52.9%)	41 (52.6%)	59 (52.7%)
Serious AEs	1 (6.3%)	0	1 (2.9%)	5 (6.4%)	6 (5.4%)
AEs leading to death	0	0	0	0	0
AEs leading to discontinuation of study intervention	0	0	0	2 (2.6%)	2 (1.8%)
AEs reasonably related to study intervention	1 (6.3%)	0	1 (2.9%)	5 (6.4%)	6 (5.4%)
AEs of severe intensity	1 (6.3%)	0	1 (2.9%)	4 (5.1%)	5 (4.5%)
Infections	7 (43.8%)	3 (16.7%)	10 (29.4%)	16 (20.5%)	26 (23.2%)
Serious infections	0	0	0	1 (1.3%)	1 (0.9%)
Infection requiring oral and/or parenteral antimicrobial treatment	0	1 (5.6%)	1 (2.9%)	3 (3.8%)	4 (3.6%)
Malignancy	0	0	0	0	0
Active tuberculous infections	0	0	0	0	0
Opportunistic infections	0	0	0	0	0
AEs temporally associated with the infusion of study intervention at Week I-0	0	0	0	3 (3.8%)	3 (2.7%)

Key: AE = adverse event, Avg = average
Note: Infections as assessed by the investigator.

Maintenance Period; Weight Subgroup Analysis Set (PUC3001)

When evaluating the impact of baseline weight (<40 kg [n=33] vs ≥40 kg [n=76]) on the overall summary of AEs in the maintenance period, a similar proportion of participants reported one or more AE in each weight subgroup (87.9% of participants <40 kg and 93.4% of participants ≥40 kg).

From Week M-0 through Week M-44, a numerically higher proportion of participants in the q12w treatment group in the <40 kg subgroup had 1 or more infections (12 [80.0%] of 15 participants) compared with the q8w treatment group (9 [50.0%] of 18 participants) or the combined ≥40 kg subgroup (48 [63.2%] of 76 participants).

Infections and infection requiring oral and/or parenteral antimicrobial treatment were similar in the <40 kg subgroup and the ≥40 kg subgroup. SAEs were reported in 2 (6.1%) participants with baseline weight <40 kg and 5 (6.6%) participants with baseline weight ≥40 kg. AEs leading to discontinuation of study intervention were reported in no participants in the <40 kg subgroup and 5 (6.6%) participants in the ≥40 kg subgroup.

Table 63: Overall summary of treatment-emergent adverse events from Week M-0 through Week M-44 by baseline weight; safety randomised analysis set (Study CNTO1275PUC3001) (Ref table TSFAE02h, CNTO1275PUC3001 CSR)

TSFAE02h: Overall Summary of Treatment-emergent Adverse Events From Week M-0 Through Week M-44 by Baseline Weight; Safety Randomized Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab SC					
	Baseline Weight					
	<40 kg			≥ 40 kg		
	q12w[a]	q8w[a]	Combined	q12w[a]	q8w[a]	Combined
Analysis set: Safety Randomized	15	18	33	40	36	76
Avg duration of follow-up (weeks)	37.9	40.3	39.2	36.7	38.2	37.4
Avg exposure (number of administrations)	11.7	11.2	11.5	6.3	6.7	6.5
Subjects with 1 or more:						
AEs	14 (93.3%)	15 (83.3%)	29 (87.9%)	38 (95.0%)	33 (91.7%)	71 (93.4%)
Serious AEs	0	2 (11.1%)	2 (6.1%)	2 (5.0%)	3 (8.3%)	5 (6.6%)
AEs leading to death	0	0	0	0	0	0
AEs leading to discontinuation of study intervention	0	0	0	3 (7.5%)	2 (5.6%)	5 (6.6%)
AEs reasonably related to study intervention	0	1 (5.6%)	1 (3.0%)	2 (5.0%)	3 (8.3%)	5 (6.6%)
AEs of severe intensity	0	2 (11.1%)	2 (6.1%)	1 (2.5%)	4 (11.1%)	5 (6.6%)
Infections	12 (80.0%)	9 (50.0%)	21 (63.6%)	25 (62.5%)	23 (63.9%)	48 (63.2%)
Serious infections	0	0	0	0	1 (2.8%)	1 (1.3%)
Infection requiring oral and/or parenteral antimicrobial treatment	3 (20.0%)	2 (11.1%)	5 (15.2%)	8 (20.0%)	5 (13.9%)	13 (17.1%)
Malignancy	0	0	0	0	0	0
Active tuberculous infections	0	0	0	0	0	0
Opportunistic infections	0	0	0	1 (2.5%)	0	1 (1.3%)
Injection site-reactions[b]	0	0	0	0	1 (2.8%)	1 (1.3%)

Key: AE = adverse event, Avg = average
Note: Infections as assessed by the investigator.
Note: Data from the time of substudy onward are not included.
[a] Subjects who dose adjust will be counted in the treatment group they were randomized to at Week M-0
[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.

Table 64: Overall summary of treatment-emergent adverse events from Week M-0 through Week M-44 by baseline weight among subjects with weight less than 40 kg; safety randomised analysis set (Study CNTO1275PUC3001) (Ref table TSFAE02i, CNTO1275PUC3001 CSR)

TSFAE02i: Overall Summary of Treatment-emergent Adverse Events From Week M-0 Through Week M-44 by Baseline Weight Among Subjects With Weight Less Than 40 kg; Safety Randomized Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab SC					
	Baseline Weight					
	<30 kg			≥30 - <40 kg		
	q12w[a]	q8w[a]	Combined	q12w[a]	q8w[a]	Combined
Analysis set: Safety Randomized	8	7	15	7	11	18
Avg duration of follow-up (weeks)	38.0	38.3	38.1	37.7	41.5	40.0
Avg exposure (number of administrations)	12.5	12.7	12.6	10.9	10.3	10.5
Subjects with 1 or more:						
AEs	8 (100.0%)	5 (71.4%)	13 (86.7%)	6 (85.7%)	10 (90.9%)	16 (88.9%)
Serious AEs	0	1 (14.3%)	1 (6.7%)	0	1 (9.1%)	1 (5.6%)
AEs leading to death	0	0	0	0	0	0
AEs leading to discontinuation of study intervention	0	0	0	0	0	0
AEs reasonably related to study intervention	0	0	0	0	1 (9.1%)	1 (5.6%)
AEs of severe intensity	0	1 (14.3%)	1 (6.7%)	0	1 (9.1%)	1 (5.6%)
Infections	7 (87.5%)	4 (57.1%)	11 (73.3%)	5 (71.4%)	5 (45.5%)	10 (55.6%)
Serious infections	0	0	0	0	0	0
Infection requiring oral and/or parenteral antimicrobial treatment	3 (37.5%)	0	3 (20.0%)	0	2 (18.2%)	2 (11.1%)
Malignancy	0	0	0	0	0	0
Active tuberculous infections	0	0	0	0	0	0
Opportunistic infections	0	0	0	0	0	0
Injection site-reactions[b]	0	0	0	0	0	0

Key: AE = adverse event, Avg = average
Note: Infections as assessed by the investigator.
Note: Data from the time of substudy onward are not included.
[a] Subjects who dose adjust will be counted in the treatment group they were randomized to at Week M-0
[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.

LTE; Weight Subgroup Analysis Set (ISD3001)

When evaluating the impact of LTE baseline weight (<40 kg [n=15] vs ≥40 kg [n=51]) on the overall summary of AEs in the LTE through the end of the reporting period, a similar proportion of participants reported 1 or more AE in each weight subgroup (86.7% of participants <40 kg and 78.4% of participants ≥40 kg).

Infections and infection requiring oral and/or parenteral antimicrobial treatment were numerically higher in the <40 kg subgroup than the ≥40 kg subgroup. No SAEs were reported in participants with baseline LTE weight <40 kg; SAEs were reported in 6 (11.8%) participants with baseline LTE weight ≥40 kg. AEs leading to discontinuation of study intervention were reported in 2 (13.3%) participants in the <40 kg subgroup and 5 (9.8%) of 51 participants in the ≥40 kg subgroup.

Table 65: Overall summary of adverse events in the LTE by LTE baseline weight through 28 April 2025; all enrolled analysis set (Study CNTO1275ISD3001) (Ref table TSFAE14b, Summary of Clinical Safety)

TSFAE14b: Overall Summary of Adverse Events in the LTE by LTE Baseline Weight Through 28 April 2025; All Enrolled Analysis Set (Study CNTO1275ISD3001)

	Ustekinumab SC PUC3001 Baseline Weight				
	<40 kg				
	<30 kg	≥30 - <40 kg	Combined	≥40 kg	Total
Analysis set: All enrolled	6	9	15	51	66
Avg duration of follow-up (weeks)	55.0	78.8	69.3	53.1	56.8
Avg exposure (number of administrations)	12.2	14.7	13.7	7.2	8.6
Subjects with 1 or more:					
AEs	5 (83.3%)	8 (88.9%)	13 (86.7%)	40 (78.4%)	53 (80.3%)
Serious AEs	0	0	0	6 (11.8%)	6 (9.1%)
AEs leading to death	0	0	0	1 (2.0%)	1 (1.5%)
AEs leading to discontinuation of study intervention	0	2 (22.2%)	2 (13.3%)	5 (9.8%)	7 (10.6%)
AEs related to study intervention	0	0	0	1 (2.0%)	1 (1.5%)
AEs of severe intensity	0	0	0	3 (5.9%)	3 (4.5%)
Infections	5 (83.3%)	6 (66.7%)	11 (73.3%)	29 (56.9%)	40 (60.6%)
Serious infections	0	0	0	2 (3.9%)	2 (3.0%)
Infection requiring oral and/or parenteral antimicrobial treatment	3 (50.0%)	5 (55.6%)	8 (53.3%)	12 (23.5%)	20 (30.3%)
Malignancy	0	0	0	0	0
Active Tuberculous infections	0	0	0	0	0
Opportunistic infections	0	0	0	1 (2.0%)	1 (1.5%)
Possible anaphylactic or serum-sickness like reactions	0	0	0	0	0
Injection site reactions	0	0	0	0	0

Key: AE = adverse event, Avg = average

Biologic failure history

Induction Period; Prior Biologic Status Subgroup Analysis Set (PUC3001)

Through Week I-8, a numerically higher proportion of participants with prior biologic failure compared with those without biologic failure had one or more AEs (28 [63.6%] of 44 participants versus 31 [45.6%] of 68 participants), SAEs (3 [6.8%] versus 3 [4.4%), AEs leading to discontinuation (1 [2.3%] versus 1 [1.5%]), and infections (16 [36.4%] versus 10 [14.7%] of 68).

Table 66: Overall summary of treatment-emergent adverse events through Week I-8 by prior biologic failure status; safety analysis set (Study CNTO1275PUC3001) (Ref table TSFAE01p, CNTO1275PUC3001 CSR)

TSFAE01p: Overall Summary of Treatment-emergent Adverse Events Through Week I-8 by Prior Biologic Failure Status; Safety Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab IV	
	Biologic Failure	Non-biologic Failure
Analysis set: Safety	44	68
Avg duration of follow-up (weeks)	8.3	8.2
Avg exposure (number of administrations)	1.0	1.0
Subjects with 1 or more:		
AEs	28 (63.6%)	31 (45.6%)
Serious AEs	3 (6.8%)	3 (4.4%)
AEs leading to death	0	0
AEs leading to discontinuation of study intervention	1 (2.3%)	1 (1.5%)
AEs reasonably related to study intervention	3 (6.8%)	3 (4.4%)
AEs of severe intensity	2 (4.5%)	3 (4.4%)
Infections	16 (36.4%)	10 (14.7%)
Serious infections	0	1 (1.5%)
Infection requiring oral and/or parenteral antimicrobial treatment	3 (6.8%)	1 (1.5%)
Malignancy	0	0
Active tuberculous infections	0	0
Opportunistic infections	0	0
AEs temporally associated with the infusion of study intervention at Week I-0	1 (2.3%)	2 (2.9%)

Key: AE = adverse event, Avg = average
Note: Infections as assessed by the investigator.

Maintenance Period; Prior Biologic Status Subgroup Analysis Set (PUC3001)

The frequency of AEs was similar between groups based on prior biologic failure during the maintenance period (39 [90.7%] of 43 participants versus 61 [92.4%] of 66 participants).

Similar to the induction period, a numerically higher proportion of participants with prior biologic failure compared with those without biologic failure had one or more SAEs (4 [9.3%] of 43 participants versus 3 [4.5%] of 66 participants), and AEs leading to discontinuation (4 [9.3%] versus 1 [1.5%]).

From Week M-0 through Week M-44, a numerically higher proportion of participants without biologic failure in the q12w treatment group had 1 or more infections (23 [79.3%] of 29 participants) compared with participants without biologic failure in the q8w treatment group (21 [56.8%] of 37 participants) and those in the combined treatment group with biologic failure (25 [58.1%] of 43 participants).

From Week M-0 through Week M-44, within participants with biologic failure, a numerically higher proportion of participants in the q8w treatment group had 1 or more infections (11 [64.7%] of 17 participants) compared with participants in the q12w treatment group (14 [53.8%] of 26 participants).

Table 67: Overall summary of treatment-emergent adverse events from Week M-0 through Week M-44 by prior biologic failure status; safety randomised analysis set (Study CNTO1275PUC3001) (Ref table TSFAE02p, CNTO1275PUC3001 CSR)

TSFAE02p: Overall Summary of Treatment-emergent Adverse Events From Week M-0 Through Week M-44 by Prior Biologic Failure Status; Safety Randomized Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab SC					
	Biologic Failures			Non-Biologic Failures		
	q12w[a]	q8w[a]	Combined	q12w[a]	q8w[a]	Combined
Analysis set: Safety Randomized	26	17	43	29	37	66
Avg duration of follow-up (weeks)	32.4	36.4	34.0	41.1	40.1	40.5
Avg exposure (number of administrations)	7.0	7.2	7.0	8.5	8.6	8.6
Subjects with 1 or more:						
AEs	24 (92.3%)	15 (88.2%)	39 (90.7%)	28 (96.6%)	33 (89.2%)	61 (92.4%)
Serious AEs	2 (7.7%)	2 (11.8%)	4 (9.3%)	0	3 (8.1%)	3 (4.5%)
AEs leading to death	0	0	0	0	0	0
AEs leading to discontinuation of study intervention	3 (11.5%)	1 (5.9%)	4 (9.3%)	0	1 (2.7%)	1 (1.5%)
AEs reasonably related to study intervention	1 (3.8%)	3 (17.6%)	4 (9.3%)	1 (3.4%)	1 (2.7%)	2 (3.0%)
AEs of severe intensity	1 (3.8%)	3 (17.6%)	4 (9.3%)	0	3 (8.1%)	3 (4.5%)
Infections	14 (53.8%)	11 (64.7%)	25 (58.1%)	23 (79.3%)	21 (56.8%)	44 (66.7%)
Serious infections	0	1 (5.9%)	1 (2.3%)	0	0	0
Infection requiring oral and/or parenteral antimicrobial treatment	4 (15.4%)	4 (23.5%)	8 (18.6%)	7 (24.1%)	3 (8.1%)	10 (15.2%)
Malignancy	0	0	0	0	0	0
Active tuberculous infections	0	0	0	0	0	0
Opportunistic infections	1 (3.8%)	0	1 (2.3%)	0	0	0
Injection site-reactions[b]	0	0	0	0	1 (2.7%)	1 (1.5%)

Key: AE = adverse event, Avg = average
Note: The subjects included have prior biologic experience.
Note: Infections as assessed by the investigator.
Note: Data from the time of substudy onward are not included.
[a] Subjects are counted in the treatment group they were randomized to at Week M-0
[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.

Pregnancy and lactation

There were no pregnancies reported in the paediatric ulcerative colitis population in studies PUC3001 or ISD3001.

Safety related to drug-drug interactions and other interactions

In keeping with adult ustekinumab studies in ulcerative colitis and Crohn's disease, immunogenicity was low in the paediatric ulcerative colitis population.

Among the 108 paediatric participants who received ustekinumab during the induction period and had appropriate samples, no participants were positive for antibodies to ustekinumab through Week I-8.

Among paediatric participants who received ustekinumab during both induction and maintenance (this population comprised participants who were in clinical response to ustekinumab therapy at Week I-8/M-0 or at Week M-8, and had received at least 1 administration of ustekinumab during maintenance, and had appropriate samples for detection of antibodies to ustekinumab), 2 (2.1%) of 97 participants were positive for antibodies to ustekinumab from Week M-0 through Week M-44 (Table 68). Both participants positive for antibodies to ustekinumab were positive for NAbs.

Table 68: Summary of antibody status from Week I-0 through Week M-44; immunogenicity all responder analysis set (Study CNTO1275PUC3001) (Ref table 34, CNTO1275PUC3001 CSR)

	Ustekinumab SC						
	Clinical Responders at Week M-0		Delayed Responders at Week M-8		All Responders		
	q12w	q8w	q12w	q8w	q12w	q8w	Combined
Analysis set: Immunogenicity All Responder Analysis Set	40	39	9	9	49	48	97
Subjects with appropriate samples[a]	40 (100.0%)	39 (100.0%)	9 (100.0%)	9 (100.0%)	49 (100.0%)	48 (100.0%)	97 (100.0%)
Subjects positive for treatment-emergent antibodies to Ustekinumab[b]	1 (2.5%)	1 (2.6%)	0	0	1 (2.0%)	1 (2.1%)	2 (2.1%)
Peak titers							
1:200	1	0	-	-	1	0	1
1:3200	0	1	-	-	0	1	1
Peak titer group							
<10	0	0	-	-	0	0	0
10-<100	0	0	-	-	0	0	0
100-<1000	1	0	-	-	1	0	1
≥1000	0	1	-	-	0	1	1
Subjects negative for treatment-emergent antibodies to Ustekinumab[c]	39 (97.5%)	38 (97.4%)	9 (100.0%)	9 (100.0%)	48 (98.0%)	47 (97.9%)	95 (97.9%)

[a] Subjects with appropriate samples defined as having at least one post-dose ADA time point collected for anti-ustekinumab antibody detection.
[b] Subjects positive for treatment-emergent antibodies to ustekinumab includes all subjects who were positive (treatment-boosted or treatment-induced) at any time after their first ustekinumab administration through Week M-44. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.
[c] Excludes subjects who were treatment-emergent positive at any time through Week M-44.

Discontinuation due to adverse events

AEs leading to discontinuation of study intervention were reported infrequently during the induction period (2 [1.8%] of 112 participants) and the maintenance period (5 [4.6%] of 109 total participants) of the primary study and the reporting period of the LTE (7 [10.6%] of 66 total participants).

Most AEs leading to discontinuation of study intervention were coded to the SOC Gastrointestinal disorders. The only PT in that SOC was colitis ulcerative (1 [0.9%] of 112 participants in the induction period of PUC3001, 4 [3.7%] of 109 participants in the maintenance period of PUC3001, and 4 [6.1%] of 66 participants in ISD3001). Other AEs reported by one participant included urticaria, malnutrition, cytomegalovirus colitis, neuropathy peripheral, and completed suicide.

- 3 (5.5%) of 55 participants in the q12w treatment group and 2 (3.7%) of 54 participants in the q8w treatment group in the maintenance portion of the PUC3001 study.
- 6 (10.7%) of 56 participants in the q8w treatment group and 1 (10.0%) of 10 participants in the q4w treatment group in the LTE study (ISD3001).

Comparisons of safety data between paediatric and adult UC studies

The MAH has provided a summary of relevant safety results during the induction and the maintenance period for the paediatric study CNTO1275PUC3001 and adult study CNTO1275UCO3001.

To more closely approximate the paediatric induction dose, only the 6 mg/kg adult induction dose data from CNTO1275UCO3001 are presented in comparison with data from CNTO1275PUC3001. A summary of relevant maintenance period safety results for the paediatric study (CNTO1275PUC3001 through Week M-44) and the adult study (CNTO1275UCO3001 through Week 44) is also provided. In the paediatric UC studies, patients with weight >40 kg received a dose corresponding to the adult posology

Induction Period (CNTO1275PUC3001 and CNTO1275UCO3001)

Table 69: Overall Summary of Treatment-emergent Adverse Events From Week I-0 Through Week I-8; Safety Analysis Set (Studies CNTO1275PUC3001 and CNTO1275UCO3001) (Ref table 7, Summary of clinical safety)

	Ustekinumab IV	
	Pediatric UC (2-<18 Years)	Adult UC (≥18 Years)
	PUC3001	UCO3001 6 mg/kg
Analysis set: Safety[a]	112	320
Avg duration of follow-up (weeks)	8.2	8.2
Avg exposure (number of administrations)	1.0	1.0
Subjects with 1 or more:		
AEs	59 (52.7%)	160 (50.0%)
Serious AEs	6 (5.4%)	10 (3.1%)
AEs leading to death	0	1 (0.3%)
AEs leading to discontinuation of study intervention	2 (1.8%)	0
AEs reasonably related to study intervention[b]	6 (5.4%)	44 (13.8%)
AEs of severe intensity	5 (4.5%)	12 (3.8%)
Infections[c]	26 (23.2%)	49 (15.3%)
Serious infections[c]	1 (0.9%)	1 (0.3%)
Infections[c] requiring oral and/or parenteral antimicrobial treatment	4 (3.6%)	10 (3.1%)
Active tuberculous infections	0	0
Opportunistic infections	0	0
AEs temporally associated with the infusion of study intervention at Week I-0[d]	3 (2.7%)	3 (0.9%)
Malignancy	0	0

Key: AE = adverse event, Avg = average
[a] Study CNTO1275PUC3001: Includes all subjects who received an administration of ustekinumab in induction at Week I-0. Study CNTO1275UCO3001: Includes all subjects who received an administration of ustekinumab 6 mg/kg in induction at Week I-0.
[b] An adverse event that is assessed by the investigator as related to study agent or if the relationship to study agent is missing.
[c] Infections as assessed by the investigator.
[d] These are AEs that occurred during or within 1 hour after the intravenous infusion of study intervention.

Comparison of the SOCs with the highest proportions of AEs through the induction period in the paediatric (PUC3001) and the adult (UCO3001)

The SOCs with the highest proportions (≥10%) of AEs through the induction period in the paediatric and the adult studies were Infections and infestations, Blood and lymphatic system disorders, and Gastrointestinal disorders. The most frequently reported PTs (reported in >5% of participants), based on the paediatric study, were anaemia (10.7%) and COVID-19 (6.3%). Within the Infections and infestations SOC, a numerically higher proportion of paediatric participants had a reported event of upper respiratory tract infection (4 [3.6%]) than the adult participants (4 [1.3%]). In addition, the proportion of participants reporting an AE of nasopharyngitis was 18 (5.6%) in adult participants and 2 (1.8%) in the paediatric participants. Within the Blood and lymphatic system disorders SOC, a numerically higher

proportion of paediatric participants (12 [10.7%]) reported an AE of anaemia compared with adult participants (8 [2.5%]).

Maintenance Period (CNTO1275PUC3001 and CNTO1275UCO3001)

Table 70: Overall Summary of Treatment-emergent Adverse Events From Week M-0 Through Week M-44; Safety Randomised Analysis Set (Studies CNTO1275PUC3001 and CNTO1275UCO3001) (Ref table 8, Summary of clinical safety)

	Ustekinumab	
	Pediatric UC (2-<18 Years)	Adult UC (≥18 Years)
	PUC3001	UCO3001
Analysis set: Safety Randomized[a]	109	348
Avg duration of follow-up (weeks)	38.0	42.0
Avg exposure (number of administrations)	8.0	7.4
Subjects with 1 or more:		
AEs	100 (91.7%)	255 (73.3%)
Serious AEs	7 (6.4%)	28 (8.0%)
AEs leading to death	0	0
AEs leading to discontinuation of study intervention	5 (4.6%)	14 (4.0%)
AEs reasonably related to study intervention[b]	6 (5.5%)	76 (21.8%)
AEs of severe intensity	7 (6.4%)	21 (6.0%)
Infections[c]	69 (63.3%)	144 (41.4%)
Serious infections[c]	1 (0.9%)	9 (2.6%)
Infections[c] requiring oral and/or parenteral antimicrobial treatment	18 (16.5%)	67 (19.3%)
Active tuberculous infections	0	0
Opportunistic infections	1 (0.9%)	3 (0.9%)
Injection site-reaction[d]	1 (0.9%)	6 (1.7%)
Malignancy	0	3 (0.9%)

Key: AE = adverse event, Avg = average
[a] Study CNTO1275PUC3001: Includes all subjects who were randomized (induction responders and nonresponders) into the maintenance period (Week M-0) of the study and received at least one dose of ustekinumab during maintenance. Study CNTO1275UCO3001: Includes all subjects who were randomized (induction responders regardless of the treatment group randomized at Week I-0) into the maintenance period at Week M-0 of the study and received at least one dose of ustekinumab during maintenance.
[b] An adverse event that is assessed by the investigator as related to study agent or if the relationship to study agent is missing.
[c] Infections as assessed by the investigator.
[d] 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: Data from the time of exposure optimization substudy onward in study CNTO1275PUC3001 are not included and are summarized separately.

Comparison of the SOCs with the highest proportions of AEs through the maintenance period in the paediatric (CNTO1275PUC3001) and the adult (CNTO1275UCO3001)

The SOCs with the highest proportions of AEs through the maintenance period in the paediatric and adult studies were Infections and infestations and Gastrointestinal disorders. The most frequently reported PTs (>10% of participants), based on the paediatric study, were colitis ulcerative, upper respiratory tract infection, nasopharyngitis and anaemia. A numerically higher proportion of participants in the paediatric study reported colitis ulcerative (34 [31.2%]) than the adult study (37 [10.6%]). Similarly for upper respiratory tract infection and anaemia a numerically higher proportion of participants in the paediatric study had this event compared to the adult study (27 [24.8%]) vs (21 [6.0%]) and (13 [11.9%]) vs (16 [4.6%]) respectively. A numerically higher proportion of participants in the paediatric study reported COVID-19 (7 [6.4%] compared with than the adult study (none). A numerically higher proportion of participants in the paediatric study reported RTI compared with the adult study (6 [5.5%]) vs (1 [0.3%]).

Table 71: Incidence of Key Safety Events Per 100 Person-years of Follow-up From Week I-0 Through Week M-44; Safety Analysis Set (Studies CNTO1275PUC3001 and CNTO1275UCO3001) (Ref table, TSFAEAP03c Summary of clinical safety)

	Ustekinumab	
	Pediatric UC (2-<18 Years)	Adult UC (≥18 Years)
	PUC3001	UCO3001
Analysis set: Safety[a]	112	825
Avg duration of follow-up (weeks)	45.4	39.5
Avg exposure (number of administrations)	8.8	4.3
Total person-year of follow-up	97.45	625.05
Events per 100 person-years (n/incidence rate (95% CI))		
AEs	454/465.9 (424.0, 510.8)	2397/383.5 (368.3, 399.2)
AEs by intensity		
Mild	331/339.7 (304.0, 378.3)	1607/257.1 (244.7, 270.0)
Moderate	109/111.9 (91.8, 134.9)	698/111.7 (103.5, 120.3)
Severe	14/14.4 (7.9, 24.1)	92/14.7 (11.9, 18.1)
Serious AEs	15/15.4 (8.6, 25.4)	101/16.2 (13.2, 19.6)
AEs leading to discontinuation of study intervention	7/7.2 (2.9, 14.8)	26/4.2 (2.7, 6.1)
Infections[b]	166/170.3 (145.4, 198.3)	569/91.0 (83.7, 98.8)
Serious infections[b]	2/2.1 (0.2, 7.4)	23/3.7 (2.3, 5.5)
Opportunistic infections	1/1.0 (0.0, 5.7)	5/0.8 (0.3, 1.9)
Death	0/0.0 (0, 3.1)	2/0.3 (0.0, 1.2)

Key: AE = adverse event, Avg = average, CI = confidence interval, n = number of events
[a] Study CNTO1275PUC3001: Includes all subjects who received at least one dose of ustekinumab from Week I-0 through Week M-44. Study CNTO1275UCO3001: Includes subjects who received an administration of ustekinumab 6 mg/kg or 130 mg/kg in induction period at Week I-0, and subjects who received placebo in induction period at Week I-0 and crossed over to receive ustekinumab.
[b] Infections as assessed by the investigator.
Note: Person-year of follow-up for a subject is calculated as (days of follow-up)/365.25. Incidence rate is calculated per 100 person-year and equals to 100 × (number of events) / (sum of person-year of follow-up).
Note: The 95% CI is computed using an exact Poisson approach.
Note: Data from the time of exposure optimization substudy onward in study CNTO1275PUC3001 are not included and are summarized separately.
Note: Study CNTO1275UCO3001, includes data up to 16 weeks from the first ustekinumab dose for subjects who were crossed over or rerandomized to placebo maintenance

Additional clinical data: Exposure Optimisation Substudy Data (PUC3001 and CRD3004) and LTE (ISD3001

Exposure Optimisation Substudy Data (PUC3001 and CRD3004) and LTE (ISD3001)

Exposure Optimisation Substudy (PUC3001)

Overview

Participants who had a confirmed LOR by Week 8 and had low steady-state trough ustekinumab concentrations (low exposure: 8-week steady state trough ustekinumab exposure of <1.4 µg/mL) or met the early escape criteria as nonresponders at the end of induction and had low ustekinumab exposure were eligible to participate in the optional EOS and received a modified dose regimen of **SC q4w**. During this substudy, ustekinumab wase administered subcutaneously q4w for a total duration of 16 weeks (5 doses) or through the Week M-40 visit, whichever was the longer duration of exposure.

Demographics

Overall, the demographic and clinical characteristics of the EOS participants at Week I-0 were similar to those of the main study participants except for the following:

- More than half of the EOS participants were male (14 [66.7%] of 21 participants versus 51 [45.5%] of 112 main study participants).
- A numerically higher proportion of EOS participants had a history of biologic failure (12 [57.1%] of 21 participants versus 44 [39.3%]) of 112 main study participants.

Among paediatric participants who entered the EOS and had appropriate samples, 1 (5.3%) of 19 participants was positive for antibodies to ustekinumab.

Exposure

A total of 22 participants enrolled into the EOS and a total of 21 participants received treatment (12 participants from the q12w treatment group and 9 participants from the q8w treatment group):

- Four (3.7%) participants (q12w: n=1; q8w: n=3) were induction nonresponder participants with low ustekinumab exposure levels who met the early escape criteria by Week M-8.
- Eighteen (18.6%) participants (q12w: n=12; q8w: n=6) were randomised into the maintenance period of the main study and experienced a confirmed LOR and had low ustekinumab exposure levels.
- One participant who entered the EOS from the q12w treatment group did not receive treatment during the EOS and was therefore not considered to be a part of the Substudy Analysis Set.
- Median total duration of exposure (weeks) in the substudy was 16.4 and 20.1 weeks in patients who entered from the q12w and q8w treatment groups, respectively.
- The median total number of SC injections in the substudy was 6.5 and 6.0 in patients who entered from the q12w and 6 q8w treatment groups, respectively.

Table 72: Number of subjects who received scheduled SC study agent by time point from the initiation of the substudy; Substudy Analysis Set (Study CNTO1275PUC3001) (CNTO1275PUC3001 CSR)

TSSEX03B: Number of Subjects Who Received Scheduled SC Study Agent by Time Point From the Initiation of the Substudy; Substudy Analysis Set (Study CNTO1275PUC3001)

	Ustekinumab SC		
	q12w→q4w	q8w→q4w	Combined
Analysis set: Substudy	12	9	21
Subjects receiving a scheduled study agent			
Substudy Baseline	12 (100.0%)	9 (100.0%)	21 (100.0%)
Substudy Week 4	10 (83.3%)	9 (100.0%)	19 (90.5%)
Substudy Week 8	8 (66.7%)	8 (88.9%)	16 (76.2%)
Substudy Week 12	8 (66.7%)	7 (77.8%)	15 (71.4%)
Substudy Week 16	7 (58.3%)	8 (88.9%)	15 (71.4%)
Substudy Week 20	1 (8.3%)	5 (55.6%)	6 (28.6%)
Substudy Week 24	2 (16.7%)	3 (33.3%)	5 (23.8%)
Substudy Week 28	2 (16.7%)	2 (22.2%)	4 (19.0%)

Table 73: Summary of Treatment with Study Agent From the Initiation of the Substudy; Substudy Analysis Set (Study CNTO1275PUC3001) (Ref table TSSEX01, CNTO1275PUC3001 CSR)

	Ustekinumab SC	
	Randomized at Week M-0	
	q12w	q8w
Analysis set: Substudy	12	9
Total duration of Ustekinumab exposure (weeks)[a]		
N	12	9
Mean (SD)	15.1 (9.82)	21.1 (6.56)
Median	16.4	20.1
Range	(0; 32)	(8; 29)
Total number of Ustekinumab injections received		
N	12	9
Mean (SD)	6.3 (3.31)	7.1 (3.48)
Median	6.5	6.0
Range	(1; 12)	(5; 16)
Total dose of Ustekinumab administrations (mg)		
N	12	9
Mean (SD)	348.0 (197.29)	477.5 (178.31)
Median	321.8	540.0
Range	(77; 720)	(176; 720)

[a] Total duration of Ustekinumab exposure is defined as [(date of last dose of Ustekinumab) – (date of first dose of Ustekinumab) +1]/7.

Summary of Adverse Events

Table 74: Overall Summary of Treatment-emergent Adverse Events; Substudy Analysis Set (StudyCNTO1275PUC3001) (Ref table 29, CNTO1275PUC3001 CSR)

	Ustekinumab SC		
	q12w→q4w	q8w→q4w	Combined
Analysis set: Substudy	12	9	21
Avg duration of follow-up (weeks)	20.2	28.0	23.5
Avg exposure (number of administrations)	6.3	7.1	6.7
Subjects with 1 or more:			
AEs	8 (66.7%)	9 (100.0%)	17 (81.0%)
Serious AEs	1 (8.3%)	1 (11.1%)	2 (9.5%)
AEs leading to death	0	0	0
AEs leading to discontinuation of study intervention	1 (8.3%)	0	1 (4.8%)
AEs reasonably related to study intervention	0	0	0
AEs of severe intensity	1 (8.3%)	1 (11.1%)	2 (9.5%)
Infections	5 (41.7%)	7 (77.8%)	12 (57.1%)
Serious infections	0	0	0
Infection requiring oral and/or parenteral antimicrobial treatment	2 (16.7%)	0	2 (9.5%)
Malignancy	0	0	0
Active tuberculous infections	0	0	0
Opportunistic infections	1 (8.3%)	0	1 (4.8%)
Injection site-reactions[a]	0	0	0

AEs were most frequently reported in the following SOCs and PTs:

- Infections and infestations (12 [57.1%] of 21 participants)
    - Upper respiratory tract infection was the most frequently reported PT (6 [28.6%] participants).
- Blood and lymphatic system disorders (7 [33.3%] of 21 participants)
    - AEs reported in more than 1 participant for the PTs of anaemia (4 [19%]) and iron deficiency anaemia (3 [14.3%] participants).
- Gastrointestinal disorders (6 [28.6%] of 21 participants)
    - Colitis ulcerative was the most frequently reported PT (4 [19.0%] participants).

There were no AEs judged by the investigators to be related to study intervention, no malignancies, no cases of TB, no deaths, and no injection-site reactions. One opportunistic infection of cytomegalovirus infection occurred during the EOS.

There were 2 SAES colitis ulcerative and iron deficiency anaemia reported in the q12w → q4w and q8w → q4w treatment groups respectively.

Comparison between 21 paediatric participants with UC in PUC3001 and 26 paediatric CD participants in CRD3004 who were treated in the EOS and Long-term Extension Period ISD3001

Participants from the PUC3001 unblinded EOS continued to receive ustekinumab q4w or q8w in the ISD3001 LTE study. For CRD3004, early escape criteria (induction nonresponders) were the same as for PUC3001.

A total of 26 (26.8%) of 97 participants in CRD3004 (Crohn's disease) enrolled in the EOS. Among these 26 participants who were treated, 5 (19.2%) discontinued the q4w EOS treatment: 1 (3.8%) EOS participant each due to an AE of worsening CD, initiated prohibited medication, lack of efficacy, withdrawal by parent or guardian, and for the reason of "other" (high ustekinumab exposure so not able to proceed on q4w).

Table 75: Incidence of Key Safety Events Per 100 Person-years of Follow-up During Exposure Optimisation Substudy and Long-term Extension Period; Safety Analysis Set (Studies CNTO1275PUC3001, CNTO1275CRD3004 and CNTO1275ISD3001)

	Ustekinumab							
	Exposure Optimization Substudy						Long-term Extension	
	PUC3001			CRD3004			ISD3001	
							PUC3001[a]	CRD3004[b]
	q12w → q4w	q8w → q4w	Total	q12w → q4w	q8w → q4w	Total	q4w	q4w
Analysis set: Safety[c] or Enrolled Analysis Set	12	9	21	11	15	26	10	20
Avg duration of follow-up (weeks)	20.2	28.0	23.5	22.4	20.4	21.3	34.7	44.1
Avg exposure (number of administrations)	6.3	7.1	6.7	7.3	5.4	6.2	8.9	9.0
Total person-year of follow-up	4.65	4.82	9.47	4.72	5.87	10.59	6.65	16.89
Events per 100 person-years (n/incidence rate (95% CI))								
AEs	24/516.6 (331.0, 768.6)	27/559.7 (368.8, 814.3)	51/538.5 (401.0, 708.1)	32/677.6 (463.5, 956.5)	37/630.6 (444.0, 869.2)	69/651.6 (507.0, 824.6)	31/466.1 (316.7, 661.7)	100/592.1 (481.7, 720.1)
AEs by intensity								
Mild	17/365.9 (213.1, 585.8)	18/373.1 (221.1, 589.7)	35/369.6 (257.4, 514.0)	17/360.0 (209.7, 576.3)	26/443.1 (289.5, 649.3)	43/406.0 (293.9, 546.9)	23/345.9 (219.2, 518.9)	75/444.1 (349.3, 556.6)
Moderate	6/129.1 (47.4, 281.1)	7/145.1 (58.3, 299.0)	13/137.3 (73.1, 234.7)	12/254.1 (131.3, 443.8)	10/170.4 (81.7, 313.4)	22/207.7 (130.2, 314.5)	8/120.3 (51.9, 237.0)	20/118.4 (72.3, 182.9)
Severe	1/21.5 (0.5, 119.9)	2/41.5 (5.0, 149.8)	3/31.7 (6.5, 92.6)	3/63.5 (13.1, 185.6)	1/17.0 (0.4, 95.0)	4/37.8 (10.3, 96.7)	0/0.0 (0, 45.0)	5/29.6 (9.6, 69.1)
Serious AEs	1/21.5 (0.5, 119.9)	2/41.5 (5.0, 149.8)	3/31.7 (6.5, 92.6)	5/105.9 (34.4, 247.1)	1/17.0 (0.4, 95.0)	6/56.7 (20.8, 123.3)	0/0.0 (0, 45.0)	8/47.4 (20.4, 93.3)
AEs leading to discontinuation of study intervention	1/21.5 (0.5, 119.9)	0/0.0 (0, 62.1)	1/10.6 (0.3, 58.8)	1/21.2 (0.5, 118.0)	3/51.1 (10.5, 149.4)	4/37.8 (10.3, 96.7)	1/15.0 (0.4, 83.8)	6/35.5 (13.0, 77.3)
Infections[d]	10/215.2 (103.2, 395.8)	11/228.0 (113.8, 408.0)	21/221.7 (137.3, 339.0)	13/275.3 (146.6, 470.7)	12/204.5 (105.7, 357.3)	25/236.1 (152.8, 348.5)	15/225.6 (126.2, 372.0)	28/165.8 (110.2, 239.6)
Serious infections[d]	0/0.0 (0, 64.5)	0/0.0 (0, 62.1)	0/0.0 (0, 31.6)	4/84.7 (23.1, 216.9)	1/17.0 (0.4, 95.0)	5/47.2 (15.3, 110.2)	0/0.0 (0, 45.0)	2/11.8 (1.4, 42.8)
Opportunistic infections	1/21.5 (0.5, 119.9)	0/0.0 (0, 62.1)	1/10.6 (0.3, 58.8)	3/63.5 (13.1, 185.6)	0/0.0 (0, 51.1)	3/28.3 (5.8, 82.8)	0/0.0 (0, 45.0)	0/0.0 (0, 17.7)
Death	0/0.0 (0, 64.5)	0/0.0 (0, 62.1)	0/0.0 (0, 31.6)	0/0.0 (0, 63.4)	0/0.0 (0, 51.1)	0/0.0 (0, 28.3)	0/0.0 (0, 45.0)	0/0.0 (0, 17.7)

Key: AE = adverse event, Avg = average, CI = confidence interval, n = number of events
[a] Includes subjects from study CNTO1275PUC3001 exposure optimization substudy who signed the ICF and entered the long-term extension study. Includes data from the date of informed consent for long-term extension study up to 28Apr2025.
[b] Includes subjects from study CNTO1275CRD3004 exposure optimization substudy who signed the ICF and entered the long-term extension study. Includes data from the date of informed consent for long-term extension study up to 18Nov2024.
[c] CNTO1275PUC3001 and CNTO1275CRD3004 substudy: Includes all subjects who entered the exposure optimization substudy and received at least one dose of ustekinumab during the substudy.
[d] Infections as assessed by the investigator.
Note: Person-year of follow-up for a subject is calculated as (days of follow-up)/365.25. Incidence rate is calculated per 100 person-year and equals to 100 × (number of events) / (sum of person-year of follow-up).
Note: The 95% CI is computed using an exact Poisson approach.

Comparisons across ustekinumab paediatric indications

While differences in participant baseline characteristics, dosing, and exposure exist for the different diseases under study, this comparison evaluates whether the safety results in paediatric UC are generally consistent with the safety results in paediatric CD and paediatric PsO populations. Differences in exposure across disease states, IBD (UC and CD) and PsO, are due to the induction and maintenance dosing study regimens. Paediatric participants with UC and CD received a weight-tiered (participants weighing ≥40 kg)

or BSA-tiered (participants weighing <40 kg) IV induction dose and 1 of 2 SC maintenance dose regimens (q12w or q8w) of ustekinumab. Paediatric PsO participants in PSO3006 received an SC standard dose or half-standard dose of ustekinumab, and paediatric PsO participants in PSO3013 received weight-tiered SC doses of ustekinumab. The average number of ustekinumab administrations was 8.8 (2 to <18 years) for paediatric UC, 8.3 (2 to <18 years) for paediatric CD, and 4.8 (6 to <12 years) or 5.8 (12 to <18 years) for paediatric PsO.

Infections and infestations were the most commonly reported SOC, and the proportions of participants were comparable across studies.

- Upper respiratory infection and nasopharyngitis were the most reported PTs across studies. Proportions of participants reporting COVID-19 were comparable in UC and CD studies; no cases were reported in the PsO studies based on the dates these studies occurred.
- Blood and lymphatic system disorders, Gastrointestinal disorders, and Metabolism and nutrition disorders were more common in UC and CD studies, consistent with the underlying diseases being investigated. Anaemia and iron deficiency anaemia rates amongst participants with UC (20.5%, 6.3%) and CD (18.8%, 5.0%) were comparable.
- The majority of the PTs were consistent with the underlying disease under study. The most common PTs in UC and CD were colitis ulcerative (33.9%) and CD (37.6%), respectively.
- The incidence rates of AEs, AEs by intensity, and AEs leading to discontinuation of study intervention per 100 PY were comparable in UC and CD studies and lower in the PsO studies.

Table 76: ***Overall Summary of Treatment-emergent Adverse Events Through Approximately One; Safety Analysis Set (Studies CNTO1275PUC3001, CNTO1275CRD3004, CNTO1275PSO3006 and CNTO1275PSO3013) SCS Table 11***

	Ustekinumab			
	Pediatric UC (2-<18 Years)	Pediatric CRD (2-<18 Years)	Pediatric PSO (6-<18 Years)	
	PUC3001	CRD3004	PSO3013 (6-<12 Years)	PSO3006 (12-<18 Years)
Analysis set: Safety[a]	112	101	44	73
Avg duration of follow-up (weeks)	45.4	44.2	53.1	56.6
Avg exposure (number of administrations)	8.8	8.3	4.8	5.8
Subjects with 1 or more:				
AEs	105 (93.8%)	94 (93.1%)	34 (77.3%)	62 (84.9%)
Serious AEs	12 (10.7%)	17 (16.8%)	3 (6.8%)	6 (8.2%)
AEs leading to death	0	0	0	1 (1.4%)
AEs leading to discontinuation of study intervention	7 (6.3%)	8 (7.9%)	0	2 (2.7%)
AEs reasonably related to study intervention[b]	11 (9.8%)	11 (10.9%)	19 (43.2%)	18 (24.7%)
AEs of severe intensity	11 (9.8%)	10 (9.9%)	0	4 (5.5%)
Infections[c]	71 (63.4%)	66 (65.3%)	29 (65.9%)	50 (68.5%)
Serious infections[c]	2 (1.8%)	6 (5.9%)	1 (2.3%)	2 (2.7%)
Infections[c] requiring oral and/or parenteral antimicrobial treatment	20 (17.9%)	26 (25.7%)	12 (27.3%)	20 (27.4%)
Active tuberculous infections	0	0	0	0
Opportunistic infections	1 (0.9%)	0	0	0
AEs temporally associated with the infusion of study intervention at Week I-0[d]	3 (2.7%)	4 (4.0%)	0	0
Injection site-reaction[e]	1 (0.9%)	0	6 (13.6%)	1 (1.4%)
Malignancy	0	0	0	0

Key: AE = adverse event, Avg = average
Note: Studies CNTO1275PUC3001 and CNTO1275CRD3004: From Week I-0 through Week M-44, a total of 52 weeks. Study CNTO1275PSO3006: From Week 0 through Week 60, a total of 60 weeks. Study CNTO1275PSO3013: From Week 0 through Week 56, a total of 56 weeks.
[a] Studies CNTO1275PUC3001, CNTO1275CRD3004 and CNTO1275PSO3013: Includes all subjects who received at least one dose of ustekinumab. Study CNTO1275PSO3006: Includes all subjects who were randomized to the ustekinumab half-standard and standard dosage groups and received at least one dose of ustekinumab.
[b] An adverse event that is assessed by the investigator as related to study agent or if the relationship to study agent is missing.
[c] Infections as assessed by the investigator.
[d] These are AEs that occurred during or within 1 hour after the intravenous infusion of study intervention.
[e] 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: Data from the time of exposure optimization substudy onward in study CNTO1275PUC3001 and CNTO1275CRD3004 are not included and are summarized separately.

Table 77: Incidence of Key Safety Events Per 100 Person-years of Follow-up Through Approximately One Year; Safety Analysis Set (Studies CNTO1275PUC3001, CNTO1275CRD3004, CNTO1275PSO3006 and CNTO1275PSO3013) (Ref table 12, SCS)

	Ustekinumab			
	Pediatric UC (2-<18 Years)	Pediatric CRD (2-<18 Years)	Pediatric PSO (6-<18 Years)	
	PUC3001	CRD3004	PSO3013 (6-<12 Years)	PSO3006 (12-<18 Years)
Analysis set: Safety[a]	112	101	44	73
Avg duration of follow-up (weeks)	45.4	44.2	53.1	56.6
Avg exposure (number of administrations)	8.8	8.3	4.8	5.8
Total person-year of follow-up	97.45	85.60	44.82	79.20
Events per 100 person-years (n/incidence rate (95% CI))				
AEs	454/465.9 (424.0, 510.8)	528/616.8 (565.3, 671.7)	117/261.1 (215.9, 312.9)	289/364.9 (324.0, 409.5)
AEs by intensity				
Mild	331/339.7 (304.0, 378.3)	378/441.6 (398.2, 488.4)	93/207.5 (167.5, 254.2)	175/221.0 (189.4, 256.2)
Moderate	109/111.9 (91.8, 134.9)	130/151.9 (126.9, 180.3)	24/53.5 (34.3, 79.7)	108/136.4 (111.9, 164.6)
Severe	14/14.4 (7.9, 24.1)	20/23.4 (14.3, 36.1)	0/0.0 (0, 6.7)	6/7.6 (2.8, 16.5)
Serious AEs	15/15.4 (8.6, 25.4)	23/26.9 (17.0, 40.3)	3/6.7 (1.4, 19.6)	7/8.8 (3.6, 18.2)
AEs leading to discontinuation of study intervention	7/7.2 (2.9, 14.8)	13/15.2 (8.1, 26.0)	0/0.0 (0, 6.7)	5/6.3 (2.0, 14.7)
Infections[b]	166/170.3 (145.4, 198.3)	162/189.2 (161.2, 220.7)	65/145.0 (111.9, 184.9)	133/167.9 (140.6, 199.0)
Serious infections[b]	2/2.1 (0.2, 7.4)	7/8.2 (3.3, 16.8)	1/2.2 (0.1, 12.4)	2/2.5 (0.3, 9.1)
Opportunistic infections	1/1.0 (0.0, 5.7)	0/0.0 (0, 3.5)	0/0.0 (0, 6.7)	0/0.0 (0, 3.8)
Death	0/0.0 (0, 3.1)	0/0.0 (0, 3.5)	0/0.0 (0, 6.7)	1/1.3 (0.0, 7.0)

Key: AE = adverse event, Avg = average, CI = confidence interval, n = number of events
Note: Studies CNTO1275PUC3001 and CNTO1275CRD3004: From Week I-0 through Week M-44, a total of 52 weeks. Study CNTO1275PSO3006: From Week 0 through Week 60, a total of 60 weeks. Study CNTO1275PSO3013: From Week 0 through Week 56, a total of 56 weeks.
[a] Studies CNTO1275PUC3001, CNTO1275CRD3004 and CNTO1275PSO3013: Includes all subjects who received at least one dose of ustekinumab. Study CNTO1275PSO3006: Includes all subjects who were randomized to the ustekinumab half-standard and standard dosage groups and received at least one dose of ustekinumab.
[b] Infections as assessed by the investigator.
Note: Person-year of follow-up for a subject is calculated as (days of follow-up)/365.25. Incidence rate is calculated per 100 person-year and equals to 100 × (number of events) / (sum of person-year of follow-up).
Note: The 95% CI is computed using an exact Poisson approach.
Note: Data from the time of exposure optimization substudy onward in study CNTO1275PUC3001 and CNTO1275CRD3004 are not included and are summarized separately.

Post marketing experience

Postmarketing information has been accruing since the first approval of ustekinumab in December 2008. Ustekinumab is authorised for use in the treatment of adult and paediatric patients with chronic moderate to severe plaque PsO, adult and paediatric patients with active PsA, adult patients with moderately to severely active CD, and adult patients with moderately to severely active UC. Ustekinumab has also been approved in the EU for the treatment of moderately to severely active CD in paediatric patients >40 kg body weight who have had an inadequate response to or were intolerant to either conventional or biologic therapy.

In completed studies, a total of 12,905 participants have been exposed to ustekinumab across all disease indications, including 826 participants with UC (IB Ustekinumab 2025). Based on the 1,354,863,162 mg of ustekinumab distributed worldwide from launch to 31 December 2024, the estimated cumulative global postmarketing exposure to ustekinumab is 5,708,422 PY.

Based on the postmarketing safety surveillance, no new ADRs have been identified for ustekinumab. The safety profile in paediatrics has been considered similar to that seen in adults.

Observational Paediatric IBD Post Authorisation Safety Study (DEVELOP)

The DEVELOP registry is a multicentre, prospective, observational, ongoing PASS of the long-term safety and clinical status of paediatric patients with IBD, created to fulfil postmarketing commitments to health authorities in North America and the European Union. Enrolment of patients with additional IBD diagnoses (UC and IC) was added per protocol amendment in 2010 and the first patient with UC was enrolled on 26 August 2010. The DEVELOP registry completed enrolment in November 2017 and is ongoing. Safety data from the UC patients >2 and <18 years of age upon initial ustekinumab exposure were summarised (with

a data cutoff of 28 June 2024), to supplement the safety data for children with UC treated with ustekinumab.

Overall Extent of Exposure

In the DEVELOP registry,51 patients with UC who were >2 and <18 years of age upon initial ustekinumab exposure received ustekinumab, reflecting 119.6 patient-years of ustekinumab exposure. Of the 51 patients exposed to ustekinumab, 12 patients discontinued ustekinumab administration during the study, of whom 6 discontinued due to an AE. The mean (SD) time to discontinuation was 10.7 (14.13) months. All of the ustekinumab administered to patients >2 and <18 years of age in this PASS was prescribed off-label.

Baseline demographic and disease characteristics

The median age at initial ustekinumab exposure was 15.0 years. 32 (62.7%) of the 51 patients were white. A majority (32 [62.7%] patients) was female. Approximately half (25 [49.0%] patients) had a history of prior IBD-related surgery at initial ustekinumab exposure.

The majority of the ustekinumab-treated population were children with refractory disease as demonstrated by the prior UC medications received. All patients (51 [100%]) received at least 1 IBD-targeted biologic prior to ustekinumab treatment in the study, with 23 (45.1%) patients receiving at least 2 prior biologics and 15 (29.4%) patients receiving at least 3 prior biologics. Additionally, prior to ustekinumab treatment in the DEVELOP study, the majority of patients received immunomodulators (40 [78.4%] patients). Twenty-seven (52.9%) patients received thiopurines and 26 (51.0%) patients received MTX. The majority of patients also received steroids (47 [92.2%] patients) and 5-ASA (45 [88.2%] patients).

Adverse Events

Of the 51 patients (>2 and <18 years of age), 35 experienced AEs at a rate of 135.49 AEs per 100 patient-years of exposure. The SOCs with the most common AEs were Gastrointestinal disorders and Infections and infestations. (See Table 78)

Deaths and SAEs

None of the 51 patients died during the registry follow-up or transition periods. During ustekinumab exposure, the rate of patients with ≥1 SAE per 100 patient-years of exposure was 10.04 (12 patients with events during 119.6 patient-years of exposure). The rate of SAEs per 100 patient-years of exposure was 30.94 (37 events). There were 9 SAEs in the SOC of Gastrointestinal disorders (7.53 SAEs per 100 patient-years). The most commonly reported SAE in this SOC was colitis ulcerative (5 SAEs). One patient with known sickle cell disease, diagnosed prior to study enrolment, reported 12 SAEs of sickle cell anaemia with crisis and 4 SAEs of acute chest syndrome, accounting for 16 of the 37 SAEs reported. In all other patients, SAEs occurred ≤2 times.

The rate of patients experiencing at least 1 serious infection was 4.18 per 100 patient-years of exposure (5 patients). The rate of serious infections was 5.85 per 100 patient-years of exposure (7 events). All serious infections were reported only once.

There were no reported cases of malignancies, TB, colonic dysplasia, or new autoimmune diseases in the 51 patients with data presented in this report. There was 1 case of opportunistic infection reported: 1 AE of Epstein-Barr virus infection, which was not serious (total event rate, 0.84 per 100 patient-years of exposure.

Discontinuations

Six patients discontinued ustekinumab due to an AE; all AEs leading to discontinuation were serious. Two patients each discontinued ustekinumab treatment due to events of colitis ulcerative and IBD. One of the patients who discontinued due to IBD also discontinued due to an event of pain management. One patient discontinued ustekinumab treatment due to events of abscess limb and vulval abscess, and another patient discontinued treatment due to 2 events of sickle cell anaemia with crisis.

Table 78: Summary of Adverse Events With >1 Occurrence During Registry Ustekinumab Exposure by System Organ Class and Preferred Term: All Children and young adults >2 to <18 years at first dose) with Exposure to Ustekinumab (UST) During Registry For Ulcerative Colitis in DEVELOP Registry Data (Ref table 13, SCS)

	All
Analysis Set: Total Patient Number	51
Total Patient Years of UST Exposure During Registry	119.6
Patients per 100 PT Years During Registry [Number of Patients]	29.27 [35]
95% Confidence Interval	[20.39, 40.71]
Events per 100 PT Years During Registry [Number of Events]	135.49 [162]
95% Confidence Interval	[115.43, 158.03]
Blood and lymphatic system disorders	12.55 [15]
Anaemia	1.67 [2]
Sickle cell anaemia with crisis	10.04 [12]
Gastrointestinal disorders	45.16 [54]
Abdominal pain	7.53 [9]
Abdominal pain upper	1.67 [2]
Colitis ulcerative	6.69 [8]
Diarrhoea	2.51 [3]
Frequent bowel movements	2.51 [3]
Haematochezia	4.18 [5]
Inflammatory bowel disease	2.51 [3]
Irritable bowel syndrome	1.67 [2]
Nausea	1.67 [2]
Vomiting	2.51 [3]
General disorders and administration site conditions	10.87 [13]
Adverse drug reaction	1.67 [2]
Asthenia	1.67 [2]
Fatigue	2.51 [3]
Pain	2.51 [3]
Pyrexia	2.51 [3]
Infections and infestations	25.09 [30]
COVID-19	1.67 [2]
Clostridium difficile infection	3.35 [4]
Influenza	1.67 [2]
Nasopharyngitis	1.67 [2]
Pharyngitis	1.67 [2]
Pneumonia	1.67 [2]
Upper respiratory tract infection	1.67 [2]
Viral infection	1.67 [2]
Metabolism and nutrition disorders	5.02 [6]
Dehydration	2.51 [3]
Nervous system disorders	2.51 [3]
Dizziness	1.67 [2]
Psychiatric disorders	5.85 [7]
Dysphoria	1.67 [2]
Respiratory, thoracic and mediastinal disorders	5.02 [6]
Acute chest syndrome	3.35 [4]

Observational Post Authorisation Safety Study CNTO1275PSO4056 (STELLAR Teens)

CNTO1275PSO4056 is a prospective, observational, international, multicenter PASS of ustekinumab conducted to monitor the long-term safety and potential impact on growth and development of ustekinumab in the treatment of paediatric patients (aged ≥6 years to <18 years) with plaque PsO within clinical practice. The postmarketing data provided below, although generated in non-IBD patients, provide additional substantial long-term safety data and support the overall safety profile of ustekinumab in paediatric patients.

STELLAR Teens completed enrollment in August 2024 and is ongoing. At data cutoff (08 January 2025), a total of 135 patients were enrolled in the study, all of whom were included in the FAS. Exposure data and demographic and other characteristics for these patients are provided in Sections 6.3.1 and 6.3.2, respectively. All AEs after first administration of ustekinumab up to data cutoff were included in the analysis.

A total of 79 (58.5%) of 135 patients initiated treatment with a 45 mg dose of ustekinumab, while the remaining 56 (41.5%) patients received a weight-adjusted first dose (neither 45 mg nor 90 mg). The median first dose received per administration was 45.0 mg (IQ range: 30.0 to 45.0 mg). The median number of injections per patient from the beginning of the study up to data cutoff was 7.0 (IQ range: 4.0 to 10.0). The median duration of exposure to ustekinumab was 761.0 days (IQ range: 378.0 to 1068.0).

Adverse Events

Predefined safety outcomes (malignancies, serious infections, or autoimmunity-related AEs) were reported. There were no reports of malignancy. One (0.7%) patient reported a serious infection (PT appendicitis), and 5 (3.7%) patients reported autoimmunity-related AEs (4 [3.0%] reports of PT psoriasis and 1 [0.7%] report of PT cholangitis sclerosing).

No deaths were reported during the study. At the data cutoff, 14 (10.4%) patients reported a total of 18 SAEs. Of the 18 reported SAEs, 14 events were considered not related to ustekinumab, 2 events were considered to have a doubtful relation with ustekinumab, 1 event of appendicitis was considered possibly related, and 1 event of acute urticaria (PT: urticaria) was considered very likely related to ustekinumab.

A total of 5 (3.7%) patients reported at least 1 AE leading to discontinuation of ustekinumab. No new safety concerns were identified based on review of the available data collected after start of recruitment of patients initiating ustekinumab up to data cutoff. The safety profile is consistent with the known safety profile of ustekinumab in this paediatric population. No apparent impact of ustekinumab on growth and development was identified upon review of available data up to data cutoff.

2.5.1. Discussion on clinical safety

Introduction, scope of variation, and outline of package

The primary evidence of safety of ustekinumab in paediatric patients with UC is based on data from study PUC3001 (UNIFI Jr) for induction (n=112) and maintenance (n=109) treatment of UC in the paediatric population and study UCO3001 (UNIFI) for induction (n=961) and maintenance (n=783) treatment of UC in the adult population (incl. LTE).

In addition, an ongoing long-term extension study (ISD3001, so called basket study) including paediatric patients receiving treatment for UC, CD or juvenile psoriatic arthritis.

Safety data on paediatric CD patients from study CRD3004 (UNITI Jr.) is also included (induction n=101; maintenance n=97) as well as data from paediatric patients treated for psoriasis PSO3006 (CADMUS) (n=73) and PSO3013 (CADMUS Jr) (n=44)

Data from post authorisation safety studies C0168Z02 (DEVELOP) from paediatric IBD patients (n=51) and paediatric psoriasis patients PSO4056 (Stellar Teens; n=135) is also included.

Exposure in UC and CD is similar in adults and children (median cumulative total dose), and numerically higher in IBD compared to PsO.

It should be noted that studies PUC3001 or ISD3001 did not include a placebo or active comparator arm, which limits the ability to make definitive safety comparisons. Although PUC3001 was not placebo-controlled, placebo injections were administered during the maintenance phase to maintain blinding, as

the two treatment arms followed different dosing frequencies. The MAH further proposes that the efficacy and safety data generated in adult patients with UC may be extrapolated to the paediatric UC population. As per ICH guideline E11 (R1), the process of paediatric extrapolation requires a thorough understanding of the differences between the paediatric and the reference populations, including disease pathogenesis, measures of disease progression, and organ systems physiology, as well as the mechanism of action of the drug and its pharmacological behaviour. Based on sufficient similarities in the course of the disease and the treatment effects of ustekinumab in adults and paediatric patients with UC, it is accepted that safety data from adults can be extrapolated to further support the paediatric UC studies.

Additionally, safety data from paediatric participants with CD aged 2 years and older, which has been reviewed by the EMA (EMA/VR/0000290099), are provided to support the safety profile of ustekinumab in the treatment of paediatric participants with UC. The clinical data relating to a proposed q4w dosing in paediatric UC patients comes from an optional EOS of PUC3001 and ISD3001. There are also data from paediatric CD patients whose dose was adjusted to the q4w regimen in a similar EOS of CRD3004. Of note, a q4w dosing interval has not currently been approved for any age group.

Proposed posology and doses used in the studies

Initial IV induction dose

The proposed wording for the posology and method of administration of the STELARA 130 mg Concentrate for solution for infusion is as follows:

Paediatric Crohn's disease and ulcerative colitis (2 years and older)
Patients weighing less than 40 kg (BSA-based dosing)
Treatment is to be initiated with a single intravenous (IV) dose based on the patient's body surface area (BSA), see Table 79. The infusion solution is to be composed of infusion solution volume from the total number of vials of STELARA 130 mg as specified in Table 79.

Table 79: Initial intravenous dose of STELARA

BSA Range (m^2) of patient at time of dosing Body weight < 40 kg	**Recommended Dose (mg)**	**Volume of Infusion solution (mL)**	**Number of 130 mg Vials**
0.40 to <0.62	130 mg	26 mL	1 vial
0.62 to <0.95	200 mg	40 mL	2 vials
0.95 to <1.25	260 mg	52 mL	2 vials
≥1.25	325 mg	65 mL	3 vials

Patients weighing at least 40 kg (weight-based dosing)
STELARA treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of STELARA 130 mg as specified in Table 80 (see section 6.6 for preparation).

Table 80: Initial intravenous dose of STELARA

Body weight of patient at the time of dosing	Recommended dosea	Number of 130 mg Vials
≥ 40 kg to ≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

The proposed posology is the same as was used in PUC3001. All participants received a single open-label IV administration of ustekinumab at Week I-0. Participants weighing <40 kg received 250mg/m2 IV (BSA adjusted), and those weighing ≥40 kg received a dose depending on weight.

The total injection volumes for paediatric UC patients weighing <40 kg at time of dosing could range from 100 mg (BSA 0.40 m^2) to 415 mg (BSA 1.66 m^2) or greater. STELARA concentrate for solution for infusion is provided as a 130 mg concentrate for dilution in 26 mL to give a final concentration of 5 mg/mL. Based on this dose calculation, the amount of ustekinumab supplied per vial may substantially exceed the quantity needed for an administered dose (e.g. 275 mg required for a BSA of 1.1 m^2 would require dilution of three vials containing a total of 390 mg ustekinumab). As per section 6.6 each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements. Section 4.2 of the SmPC has been updated to include the BSA-based induction dosing table, aligned with the paediatric Crohn's disease wording as presented above. The BSA-based induction and maintenance dosing follows a simplified four-tier BSA dosing approach, which is intended to minimise drug wastage and facilitate a more efficient use of the existing presentations. This is acceptable.

SC maintenance dose

The proposed wording for the posology and method of administration of STELARA 45 mg solution for injection, STELARA 45 mg solution for injection in pre-filled syringe, and STELARA 90 mg solution for injection in pre-filled syringe in the paediatric UC indication is as follows:

Paediatric Crohn's disease and ulcerative colitis (2 years and older)
Patients weighing less than 40 kg
In paediatric patients weighing less than 40 kg the recommended maintenance dose is a subcutaneous dose administered based on the patient's BSA, see Table 81. The calculated volume should be rounded to the nearest 0.1 mL and administered using a 1 mL graduated syringe.

Table 81: Injection volumes for paediatric patients weighing less than 40 kg

BSA Range (m^2) of patient at time of dosing Body weight < 40 kg	**Recommended Dose (mg)**	**Volume of injection (mL)**	**Number of 45 mg/0.5 mL Vials**
0.40 to <0.62	36 mg	0.4	1 vial
0.62 to <0.95	45 mg	0.5	1 vial*
0.95 to <1.25	63 mg	0.7	2 vials
≥1.25	90 mg	1.0	2 vials*
* The pre-filled syringe (PFS) presentation may be used as an alternative to the 45 mg/0.5 mL vial for administration of the required dose			

Patients weighing at least 40 kg (weight-based dosing)
In paediatric patients weighing at least 40 kg, the recommended maintenance dose is a subcutaneous 90 mg dose.

The proposed 90 mg SC maintenance dose is the same dose as was used in the PUC3001 study and the LTE ISD3001 study. The inclusion of a Table in Section 4.2 of the SmPC with clear injection volumes presented for different BSA ranges helps to minimise the risk of dosing errors associated with manual calculations.

Dose Adjustments and Optimisation in paediatric patients

The proposed wording for the posology and method of administration of STELARA 45 mg solution for injection, STELARA 45 mg solution for injection in pre-filled syringe, and STELARA 90 mg solution for injection in pre-filled syringe in the paediatric UC indication is as follows:

Dosing frequency in paediatric patients (2 years and older)
The first subcutaneous administration of STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

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

Patients receiving treatment every 12 weeks who have a loss of response may increase their frequency to every 8 weeks (see sections 5.1 and 5.2). Patients receiving treatment every 12 or 8 weeks who lose response and have low ustekinumab trough levels (<1.4 µg/mL by a validated ECLIA or ELISA testing method or equivalent assay) may benefit from shortening the dosing interval to every 4 weeks if clinically indicated.

To address the issue that dosing of ustekinumab in patients who lose response is common in paediatric IBD clinical practice the applicant included an exposure optimisation substudy (EOS). The EOS was designed to evaluate dose optimisation for participants with LOR who previously responded to ustekinumab to see if they could regain that response or to achieve optimal response following induction. This EOS was identical in design to the EOS for the paediatric Crohn's study CRD3004 which has been reviewed in EMA/VR/0000290099.

21 paediatric subjects with UC met the criteria (LOR and trough concentration <1.4 µg/mL) and moved to the EOS, where they were followed for approximately 20 weeks (6 doses). The serum concentration steady state threshold (<1.4 µg/mL) used in Study 3001 for entry into the EOS is based on E-R analyses in adults with Crohn's disease. Ten participants moved into the LTE ISD3001 (UNITED) study and continued to receive the q4w dose as their 4-week ustekinumab trough concentration at the end of EOS (after at least 3 doses) was <7.2 µg/mL. The recommended target exposure of ≤7.2 µg/ml was defined based on matching exposures in adults with UC and CD treated with ustekinumab.

The EOS patients were generally demographically similar to those in the main study however a numerically higher proportion of EOS participants had a history of biologic failure 12 [57.1%] of 21 participants versus 44 [39.3%]) of 112 main study participants.

The safety profile of the q12w→ q4w or q8w → q4w treatment groups in EOS for PUC3001 were broadly similar. There was a slightly higher reporting rate of AEs, SAEs and infections in the q8w → q4w treatment group compared to the q12w→ q4w treated group. The overall safety profile for patients treated q4w in the EOS was similar to the UC patients who were treated with q4w in the LTE study The overall distribution of AEs by SOC/PT generally reflects the trends observed in the main PUC3001 study, with most events falling under the Infections and Infestations SOC, Blood and Lymphatic Disorders SOC and Gastrointestinal Disorders SOCs. Across all participants in the EOS, Upper respiratory tract infection was the most frequently reported AE (6 [28.6%] participants). Other commonly reported AEs included anaemia (4 [19%]) and iron deficiency anaemia (3 [14.3%] participants). Colitis ulcerative was also frequently reported (4 [19%] participants).

When comparing exposure adjusted incidence of key safety events per 100 Person-years of follow-up during the EOS for PUC3001 and Study CRD3004 in paediatric Crohn's disease (CD), the incidence of AEs, SAEs, AEs resulting in discontinuations, infections and serious infections tended to be higher in patients with Crohn's disease in the EOS. A similar picture was evident when comparing the UC and CD participants exposed to q4w dosing in the Long-term Extension Period (ISD3001) except that infections were reported more frequently in the PUC3001 subgroup in the LTE.

Overall, there were no clinically relevant differences for patients treated with the q4w regimen in the overall AE profile for the PUC3001 16-week EOS, CRD3004 and in the ISD3001. The very limited data relating to q4w dosing makes it difficult to definitively compare the safety of this interval with q8w and q12w intervals; however on the basis of the data presented there is no evidence of a clinically relevant increased reporting of AEs with q4w dosing in paediatric patients with UC. Of note no data supporting q4w dosing in adult UC patients has been presented for review.

The SmPC section 4.2 currently proposes a 4 weekly dose interval for patients experiencing inadequate or loss of response and low serum ustekinumab trough levels. Shortened dosage interval to q8w for patient on the q12w regime with LOR without evaluating ustekinumab levels has been proposed for the paediatric Crohn's disease population on the basis that a q8w regimen could potentially be better tolerated than q4w regimen.

While a move from 12 weekly to 8 weekly treatment is a logical step in intensification with a lower-risk escalation, some children particularly those <40 kg or with high inflammatory burden, may not achieve therapeutic levels even at q8w.

Delaying appropriate dosing could result in slower time to improvement in children with high disease burden. Therefore, the possibility of switching from q12w to q4w in cases of LOR with low ustekinumab trough levels (<1.4 µg/mL) is acceptable if clinically indicated i.e. if higher exposure is needed for rapid clinical response. Careful clinical and drug level monitoring is required if dose is adjusted from q8w or q12w to q4w.). Section 4.2 of the SmPC outlining dose optimisation for paediatric patients with UC has been updated with practical guidance for healthcare professionals including advice on ustekinumab exposure monitoring (availability and timing of blood level testing, need for follow-up measurements) and management of patients exceeding the target exposure of ≤7.2 µg/mL while maintaining response. The wording for dose optimisation in paediatric ulcerative colitis is aligned with the wording approved for paediatric Crohn's disease. This is acceptable.

Baseline Demographics and Exposure

Study PUC3001

A total of 112 paediatric UC participants were enrolled in PUC3001. Of those participants, only 30 were aged 2 to <12 years, meaning approximately 73.2% of the population were adolescents. This increased to 81.8% adolescent participation in ISD3001 LTE.

There were no notable differences between the demographics at baseline in PUC3001 treatment arms. Overall, the data reflect a paediatric population with moderate UC. More than two-thirds of participants presented with extensive colonic involvement at baseline. This is typical for a paediatric UC population as children tend to present with more extensive colonic involvement as compared with adults.

There was an imbalance seen between treatment arms in relation to prior biologic failure status. In PUC3001, the proportion of participants with biologic failure was numerically greater in the q12w treatment group compared with the q8w treatment group (47.3% vs 31.5%). A higher proportion of participants with a history of biologic failure had AEs (primarily driven by AEs of infections) than participants without a history of biologic failure (63.6% vs 45.6%, respectively) during the induction period of PUC3001. This imbalance was not seen during the maintenance period of PUC3001.

Both q12w and q8w proposed maintenance doses were evaluated in separate treatment arms during the maintenance period of PUC3001. A total of 55 participants were initiated on q12w treatment. Of these 5 were subsequently transitioned to a q8w dosing regimen. The median total duration of exposure to ustekinumab in the q12w group was 44.0 weeks. A total of 54 participants were initiated on q8w dosing and 2 of these participants were transitioned to a q4w dose during the study. The median total duration of exposure to ustekinumab in the q8w group was 48.1 weeks.

LTE Study ISD3001

Participants entering the LTE ISD3001 study (n=55) who received q12w dosing during the parent study were transitioned to a q8w dose and those who received q8w dosing during the parent study remained on q8w dose. Median total duration of exposure (weeks) in the LTE was 48.6 and 16.1 weeks in q8w and q4w treatment groups, respectively. Although patient numbers were limited, approximately 48.6 weeks of

treatment exposure data from the LTE study are available to inform the long-term safety evaluation of ustekinumab in paediatric UC.

The total duration of exposure for participants in the LTE ISD3001 through 01 September 2025 was 240.6 weeks, inclusive of their prior exposure to ustekinumab during parent study PUC3001. Analyses of the additional safety data for UC participants in the LTEISD3001 did not reveal any new or unexpected safety issues in the period after 28 April 2025 through the clinical cutoff date of 01 September 2025.

Adverse events

Induction Period

A total of 59 (52.7%) of 112 participants had one or more AEs during the induction period of PUC3001. The frequencies of SAEs, related AEs, and AEs of severe intensity were generally low. AEs leading to discontinuation of the study medication during the induction period were low (n=2, 1.8%).

AEs temporally associated with the infusion of ustekinumab occurred in 3 (2.7%) of the 112 participants. The cases involved urticaria (1 patient), increase in body temperature (1 patient), and dyspnoea and non-cardiac chest pain (1 patient). All events were resolved and only one patient with the AE of urticaria discontinued the study medication.

AEs during this period were driven by Infections and infestations SOC (n=25, 22.3%), including COVID-19 and upper respiratory tract infection (URTI). The most frequently reported AE at the PT level was anaemia (n=12, 10.7%). Gastrointestinal disorders (n=13, 11.6%), including colitis ulcerative and vomiting, along with Skin and subcutaneous tissue disorders SOC (n=9, 8.0%), including acne and urticaria were also commonly seen. No opportunistic infections, active TB, malignancy, or deaths occurred in the induction period.

Infections and infestations, in particular URTI, are commonly seen as an adverse reaction to ustekinumab and likely linked to the immunosuppressive mechanism of action and the increased propensity for URTIs in the paediatric population. Similarly, gastrointestinal disorders, driven by the UC disease pathophysiology, are regularly seen as ADRs. Overall, there were no new or unexpected safety signals arising during the induction period; hence no new additions are proposed to the SmPC Section 4.8.

Maintenance period

A total of 100 (91.7%) participants had one or more AEs during the maintenance period of PUC3001. The frequencies of SAEs, related AEs, and AEs of severe intensity were generally low. AEs leading to discontinuation of the study medication during the induction period were low (n=5, 4.6%).

Comparing the q8w and q12w arms of PUC3001 maintenance phase, there is no broad signal of increased toxicity at the more frequent (q8w) dosing frequency. AEs were comparable between arms; q12w (n=52, 94.5%) and q8w (n=48, 88.9%). SAEs (n=2, 3.6%) and severe AEs (n=1, 1.8%) were lower in the q12w treatment arm compared with the q8w treatment arm (n=5, 9.3% and n=6, 11.1%). Infections occurred at a common frequency in both arms.

As with the induction period, AEs were driven by infections (n=68, 62.4%), most commonly URTI, nasopharyngitis, COVID-19, and RTI. Gastrointestinal disorders SOC (n=50, 45.9%) were also common. The most frequently reported PT in the maintenance period was colitis ulcerative (n=34, 31.2%). Other AEs that occurred in >5% of participants were headache (n=10, 9.2%) and anaemia (n=13, 11.9%).

In total, 23 (20.5%) participants reported an AE of anaemia from Week I-0 through end of study. By comparison, a total of 8/320 (2.5%) adult participants with UC reported an AE of anaemia during the induction period and 16/348 (4.6%) reported this AE during the maintenance period in study UCO3001. The frequency of anaemia events in the paediatric UC population remained high throughout the LTE occurring in 5/66 (7.6%) participants.

Clinical and post-marketing data to date has not identified anaemia as a class-specific toxicity of IL-12/IL-23 pathway inhibition. The mechanism of action of ustekinumab, which regulates T-cell and inflammatory responses, is not known to be involved in erythropoiesis or other biological processes underlying anaemia. Clinical laboratory results from PUC3001 and ISD3001 also show no difference in the frequency of anaemia AEs or AE grades between the dosing arms. Considering the lack of evidence for a mechanistic link between ustekinumab and anaemia, along with documented elevated frequencies of anaemia in real-world paediatric UC cohorts, current data do not support a causal association with ustekinumab.

The MAH has provided data showing that paediatric patients with on-study reports of anaemia had a history of anaemia prior to entering the study. Based on the totality of the clinical data and known pathobiology of paediatric UC, anaemia is unlikely to represent a new risk related to the use of ustekinumab in the paediatric UC population; rather it reflects a known complication of the underlying disease.

Apart from anaemia, the most commonly reported AEs throughout the induction and maintenance periods of PUC3001 were in line with those adverse drug reactions listed in Section 4.8 of the SmPC. Therefore, no new additions are proposed to Section 4.8.

There were no reports of malignancy or active TB infections. There were no deaths.

Long-term safety data (ISD3001)

The overall incidence of AEs was lower in the LTE than in the first 52 weeks of the study. As for the induction and maintenance periods, overall, Infections and infestations and Gastrointestinal disorders were the most commonly represented SOCs in the LTE period. AEs leading to discontinuation of the study medication during the induction period were low (n=7, 10.6%) and included PTs colitis ulcerative, cytomegalovirus colitis, neuropathy peripheral, and completed suicide.

The case of completed suicide was the only death reported in ISD3001 study and was assessed by the investigator as not related to ustekinumab. *(See further discussion under SAEs, deaths, and AESIs section)*

There was a single AE reported as related to ustekinumab during the LTE study; an event of neuropathy peripheral in the q8w treatment group. This SAE was considered mild in severity and also led to discontinuation of ustekinumab. The SAE was preceded with a nonserious AE of nerve compression on LTE Study Day -96 (during the parent study PUC3001) that was considered unrelated to study treatment. In the LTE study, the participant received one dose of ustekinumab on Study Day 31 prior to the SAE of neuropathy peripheral. Following cessation of ustekinumab, neurological status partially improved before worsening again. The participant continued in the safety follow-up phase of the LTE study and the events of neuropathy peripheral and nerve compression were reported as not resolved at Study Day 127.

Although additional neuropathy symptoms were reported after ustekinumab initiation and temporarily improved following discontinuation, a similar pattern of worsening and subsequent gradual improvement was documented before ustekinumab treatment and again approximately 6 months after discontinuation. The clinical course is not supportive of a causal relationship with ustekinumab.

Laboratory findings

Hematologic and clinical chemistry abnormalities of Grade ≥2 were sporadic and largely attributable to underlying UC or medical history. Elevated liver enzymes is identified in study participants during maintenance treatment (ALAT (7.7%) and bilirubin (6.6%)). There were no cases of Hy's Law in any of the studies. The findings did not indicate any association between ustekinumab and laboratory abnormalities.

No meaningful trends related to physical findings and growth were observed in the paediatric UC study population.

Antibody formation (NAbs) was measured in 2 paediatric participants and no relationship to safety outcomes are presented. In the adult population the formation of anti-ustekinumab antibodies is associated with increased clearance of ustekinumab in patients with Crohn's disease or ulcerative colitis. No reduced efficacy was observed.

Special populations

No distinct trends were observed in the safety profile for ustekinumab across subgroups based on age and weight. However, it must be acknowledged that safety data in the youngest patients is very limited. Due to the low number of participants ≥2 to <12 years of age (n=30) compared with participants ≥12 to <18 years of age (n=80), no meaningful comparisons can be made between the 2 age groups.

An imbalance was noted in the frequency of participants with one or more AE of "infections" in the <30 kg subgroup, compared with the ≥30 to <40kg, and ≥40 kg groups. Infections occurred in 7 (43.8%) participants in the <30 kg subgroup compared with 3 (16.7%) and 16 (20.5%) of participants in the ≥30 to <40kg, and ≥40 kg groups, respectively during the induction period. During the maintenance period, a similar trend was seen with infections occurring in 11 (73.3%) participants in the <30 kg subgroup compared with 10 (55.6%) and 48 (63.2%) of participants in the ≥30 to <40kg, and ≥40 kg groups, respectively. A higher frequency of infections was also seen in the <30 kg subgroup during the LTE study, occurring in 5 (83.3%) of participants, compared with 6 (66.7%) and 29 (56.9%) of participants in the ≥30 to <40kg, and ≥40 kg groups, respectively.

Interpretation of these findings is limited due to the small numbers of participants in the <30 kg weight subgroup. A special warning on infections is currently included in Section 4.4 of the SmPC stating that "*Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections*". Infections and infestations are also listed as a common adverse reaction in Section 4.8 of the SmPC. The existing warning in the SmPC sufficiently addresses the clinical observations of infection AEs in the paediatric UC population, without the need for further modification.

Through Week I-8, a numerically higher proportion of female participants experienced one or more serious adverse events, adverse events leading to treatment discontinuation, and adverse events of severe intensity compared to male participants. This pattern, however, was not observed during the maintenance period.

During the maintenance period, those participants who had previously failed biologic therapy had a higher frequency of AEs leading to treatment discontinuation (n=4 [9.3%]) compared to those who had not previously failed biologic therapy (n=1 [1.5%]). Overall, the limited available data do not particularly indicate any significant impact of prior biologic failure on safety, despite the fact that prior biologic failure may indicate a more severe disease profile. These results are also noted as consistent with findings from the paediatric Crohn's disease studies.

SAEs, deaths, and AESIs

Overall, the frequency of SAEs was relatively low across both the pivotal PUC3001 induction (n=6, 5.4%) and maintenance (n=7, 6.4%) periods. SAEs were reported in 13 patients, all reported as not being drug related. Nine participants had 1 SAE, 2 participants had 2 SAEs and 2 participants had 3 SAEs.

SAEs occurred at a lower frequency in the q12w treatment arm; 2 (3.6%) participants compared with 5 (9.3%) participants in the q8w treatment group during the maintenance period. The overall incidence of SAEs was higher in the LTE (n=6, 9.1%) than in the first 52 weeks of the study, and all were reported in the q8w treatment arm. There were no deaths reported in the induction and maintenance period of PUC3001 study.

SAEs during the induction period included anaemia, colitis ulcerative, infusion-related reaction, and subcutaneous abscess. SAEs during the maintenance period included anaemia, salmonellosis, malnutrition, asthma, suicidal ideation, and colitis ulcerative. Only the event of colitis ulcerative occurred in >1 participant (n=2, 1.8%). The SAEs of anaemia and suicidal ideation are described in more detail in the other section of this Discussion. Although the incidence of SAEs was numerically higher in the q8w treatment arm, the pattern and nature of events did not indicate any clinically relevant differences between treatment groups.

In 3 participants (2.7%) AEs were temporally associated with the infusion of study intervention. In the narrative description of these incidents: 1) One participant developed urticaria (allergic reaction) (SAE) and study intervention was discontinued. Assessed as drug related. 2) One participant had increase in body temperature (SAE): Treatment was not discontinued. Sponsor assessed that the reaction was drug related. 3) The third episode cannot be identified in the CSR-narrative.

Serious hypersensitivity reaction is a known side effect to monoclonal antibody treatment and is in the Stelara SmPC classified as rare (≥ 1/10,000 to < 1/1,000).

The incidence rate of serious infections in PUC3001 induction and maintenance periods was 1.8 per 100PY, and in the LTE was 4.2 per 100 PY. A total of three opportunistic infections were reported during studies PUC3001 and ISD3001. There were no reports of malignancies or active TB.

The proportion of participants with infections requiring oral antimicrobial treatment was numerically higher in the q12w treatment group than the q8w treatment group. The most frequently reported infections (≥2 participants) were bronchitis, clostridium difficile infection, pneumonia, and respiratory tract infections.

One opportunistic infection (fungal oesophagitis) was reported in a participant in the q12w treatment arm of PUC3001 and one opportunistic infection (cytomegalovirus infection) was reported in a participant in the EOS receiving q4w treatment dose. One participant in the LTE, receiving q8w treatment experienced an opportunistic infection (cytomegalovirus colitis). IL-23 inhibition has not been shown to increase CMV infection or reactivation in clinical studies. No CMV-specific precautions are proposed for treatment of patient with known CMV history, standard monitoring for infections remains appropriate.

There does not appear to be any new signals or trends apparent in the occurrence of these AESIs and opportunistic infections are already listed under Section 4.4 of the SmPC.

There were no new trends or signals arising from the analysis of SAEs or AESIs as they are mostly consistent with expected UC disease activity or the established safety profile of ustekinumab.

There was one death during the LTE ISD3001 study. The participant did not have a history of depression or suicidal ideation at study entry or during PUC3001 study. At the last visit (M-44), the participant reported he was “very happy” with life. The event of completed suicide occurred 476 days following initiation of ustekinumab in the parent trial PUC3001, and 35 days after the most recent dose in the LTE study. The investigator assessed the event of suicide as not related to ustekinumab.

The SAE of suicidal ideation reported during the maintenance period of PUC3001 also occurred in a participant without a history of depression or suicidal ideation. The event occurred one day after receiving treatment with ustekinumab and required hospitalisation. The event was considered resolved 5 days after the start date. The nonserious event of depression was ongoing at the end of the trial, however the participant reported feeling “happy” with life at the last visit (M-44).

In June 2024, a PSUSA for ustekinumab was completed and assessed (EMEA/H/C/PSUSA/00003085/202312), providing a cumulative evaluation of all reported cases of severe depression/suicidal ideation covering the period 01/01/2023 – 31/12/2023. Following review of the PSUR,

the PRAC considered that severe depression/suicidal ideation needed to be further assessed and a follow-up LEG (EMEA/H/C/000958/LEG/058) was submitted in December 2024.

The cumulative review of severe depression/suicidal ideation data from clinical trials, registry and post-marketing cases undertaken as part of the LEG did not identify any new patterns or trends with regards to severe depression and suicidal ideation/behaviour following treatment with ustekinumab.

Currently, depression is listed in the SmPC Section 4.8 "Undesirable effects" as an uncommon adverse reaction. The SmPC does not list suicidal ideation as an ADR. In regard to the SAE of completed suicide during the LTE, the reported social stressor could plausibly explain the event. In addition, the length of exposure to ustekinumab prior to the event make an association with ustekinumab improbable. As part of the LEG procedure, the PRAC rapporteur performed a WHO-UMC Causality for this case and categorised this case Unlikely. Following conclusion of the LEG (EMA/PAM/0000274988), "serious depression including suicidality" has been removed as an important potential risk from the RMP summary of safety concerns.

Comparisons of Safety Data Between Paediatric and Adult UC Studies

The MAH provides a comparison of safety profile for paediatric patients from PUC3001 and adult UC patients from study UCO3001 across the induction phase and maintenance phase of the respective studies (Induction phase n=112 paediatric patient vs 320 adult patients; Maintenance phase 109 paediatric patients vs 348 adult patients). Only the 6 mg/kg adult induction dose data from UCO3001 are presented in comparison with data from PUC3001. This is to more closely align the paediatric and adult induction doses.

In the induction phase, the overall proportion of paediatric participants reporting AEs was comparable to adults (52.7% vs 50% respectively).

SAEs (5.4 % vs 3.1%), infections (23.2% vs 15.3%), serious infections (0.9% vs 0.3%) and infusion related AEs (2.7% vs 0.9%) were reported more frequently in the paediatric population compared to adults respectively. The SOCs with the highest proportions of AEs through the induction period in the paediatric and the adult studies were Infections and infestations, Blood and lymphatic system disorders, and Gastrointestinal disorders.

A numerically higher proportion of participants in the paediatric study reported adverse events (>5%) of colitis ulcerative, URTI, nasopharyngitis, anaemia, and Covid-19 compared to adults.

In the maintenance phase, while the overall proportion of participants in the paediatric study reporting AEs were higher compared to adults (91.7% vs 73.3%, respectively) the proportion of participants who had at least 1 reported SAE in the paediatric study was slightly lower than those in adult populations (6.4% vs 8.0%).

The SOCs with the highest proportions of AEs through the maintenance period in the paediatric and adult studies were Infections and infestations and Gastrointestinal disorders. The overall proportion (Week M-0 Through Week M-44) of paediatric participants with infections was higher compared to adults (63.3% vs 41.4%, respectively).

This imbalance in reports of infections was attributed to a numerically higher proportion of participants in the paediatric study reporting adverse events of URTI, Covid-19, RTI compared to adults. In most cases, the infections were nonserious and mild and did not result in discontinuation. Upper respiratory and lower respiratory tract infections are currently labelled events in the SmPC section 4.8. Covid 19 was seen in 7 patients in the paediatric population and none of the adults. This is explained by the fact that only the paediatric study UCO3001 was ongoing during the pandemic. The reporting rates of serious infections in the paediatric population was lower than those in adult populations (0.9% vs 2.6%). There was one report of opportunistic infection in the paediatric population (fungal oesophagitis) in this comparative analysis (through Week M-44) which was nonserious and reported as not related.

Colitis ulcerative was the most frequently reported Gastrointestinal adverse event. 31.2% of participants in the paediatric study had this event compared with 10.6% in the adult study. This did not result in increased rates of paediatric hospitalisation. There were 2 serious reports of 'colitis ulcerative' during this period. Four participants in the paediatric group discontinued due to reports of 'colitis ulcerative'. This could indicate lack of efficacy/LOR. SmPC Section 4.2 provides information for the HCP on how to proceed with Stelara treatment if LOR or if no efficacy is seen.

Within the Blood and lymphatic system disorders SOC, a numerically higher proportion of paediatric participants (12 [10.7%]) reported an AE of anaemia compared with adult participants (8 [2.5%]). *(See discussion on anaemia under Adverse events)*

In an exposure adjusted analysis across the induction and maintenance phases the comparative adult dose for the induction phase included all doses not just 6mg/kg ustekinumab. Also subjects who received placebo in induction period at Week I-0 and crossed over to receive ustekinumab were included in the maintenance phase. AEs (465.9/100PYs vs 383.5/100PYs), AELDs (7.2/100PYs vs 4.2/100PYs), infections (170.3/100PYs vs 91.0/100PYs) were reported more frequently in the paediatric population compared to the adult population respectively. SAEs (15.4/100PYs vs 16.2/100PYs) and serious infections (2.1/100PYs vs 3.7/100PYs) were reported more frequently for adults compared to the paediatric population. The most frequently reported AEs were URTI, nasopharyngitis, COVID.

The differences in study population, average number of exposures and total person years of follow up between these two populations is mitigated by the EAIR analysis but differences in cumulative dose, total person years of follow up and population size can impact the ability to detect cumulative, late, or rare AEs in the paediatric population and impact the interpretability of this data. To address the uncertainty paediatric patients will be followed up in the Phase 3, multicentre, open-label, basket, LTE study ISD3001 (UNITED). The objective of this study is to collect long-term safety data in paediatric patients 2 to <18 years of age who receive SC ustekinumab for at least 1 year. Recruitment is ongoing and will continue up to 2029 (RMP category 3 study).

Overall, despite some methodological, statistical, and clinical limitations of comparing safety data from the open label paediatric and the more robust adult ulcerative colitis studies, the paediatric safety profile is broadly comparable to adult safety data in the induction phase, maintenance phase, and across combined exposure adjusted analyses. No new paediatric safety concerns have emerged compared to adults. IL-23–driven inflammation plays a central role in UC pathogenesis in both adults and children, supporting biological continuity between age groups. Paediatric ustekinumab exposure mirrors adult PK levels supporting extrapolation of safety data between the adult and paediatric UC populations. As mentioned above, long term safety data will continue to be collected in the paediatric UC population in ISD3001, the RMP cat. 3 study.

Other paediatric indications

The MAH provided a comparison of the safety profiles for paediatric populations with ulcerative colitis (UC) Crohn's disease (CD) and psoriasis (PSO) treated with ustekinumab. Although these conditions share IL-23 pathway involvement they differ substantially in disease biology, systemic inflammatory burden, patient profiles. Differences in study design limits cross study comparability. UC and CD patient populations received nearly double the average number of administrations compared with paediatric PSO populations. PUC3001 and CRD3001 studies also enrolled larger cohorts resulting in higher treatment exposure, despite shorter follow-up times than studies PSO313 and PSO3006.

After one year of follow-up, paediatric UC safety outcomes were aligned with but were more favourable those seen in the paediatric CD population, with consistently lower rates of AEs, severe AEs, AEs leading to discontinuation, SAEs and infections (including serious infections) in the overall incidence and when

adjusted for exposure (per 100 patient-years). Reporting rates for Opportunistic infections were comparable for the UC and CD paediatric populations.

Paediatric PSO patients experienced lower overall AE rates, fewer severe AEs and SAEs, and fewer discontinuations than paediatric UC patients, with the exception of slightly higher drug-related AEs and similar infection rates.

Overall, despite some methodological, statistical and clinical limitations of comparing safety data from the paediatric UC and CD studies with PSO, the safety profile for paediatric UC and CD patients is broadly comparable and PSO patients generally experience a more favourable safety profile than paediatric UC or CD patients. The consistency of this pattern in both the overall incidence and the exposure-adjusted analyses suggests that these differences reflect the tolerability of ustekinumab in these indications despite differences in exposure and follow-up duration. This difference in reporting rate with the paediatric PsO population reflects the difference in underlying baseline systemic inflammatory disease risk (i.e. Severe systemic disease burden vs. localised skin disease), heavier prior biologic exposure and refractory disease, between the IBD and PsO patients. The majority of the AEs in the UC and CD studies (URTIs, disease flares, anaemia) were consistent with this higher age related and disease-driven vulnerability to AEs.

Safety related to drug-drug interactions and other interactions

In keeping with adult ustekinumab studies in UC and also in Crohn's disease, immunogenicity was low in the paediatric UC population (2.1%), which is consistent with the immunogenicity profile of ustekinumab in adult participants with UC (4.6%) and paediatric participants with CD (3.3%). Given the low incidence of antibodies to ustekinumab, the impact of immunogenicity on PK, efficacy, or safety could not be determined. As mentioned above, section 5.1 of the SmPC mentions that no reduced efficacy in CD and UC was observed.

Consistency with the RMP safety specification

No important identified risks are included in the current safety specification. Serious infections (including mycobacterial and salmonella infections), Malignancy, Cardiovascular events, and Venous thromboembolism are identified as important potential risks. No new safety concern has been identified in the paediatric UC population in relation to these important potential risks. No changes to the 'Important Identified Risks', 'Important Potential Risks', described in the RMP are proposed based on the safety data presented in support of this extension of indication. The proposal to include 'Long-term safety in paediatric patients 2 years and older with moderately to severely active ulcerative colitis' as missing information is endorsed. As mentioned above, this uncertainty will be mitigated by follow up of patients in the Phase 3, multicentre, open-label, basket, LTE study ISD3001 (UNITED) .The objective of this study is to collect long-term safety data in paediatric patients 2 to <18 years of age who receive SC ustekinumab for at least 1 year recruitment is ongoing and will continue up to 2029.

Implications for SmPC, RMP, and Benefit–Risk assessment

Paediatric dosing or monitoring recommendations

Section 4.2 has been updated in line with the earlier discussion.

Section 4.4 (Special warnings and precautions)

No new signals or trends are apparent in reporting rates for AESIs. A special warning on infections and opportunistic infections, malignancies, hypersensitivity reactions is already included in Section 4.4 of the SmPC. No updates to these warnings is proposed. Section 4.4 also includes a warning regarding coadministration with live viral or live bacterial vaccines.

Section 4.8 (Undesirable effects)

AEs most frequently observed from Week I-0 through Week M-44 were mainly in the SOC of Infections and infestations (22.3% and 62.4%, respectively). AEs reasonably related to ustekinumab were infrequent (5.4% and 5.5%, respectively).

A numerically higher proportion of paediatric UC participants reported an AE of anaemia compared with adult UC participants in both the induction period (12 [10.7%] versus 8 [2.5%]) and the maintenance period (13 [11.9%] versus 16 [4.6%]). Clinical and post-marketing data to date has not identified anaemia as a class-specific toxicity of IL-12/IL-23 pathway inhibition. The frequency of anaemia events also remained high in the paediatric UC population throughout the LTE occurring in 5 (7.6%) participants.

Clinical and post-marketing data to date has not identified anaemia as a class-specific toxicity of IL-12/IL-23 pathway inhibition. The mechanism of action of ustekinumab, which regulates T-cell and inflammatory responses, is not known to be involved in erythropoiesis or other biological processes underlying anaemia. Clinical laboratory results from PUC3001 and ISD3001 also show no difference in the frequency of anaemia AEs or AE grades between the dosing arms. Considering the lack of evidence for a mechanistic link between ustekinumab and anaemia, along with documented elevated frequencies of anaemia in real-world paediatric UC cohorts, current data do not support a causal association with ustekinumab.

Based on the totality of the clinical data and known pathobiology of paediatric UC, anaemia is unlikely to represent a new risk related to the use of ustekinumab in the paediatric UC population; rather it reflects a known complication of the underlying disease.

Upper respiratory tract infection and nasopharyngitis are already listed as a common adverse reaction in Section 4.8 of the SmPC. Infusion/ injection-site reactions are also listed in section 4.8 as common adverse reactions.

No new safety concerns have been in a comparative review of paediatric and adult UC regarding AEs, SAEs, AESIs of Serious infections, opportunistic infections or malignancy. Based on the postmarketing safety surveillance, no new ADRs have been identified for ustekinumab. The safety profile in paediatric patients in the post marketing setting has been considered similar to that seen in adults.

Based on this comprehensive review of the safety data from PUC3001 induction and maintenance periods, no new ADRs have been identified for ustekinumab. The safety profile in paediatrics (2 to <18 years of age) has been considered similar to adults.

2.5.2. Conclusions on clinical safety

The data provided in this study is limited in participant number and by the absence of placebo or active control however, does not give raise to additional safety concerns. The safety profile is comparable to adult patients with UC and paediatric patients with CD treated with ustekinumab. Increased reports for infections in the UC paediatric population were mainly driven by increased reports of upper respiratory tract infections, while higher rates of anaemia and ulcerative colitis likely reflected underlying UC disease activity. No new ADRs have been identified. No new identified or potential risks have been identified for inclusion in the RMP. Supportive safety data is also available from other approved indications for ustekinumab in paediatric and adult populations. Exposure in paediatric patients achieved serum concentrations comparable to adult pharmacokinetic levels, supporting the extrapolation of adult UC safety data to the paediatric UC population. Overall, the safety of ustekinumab in the target population is acceptable.

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 33.1 with this application. The (main) proposed RMP changes were the following:

- To include the paediatric ulcerative colitis indication (patients aged 2 years and older).
- To add missing information "Long-term safety in pediatric patients 2 years and older with moderately to severely active ulcerative colitis".
- Removal of "serious depression including suicidality" as an important potential risk from the summary of safety concerns (recommended following the Post-Authorisation measure LEG 058 assessment). Relevant sections of the RMP have been updated accordingly.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan: The PRAC considered that the risk management plan version 33.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 33.1 with the following content:

Safety concerns

Table 82: Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	Serious infections (including mycobacterial and salmonella infections)
	Malignancy
	Cardiovascular events
	Venous thromboembolism
Missing Information	Long-term safety in pediatric psoriasis patients 6 years and older
	Long-term impact on growth and development in pediatric 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 pediatric patients 2 years and older with moderately to severely active Crohn's disease
	Long-term safety in pediatric patients 2 years and older with moderately to severely active ulcerative colitis

Pharmacovigilance plan

Table 83: Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
Category 1: Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2: Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3: Required additional pharmacovigilance activities				
CNTO1275PSO4056 (Pediatric Psoriasis Registry): An observational postauthorisation safety study of ustekinumab in the treatment of pediatric patients aged 6 years and older with moderate to severe plaque psoriasis Ongoing	To confirm the long-term safety profile of STELARA use in pediatric patients 6 years and older and to explore any potential effect on growth and development in pediatric patients 6 years and older in-line with the consideration in the STELARA PIP.	• Long-term safety in pediatric psoriasis patients 6 years and older • Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	Protocol submission	21 December 2015
			Start of data collection	25 October 2017
			End of data collection	31 August 2032
			Final report	31 March 2033
An observational postauthorisation safety study to describe the safety of ustekinumab and other biologic treatments in a cohort of patients with ulcerative colitis or Crohn's disease using compulsory Swedish Nationwide Healthcare Registers and the independent Swedish National Quality Register for Inflammatory Bowel Disease (SWIBREG; PCSIMM002807) Ongoing	To monitor the long-term safety profile of ustekinumab in adult patients with moderately to severely active UC or CD.	• Venous thromboembolism • Malignancy • Cardiovascular events (MACE only) • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis • Long-term safety in adult patients with moderately to severely active Crohn's disease	Protocol submission	23 June 2020
			Start of data collection	30 November 2022
			End of data collection	30 November 2027
			Final report	31 December 2028
	To monitor the long-term safety profile of ustekinumab in adult patients with moderately to severely active UC.	• Venous thromboembolism • Malignancy • Cardiovascular events (MACE only)	Protocol submission	23 June 2020
			Start of data collection	31 December 2022
			End of data collection	31 December 2026

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
An observational postauthorisation safety study to describe the safety of ustekinumab and other treatments of ulcerative colitis in a cohort of patients with ulcerative colitis using the independent French Nationwide Claims Database (SNDS; PCSIMM002659) Ongoing		• Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis	Final report	31 December 2027
CNTO1275ISD3001 (UNITED) LTE: A Phase 3, multicenter, open-label, basket, long-term extension study of ustekinumab in pediatric clinical study participants (2 to <18 years of age) Ongoing	To collect long-term safety data in pediatric patients 2 to <18 years of age who receive ustekinumab for at least 1 year after participating in a primary pediatric ustekinumab trial (CNTO1275CRD1001, CNTO1275PUC3001, CNTO1275CRD3004, or CNTO1275JPA3001).	• Long-term safety in pediatric patients 2 years and older with moderately to severely active Crohn's disease • Long-term safety in pediatric patients 2 years and older with moderately to severely active ulcerative colitis	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

Table 84: Summary Table of Risk Minimisation Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious infections (including mycobacterial and salmonella infections)	**Routine risk minimisation measures** • SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) • PL sections 2 and 4 **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** TOI TFUQ for Serious Infections and Opportunistic Infections TOI TFUQ for TB **Additional pharmacovigilance activities** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS • Final study report due date: 31 December 2027

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Malignancy	**Routine risk minimisation measures** • SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) • PL section 2 **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** TOI TFUQ for Malignancies (including Lymphoma, Second and Secondary Malignancies) **Additional pharmacovigilance activities** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS • Final study report due date: 31 December 2027
Cardiovascular events	**Routine risk minimisation measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** TOI TFUQ for CV Events **Additional pharmacovigilance activities** STELARA UC/CD PASS using Swedish Registers (MACE only) • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS (MACE only) • Final study report due date: 31 December 2027
Venous thromboembolism	**Routine risk minimisation measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** TOIQ for VTE **Additional pharmacovigilance activities** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS • Final study report due date: 31 December 2027
Long-term safety in pediatric psoriasis patients 6 years and older	**Routine risk minimisation measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** CNTO1275PSO4056 (Pediatric Psoriasis Registry) • Final study report due date: 31 March 2033

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	**Routine risk minimisation measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** CNTO1275PSO4056 (Pediatric Psoriasis Registry) • Final study report due date: 31 March 2033
Long-term safety in adult patients with moderately to severely active Crohn's disease	**Routine risk minimisation measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028
Long-term safety in adult patients with moderately to severely active ulcerative colitis	**Routine risk minimisation measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS • Final study report due date: 31 December 2027
Long-term safety in pediatric patients 2 years and older with moderately to severely active Crohn's disease	**Routine risk minimisation measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** CNTO1275ISD3001 (UNITED) LTE • Final study report due date: 31 January 2030
Long-term safety in pediatric patients 2 years and older with moderately to severely active ulcerative colitis	**Routine risk minimisation measures:** **None** **Additional risk minimisation measures:** **None**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** CNTO1275ISD3001 (UNITED) LTE Final study report due date: 31 January 2030

2.7. Changes to the Product Information

As a consequence of this new indication, section(s) 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed and accepted by the CHMP.

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: Revisions are limited and in line with the previous approved indications as shown in the proposed labelling.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Ulcerative colitis is an inflammatory disorder that involves the surface mucosa, crypt epithelium, and submucosa of the colon. Clinically, patients with UC suffer from diarrhoea, rectal bleeding, weight loss, abdominal pain, and fever, and may also display prominent extra intestinal manifestations, most commonly arthritis. Ulcerative colitis is defined in the same way in adults and children down to 2 years of age, with some rare phenotypic differences in disease presentation (higher incidence of pancolitis, macroscopic rectal sparing, lack of typical architectural distortion in biopsies at diagnosis, caecal patch of inflammation, upper GI tract involvement, and occurrence of fissuring ulcerations at presentation).

The mainstay of therapy for mild to moderate UC is 5-aminosalicylic (5-ASA) agents. These agents are effective at inducing and maintaining remission in UC. Many patients with moderate to severe active UC benefit from topical, oral or parenteral glucocorticosteroids. Remission, however, cannot be maintained with steroids. Azathioprine (AZA) or mercaptopurine (MP) have been employed as glucocorticoid-sparing agents in patients unable to be weaned from glucocorticoids. Anti-tumour necrosis factor α (TNF) agents and integrin inhibitors are indicated for the treatment of UC patient's refractory to standard treatment. Surgery with colectomy is curative but can be associated with significant morbidity and is thus reserved for acute severe (fulminant) colitis or resistant cases and in some cases as cancer treatment or prevention. Intestinal continuity can be restored by construction of an ileo-anal pouch. In both the adult and paediatric UC patient populations, the overall goal of treatment is to induce remission in acute, active disease and to maintain disease remission over time. Treatment of paediatric UC generally follows the same treatment paradigms that are used to treat adult UC.

3.1.2. Available therapies and unmet medical need

Currently, there are 2 approved biologic agents for paediatric patients with UC and both of these are anti-TNF agents; infliximab and adalimumab. While infliximab and adalimumab are generally safe and well tolerated in the paediatric UC population, less than half of paediatric UC patients achieve sustained clinical remission on infliximab or adalimumab. Adults have many options for access to advanced therapies for the treatment of UC. Ustekinumab is one of the many biologic therapies approved for the

treatment of UC in adults (STELARA SmPC 2025), while adalimumab is approved from age 5 years and infliximab is approved from age 6 years.

Additionally, in a population-based study of paediatric onset IBD, approximately 70% of UC patients experienced TNF failure within 5 years. Without effective pharmacologic treatment, the only alternative is colectomy, which is associated with notable morbidity. As such, there is a need for additional safe and efficacious treatment options for paediatric patients with moderately to severely active UC.

3.1.3. Main clinical studies

The MAH presented a pivotal phase 3 study of ustekinumab in paediatric moderate to severe Ulcerative Colitis patients (Mayo score of 6-12). UNIFI Jr was a multicentre, interventional study consisting of an open-label induction period with a single IV ustekinumab 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.

3.2. Favourable effects

In the pivotal phase 3 trial PUC3001 (UNIFI Jr), clinical remission was achieved at Week I-8 in 25.0% of participants (95% CI: 17.9%, 33.8%) and at week M-44 in 40.5% of participants (95% CI: 30.4%, 51.5%). Clinical remission was maintained in 59.3% of participants and was generally consistent across both dosing frequencies. The robustness of this result was assessed using 3 alternative definitions of clinical remission. This showed that 19.6%, 25%, and 23.2% of participants were in clinical remission at I-8 and 27.8%, 40.5%, 39.2% at M-44 (these lower values of 19.6% and 27.8% are due to the increased specificity for clinical remission, enhancing the requirements of the Mayo stool frequency subscore from 0 or 1 to 0).

Clinical response was achieved in 67% (95% CI: 57.8%, 75%) and 40.5% (95% CI: 30.4%, 51.5%) of participants, symptomatic remission was achieved in 48.2% (95% CI: 39.2%, 57.4%) and 65.8% (95% CI: 54.8%, 75.3%) of participants, and endoscopic improvement was achieved in 30.4% (95% CI: 22.6%, 39.4%) and 40.5% (95% CI: 30.4%, 51.5%) of participants at week I-8 and M-44 respectively. PUCAI score showed 38.4% (95% CI: 29.9%, 47.6%) and 64.6% (95% CI: 53.6%, 74.2%) of participants attained clinical remission at week I-8 and M-44 respectively. There was a large proportion of induction responders who maintained symptomatic remission (70.6%) and clinical remission by PUCAI score (78%) for the duration of the study.

Histologic-endoscopic mucosal improvement based on GS and RHI showed 19.6% (95% CI: 13.3%, 28%) and 17.9% of patients (95% CI: 11.9%, 26%) had improvement at week I-8 and 36.7% (95% CI: 26.9%, 47.7%) and 30.4% (95% CI: 21.3%, 41.2%) at week M-44 respectively. Endoscopic normalisation went from 8.9% (95% CI: 4.9%, 15.7%) at week I-8 to 19.0% (11.9%, 29.0%) at M-44.

90-day Corticosteroid-free Clinical Remission at Week M-44 was apparent in 40.5% (95% CI: 30.4%, 51.5%) of participants. The average daily prednisone-equivalent corticosteroid dose was decreased at Week I-8 and Week M-44. At Week I-8, the mean (SD) prednisone-equivalent corticosteroid dose was 2.9 (8.55) compared with 5.6 (12.54) at baseline, while at Week M-44 the mean reduction was -3.8 (9.7).

For Week I-8 results, they were similar across key efficacy endpoints in the 2-<12 age group when compared to the 12-<18 age group.

There was a slight increase from baseline BMI z-scores for both sexes at M-44 and iron serum values, while 25-hydroxyvitamin D values, and MMA values improved on average.

There was a normalisation from elevated CRP levels in 50.0% of participants at Week I-8 with mean (SD) change in CRP concentrations from Week I-0 being -3.67 (13.911) mg/L by M-44. Among those with abnormal faecal calprotectin levels, 22.5% had normalised faecal calprotectin levels at Week I-8 with mean (SD) change from Week I-0 in faecal calprotectin of -2427.6 (4593.26) mg/kg by M-44. The mean improvement in IMPACT-III (baseline mean score of 105.1) went from 21.6 at I-8 to 26.3 at M-44.

For the exposure optimisation substudy (EOS) analysis, where participants went from either q12w or q8w dosing frequency to q4w dosing frequency, results demonstrated that at week 16, 84.6% achieved clinical response based on the partial Mayo score, 56.3% of achieved clinical remission based on the PUCAI score, mean (SD) changes from entry in the partial Mayo score were -3.8 (2.39), and the mean (SD) changes from entry in the PUCAI score were -43.4 (18.32). These results were similar to what was observed in the main study.

When assessing the comparison between the CNTO1275UCO3001 (adult) and UNIFI Jr studies, there was a greater proportion of paediatric participants in clinical remission (ratio of paediatric to adult participants in clinical remission was 1.30) and similar in symptomatic remission (ratio of paediatric to adult participants in symptomatic remission was 1.08) at I-8. This proportion remained consistent for symptomatic remission until M-44 (ratio of paediatric to adult participants in symptomatic remission was 1.01). Clinical response and endoscopic improvement were numerically higher in paediatrics than adults at I-8 (9.2% and 6.6% increase over adults respectively).

Overall, data from the phase 3 trial demonstrates positive efficacy to support the use of ustekinumab in paediatric patients (2 to <18 years of age) with moderately to severely active Ulcerative Colitis for up to 1 year of treatment. These results are broadly comparable to ustekinumab in the adult pivotal trials.

Observed PK data from CNTO1275PUC3001 showed that serum ustekinumab concentrations in paediatric participants receiving the proposed dose regimens generally fell within the range of concentrations observed in adults.

Simulations generated from the paediatric popPK model indicated that exposures following the proposed paediatric doses largely overlapped with those in adult UC participants.

Across weight groups, more than 80% of paediatric participants were predicted to have C_{trough} values within the 90% prediction interval of adult exposures under both induction and maintenance regimens.

Exposure–response analyses demonstrated that efficacy endpoints in paediatric participants followed a similar positive relationship to that observed in adults with UC, with neither age nor weight exerting a meaningful impact on the exposure–response relationship.

3.3. Uncertainties and limitations about favourable effects

A limitation of the study is the small sample size, particularly in infants with a body weight <30kg. UC in the youngest paediatric patient group is a rare condition, and it is acknowledged that there was limited feasibility of including this patient group. The MAH has appropriately acknowledged the limited numbers in these subgroups by including relevant information in section 5.1 of the SmPC.

The disease burden and effect of treatment is less favourable in the youngest patients. However, the younger cohorts are more likely to have a greater disease severity, poor treatment control, and, as the median time since diagnosis was 1.2 years across all participants, it highlights that these patients may be unfamiliar with their condition thus further exacerbating disease state. Nevertheless, the underlying pathophysiology of the disease and the mechanism of action of monoclonal antibodies in different age subsets are considered sufficiently consistent to scientifically justify the extrapolation.

A single pivotal efficacy study submitted with this application did not include a placebo or comparator group preventing direct within study comparisons and formal statistical analyses and, as such, results are mainly presented by descriptive statistics. The consistency and magnitude of the observed clinical outcomes nonetheless provide a meaningful and interpretable evidence base in paediatric patients. Furthermore, the robust efficacy data established in the adult population serves as an important reference point, strengthening the overall conclusions drawn from the paediatric study in the context of the extrapolation approach.

In line with the adult study, paediatric participants could have a dose adjustment, however only a total of 7 (6.4%) of the 109 randomised participants had a dose adjustment (5 participants who dose-adjusted to ustekinumab q8w and 2 participants who received a sham adjustment). While the small number of dose adjustments limits formal statistical conclusions, the improved efficacy seen in the q8w cohort, combined with consistency with established adult posology at maintenance, support a dose adjustment of q12w to q8w in paediatric patients experiencing loss of response.

There are also updates to the dosing frequency of every 4 weeks with the addition of an exposure optimisation substudy (EOS) for paediatric participants. Only 13 participants completed the EOS up to Week 16 and the primary endpoint was not tested limiting clinical evaluation. This increase in dosing is due to therapeutic efficacy being partially linked with serum ustekinumab levels. Encouragingly, paediatric participants had a stepwise increase in the number of clinical remissions (Quartile <1 - ≥3) at week I-8 and the ≥3rd quartile having the highest proportion of participants in clinical remission at M-44. As expected, given lower drug exposure, there were low numbers of participants across both adult and paediatric studies in clinical remission in the <1st quartile. Given the limited dataset and the absence of q4w dosing data in an adult population, the SmPC transparently communicates the extent of evidence supporting this dosing change, along with a clear recommendation to transition back to less frequent dosing once appropriate trough levels are achieved, and a sufficient treatment period has elapsed. Wording in sections 4.2 and 5.1 has been aligned with the agreed language for the Crohn's disease, ensuring consistency across indications.

While a meta-analysis was performed to compare adult placebo UC data from 7 clinical trials with similar key inclusion criteria to the treated paediatric population from UNIFI Jr, the comparability of outcomes is limited due to the heterogeneity and variations in study design affecting the method’s validity and the generalisability of the results. Given the limitations of the meta-analysis comparison, e.g. lack of placebo-controlled group in paediatric studies due to ethical challenges, these data are considered as supportive.

3.4. Unfavourable effects

The paediatric clinical safety evaluation of ustekinumab for moderately to severely active ulcerative colitis (UC) is derived from three studies: the Phase 3 prospective interventional study PUC3001, its Exposure Optimisation Substudy (PUC3001-EOS), and the long-term extension study ISD3001. Collectively, these studies provide safety data across induction, maintenance, and long-term treatment periods and are supported by a descriptive comparison with the adult UC safety dataset from study UCO3001.

Overall, across the clinical development program, AEs were common in paediatric participants, with the highest overall AE prevalence observed during maintenance, followed by the LTE and induction periods. AEs were most commonly reported in the Infections and infestations SOC across phases. Compared with adults, paediatric participants generally showed higher rates of overall AEs, reports of ulcerative colitis, infections (including respiratory infections), infusion-related reactions, and anaemia. SAE rates were comparable or modestly higher depending on the phase assessed. There were three reports of opportunistic infections No malignancies or active tuberculosis were identified in the paediatric program.

Exposure

In PUC3001, 109 participants received ustekinumab during the maintenance period (q12w n=55; q8w n=54), with median exposures of 44.0 and 48.1 weeks, respectively.

In the PUC3001-EOS, 21 participants transitioned to q4w dosing, with median exposures of 16.4 weeks (q12w→q4w) and 20.1 weeks (q8w→q4w).

ISD3001 included 65 participants (q8w n=55; q4w n=10), with median exposures of 48.6 and 16.1 weeks, respectively.

Induction Safety Findings

During induction in PUC3001, 52.7% of paediatric participants experienced at least one AE, with higher rates reported than in the adult comparator group. (52.7% vs 50%).

The SOCs with the highest proportions of participants with AEs were Infections and infestations and Blood and lymphatic system disorders with anaemia (10.7%) and COVID-19 (6.3%) reported most frequently.

Six participants (5.4%) experienced SAEs, anaemia (n=2), ulcerative colitis flares (n=2), one infusion-related reaction and one subcutaneous abscess were also reported.

SAEs were observed in 5.4% of children compared to 3.1% adults. Infections (23.2% vs 15.3%), serious infections (0.9% vs 0.3%), and infusion-related reactions (2.7% vs 0.9%) were reported more frequently in children compared to adults.

Maintenance Safety Findings

During maintenance in PUC3001, overall AE rates were higher in paediatric participants than in adults (91.7% vs 73.3%).

The SOCs with the highest proportions of AEs reported by paediatric participants were Infections and infestations (62.4%), Gastrointestinal disorders (45.9%), and Blood and lymphatic disorders (16.5%):

The most common PTs in children were (>10%) colitis ulcerative (31.2%), upper respiratory tract infection (24.8%), nasopharyngitis (15.6%), and anaemia (11.9%).

Infections and infestations were reported by 62.4% of combined participants from week M0-M44 in Study PUC3001. The proportion of participants with infections was numerically higher in the paediatric study (63.3%) than the adult (41.4%) study UCO3001. In most cases, the infections were nonserious and mild and did not result in discontinuation. A slightly higher proportion of the adult patients had infections that needed antibiotics than the paediatric population.

A numerically higher proportion of participants in the paediatric study reported UC (31.2%) than the adult study (10.6%).

Paediatric participants in the maintenance phase of PUC3001 had higher rates of URTI (24.8% vs 6.0%), COVID-19 (6.4% vs 0%), and other respiratory tract infections (5.5% vs 0.3%) compared with adults in study UCO3001. Over the same period a numerically higher proportion of participants in the paediatric study had anaemia compared to the adult study (11.9%) vs (4.6%) respectively.

During the maintenance period, 6.4% of participants experienced 1 or more SAEs. This was comparable to adults (8.4%) The most frequently reported PT reported by paediatric population was colitis ulcerative (2 [1.8%] of 109 participants); anaemia, asthma, salmonellosis, suicidal ideation, and malnutrition occurred in 1 participant each. The proportion of participants who had at least 1 reported SAE in the paediatric study was 6.4% compared to 8.0% in adult study.

There were three reports of opportunistic infection in the paediatric population, one in the EOS (fungal oesophagitis) and one in the maintenance phase of PUC3001 (CMV infection) and one case of CMV colitis in the LTE. The incidence rate of opportunistic infection in the pediatric study (Week I-0 through Week M-44) was similar to that of the adult study. No malignancies, or active tuberculosis were identified during induction or maintenance.

Long-Term Extension

In ISD3001, 80.3% of paediatric participants experienced at least 1 AE across the q8w and q4w treatment groups. The SOCs with the highest proportions of participants reporting AEs were Infections and infestations (59.1%) and Gastrointestinal disorders (42.4%), Metabolism and Nutrition disorders (15.2%) with ulcerative colitis (24.2%), URTI (18.2%) and vitamin D deficiency (15.2%) being the most commonly reported AEs.

In the LTE through the end of the reporting period, a total of 6 (9.1%) participants experienced at least one or more SAEs. Six (10.7%) of 56 participants in the q8w treatment group and 0 of 10 participants in the q4w treatment group reported an SAE. Events included one report each of colitis ulcerative, bacterial colitis, cholangitis infective, cytomegalovirus colitis, incision site abscess, completed suicide, gender dysphoria, one death (PT completed suicide) was reported in the ISD3001 study (assessed by the investigator as not related to ustekinumab.)

Infusion-related reactions were more frequent in the paediatric population during induction (2.7% vs 0.9% in adults). No new safety signals were identified during maintenance or LTE with respect to infusion-related reactions.

Dose Regimen Comparisons (q12w, q8w, q4w) From Week I-0 Through End of Study and During Long-term Extension

In an analysis of safety from week 1-0 through end of study and during LTE, AEs were reported in 538.5 vs 501.2 vs 410.3 vs 292.3 E/100PYS for the q4w, q12w q8w and LTE (q4w and q8w combined) treatment groups respectively.

AEs of severe intensity were reported for 5.9 vs 15.7 vs 31.7E/100PYs respectively in q12w, q8w andq4w treatment group in PUC3001 respectively compared with 5.6E/100PYs (all in the q8w arm) in the LTE.

SAEs were reported in 31.7 vs 11.8vs 11.8 E/100PYs for q4w group compared to the q8w and q12w treated group) in PUC3001. The overall incidence of SAEs was 12.5 events per 100 PY of follow-up in the LTE.

Infections were reported in 185.5 vs 155.1 vs 221.7 E/100PYs of the q12w vs q8w vs q4w treated groups during PUC23001 respectively compared with 116.9E/100PYs in the LTE. The most frequently reported infections (≥2 participants) were bronchitis, clostridium difficile infection, pneumonia, and respiratory tract infections.

Serious infections were reported in 2.0 vs 2.0 vs 0.0 E/100PYs of the q12w vs q8w vs q4w treated groups during PUC23001 respectively compared with 4.2 E/100PYs in the LTE.

In the q4w Escalation (EOS) for PUC3001 the safety profile of the paediatric patients that transitioned from q12w → q4w or q8w → q4w treatment groups a slightly higher proportion of patients reported AEs, SAEs, and infections in the q8w → q4w treatment group compared to the q12w → q4w treatment group.

3.5. Uncertainties and limitations about unfavourable effects

The available data do not indicate any new or additional safety concerns in this population.

Comparison with adult data is part of the extrapolation framework. Differences in population characteristics, drug exposure, and total follow-up time may limit the ability to compare adult and paediatric datasets. Nonetheless, the similar exposure–response relationships for ustekinumab in paediatric and adult participants, with a clear and positive ER trend in both populations, support the extrapolation approach.

The number of paediatric patients that transitioned from q12w → q4w or q8w → q4w treatment groups in the EOS or who were maintained on q4w dosing in the LTE supporting the characterisation of the safety profile for patients treated with q4w to manage LOR is small. Safety comparison across these subgroups is limited by the small numbers – for more information and PI mitigation measures please see section 3.3 above.

The number of paediatric UC patients and the duration of long-term exposure to ustekinumab is limited. This uncertainty will be mitigated by follow up of patients in the Phase 3, multicentre, open-label, basket, LTE study ISD3001 (UNITED). The objective of this study is to collect long-term safety data in paediatric patients 2 to <18 years of age who receive SC ustekinumab for at least 1 year. Recruitment is ongoing and will continue up to 2029.

3.6. Effects Table

Table 85: Effects Table for ustekinumab for the treatment of moderate to severe paediatric ulcerative colitis (Induction Week 8 and Maintenance Week 44)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Clinical remission	Mayo sub scores (Stool frequency of 0 or 1, rectal bleeding of 0, and endoscopy of 0 or 1 with no friability present on the endoscopy, where the stool frequency sub score had not increased from induction baseline)	%	Week I-8 28/112 (25.0%) Week M-44 32/79 (40.5%)		Unc: No active control and does not align with primary endpoint of adult study SoE: Comparable results to adult study CNTO1275UCO3001	Phase 3 trial UNIFI Jr
Clinical response	A decrease from baseline in the Modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.	%	Week I-8 75/112 (67.0%)		Unc: No active control SoE: Comparable results to adult study CNTO1275UCO3001	Phase 3 trial UNIFI Jr

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Symptomatic remission	Mayo stool frequency of 0 or 1 and rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline	%	Week M-44 52/79 (65.8%)		Unc: No active control SoE: Comparable results to adult study CNTO1275UCO3001	
Endoscopic improvement	Mayo endoscopy of 0 or 1 with no friability present on the endoscopy	%	Week M-44 32/79 (40.5%)		Unc: No active control SoE: Comparable results to adult study CNTO1275UCO3001	Phase 3 trial UNIFI Jr
Histologic-endoscopic mucosal improvement	Combination of histologic (Geboes grading system: Neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue) and endoscopic improvement (endoscopy subscore of 0 or 1 with no friability present on the endoscopy)	%	Week M-44 29/79 (36.7%)		Unc: No active control	Phase 3 trial UNIFI Jr
Corticosteroid-free clinical remission at Week M-44.	Mayo stool frequency of 0 or 1, rectal bleeding of 0, and an endoscopy of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore had not increased from induction baseline; and not receiving corticosteroids for at least 90 days prior to Week M-44	%	Week M-44 32/79 (40.5%)		Unc: No active control	Phase 3 trial UNIFI Jr

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Clinical remission at Week M-44 for participants who are in clinical remission at Week I-8.		%	Week M-44 16/27 (59.3%)		Unc: No active control SoE: Comparable results to adult study CNTO1275UCO3001	Phase 3 trial UNIFI Jr
IMPACT-III at M-44 (≥10 years)	PRO HRQoL, Change from baseline (Range: 35 to 175)	Mean (SD)	Week M-44 26.3 (21.52)		UNC: No active control and no inclusion of PRO HRQoL for <10 years of age)	Phase 3 trial UNIFI Jr
Unfavourable Effects						
AEs	Adverse events	N (%)	Induction: 59/112 (52.7%) Maintenance: 100/109 (91.7%)	Induction: 160/320 (50%) Maintenance: 255/348 (73.3%)	Unc: PUC3001 study was not placebo-controlled	PUC3001 paediatric study UCO3001 adult study (Tables 7 and 8, SCS)
SAEs	Serious adverse events	N (%)	Induction: 6/112 (5.4%) Maintenance: 7/109 (6.4%)	Induction: 10/320 (3.1%) Maintenance: 28/348 (8.0%)	Unc: PUC3001 study was not placebo-controlled	PUC3001 paediatric study UCO3001 adult study (Tables 7 and 8, SCS)
Infections	Infections	N (%)	Induction: 26/112 (23.2%) Maintenance: 69/109 (63.3%)	Induction: 49/320 (15.3%) Maintenance: 144/348 (41.4%)	Unc: PUC3001 study was not placebo-controlled	PUC3001 paediatric study UCO3001 adult study (Tables 7 and 8, SCS)
Serious infections	Serious infections	N (%)	Induction: 1/112 (0.9%) Maintenance: 1/109 (0.9%)	Induction: 1/320 (0.3%) Maintenance: 9/348 (2.6%)	Unc: PUC3001 study was not placebo-controlled	PUC3001 paediatric study UCO3001 adult study (Tables 7 and 8, SCS)
Opportunistic infections	Opportunistic infections	N (%)	Induction: 0 (0%) Maintenance: 1/109 (0.9%)	Induction: 0 (0%) Maintenance: 3/348 (0.9%)	Unc: PUC3001 study was not placebo-controlled	PUC3001 paediatric study UCO3001 adult study (Tables 7 and 8, SCS)
Blood and lymphatic system disorders SOC	Blood and lymphatic system disorders SOC	N (%)	Induction: 15/112 (13.4%)	Induction: 23/320 (7.2%)	Unc: PUC3001 study was not placebo-controlled	PUC3001 paediatric study

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			Maintenance: 18/109 (16.5%)	Maintenance: 30/348 (8.6%)		UCO3001 adult study (Tables TSFAEAP02a and TSFAEAP02b, SCS)
Gastrointestinal disorders SOC	Gastrointestinal disorders SOC	N (%)	Induction: 13/112 (11.6%) Maintenance: 50/109 (45.9%)	Induction: 39/320 (12.2%) Maintenance: 106/348 (30.5%)	PUC3001 study was not placebo-controlled	PUC3001 paediatric study UCO3001 adult study (Tables TSFAEAP02a and TSFAEAP02b, SCS)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

To support the paediatric ulcerative colitis (UC) indication, the applicant has implemented an extrapolation strategy to justify efficacy and safety in the paediatric population. It was supported by clinical data from study PUC3001 in paediatric participants with UC, along with 3 additional studies involving extrapolation, modelling, and simulation and an analysis of literature data to support presumptions of similarity regarding disease, treatment outcomes, and the E-R relationship between paediatric and adult participants with UC. The extrapolation of efficacy and/or safety from adults with UC to paediatric patients is consistent with the ICH Guideline E11A on Pediatric Extrapolation, the Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1) and was endorsed by the Paediatric Committee (PDCO) (PIP decision: EMA/PE/0000294320)

Collectively, the clinical pharmacology data support the extrapolation of adult efficacy and safety to paediatric patients as achieving comparable ustekinumab exposures across populations has been sufficiently demonstrated. Observed PK data from CNTO1275PUC3001 showed that serum ustekinumab concentrations in paediatric participants receiving the proposed dose regimens generally fell within the range of concentrations observed in adults. In addition, simulations generated from the paediatric popPK model indicated that exposures following the proposed paediatric doses largely overlapped with those in adult UC participants. Across weight groups, more than 80% of paediatric participants were predicted to have C_{trough} values within the 90% prediction interval of adult exposures under both induction and maintenance regimens. Exposure–response analyses demonstrated that efficacy endpoints in paediatric participants followed a similar positive relationship to that observed in adults with UC, with neither age nor weight exerting a meaningful impact on the exposure–response relationship.

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, and the lack of a placebo or comparator group preventing direct within study comparisons. The absence of a placebo or comparator group did not allow for formal statistical analyses and as such results are mainly presented by descriptive statistics.

The safety profile of ustekinumab has been evaluated in several different indications. It has been approved for use in adults with UC since 2019, and in children with over 6 years with plaque psoriasis since 2020. Although the overall extent and duration of ustekinumab exposure in study PUC3001 were limited due to the small paediatric sample size, the safety findings observed during both the induction and maintenance phases of the study were generally consistent with those reported in adult UC studies. Increased reports in the paediatric population of infections were mainly driven by increased reports of upper respiratory tract infections, while higher rates of anaemia and ulcerative colitis likely reflected underlying UC disease activity.

The paediatric safety profile was generally comparable to that of adults, and no new or unexpected safety signals were identified. No new identified or potential risk have been identified for inclusion in the RMP. Furthermore, ustekinumab exposure in paediatric patients achieved serum concentrations comparable to adult pharmacokinetic levels, supporting the extrapolation of adult safety data to the paediatric UC population. Long-term exposure in paediatric UC is limited. This uncertainty will be mitigated by follow up of patients in the Phase 3, multicentre, open-label, basket, LTE study ISD3001 (UNITED). The objective of this study is to collect long-term safety data in paediatric patients 2 to <18 years of age who receive SC ustekinumab for at least 1 year. Recruitment is ongoing and will continue up to 2029.

3.7.2. Balance of benefits and risks

On balance and taking the totality of evidence into consideration, the benefit-risk balance of Stelara in the treatment of paediatric Ulcerative Colitis is considered positive.

Data from the phase 3 trial demonstrated efficacy to support the use of ustekinumab in paediatric patients (2 to <18 years of age) with moderately to severely active Ulcerative Colitis.

The benefit in adults is based on substantial data as well as long-term use outside of clinical trials in a large adult UC patient population supporting the extrapolation approach. Ustekinumab is also authorised for the treatment of plaque psoriasis in children from the age of 6 and paediatric Crohn’s disease. The unmet need is greater in the youngest children compared to adolescents, due to a limited number of available treatment options in this age group.

The study showed no new safety issues or concerns, and long term follow up is planned for.

3.8. Conclusions

The overall B/R of ustekinumab for the treatment of moderately to severely active ulcerative colitis in paediatric patients from the age of 2 years and older, who have had an inadequate response to, or were intolerant to either conventional therapy or a biologic.

4. Recommendations

Outcome

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

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

Extension of indication to include treatment of ulcerative colitis in paediatric patients from the age of 2 years and older, based on results from study CNTO1275PUC3001; 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 pediatric participants (2 to <18 years of age) with moderately to severely active ulcerative colitis. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. Minor editorial changes have also been introduced. The Package Leaflet is updated in accordance. Version 33.1 of the RMP has also been updated.

The variation leads to amendments to the annexes I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

The requirements for the submitted dossier in relation to paediatrics are described in section 1 of this report.

In this procedure, the CHMP reviewed the available data from the studies conducted in accordance with the agreed PIP EMA/PE/0000294320. As part of a previous procedure(s), the CHMP also reviewed the

data from the studies conducted in accordance with the agreed PIP, namely study CNTO1275PUC3001. The results of these studies are reflected in sections 4.2, 4.8, 5.1 and 5.2 of the Summary of Product Characteristics (SmPC). Further, these results were pivotal in supporting the new indication: STELARA is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients from the age of 2 years and older, who have had an inadequate response to, or were intolerant to either conventional therapy or a biologic.