15 December 2022
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Stelara

ustekinumab

Procedure no: EMEA/H/C/000958/P46/055

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	17 Oct 2022	17 Oct 2022	☐
☐	CHMP Rapporteur Assessment Report	21 Nov 2022	21 Nov 2022	☐
☐	CHMP members comments	05 Dec 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	08 Dec 2022	n/a	☐
☒	CHMP adoption of conclusions:	15 Dec 2022	15 Dec 2022	☐

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1. Introduction

On 8th September, the MAH submitted a completed paediatric study for Stelara (ustekinumab) in subjects aged aged 2 to <18 with Moderately to Severely active Crohns Disease (CD), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody that binds both human interleukin (IL)-12 and IL-23 via a common IL-12/23p40 subunit. Ustekinumab neutralises the activities of IL-12 and IL-23 by preventing these cytokines from binding to the IL-12 receptor beta-1 receptor protein, which is expressed on the surface of immune cells.

Ustekinumab received a Marketing Authorisation in the EU in January 2009 for the treatment of adult patients with moderate to severe plaque psoriasis, followed by the MAs for the treatment of adult patients with active PsA in September 2013, of paediatric patients (age ≥12 to <18 years) with moderate to severe plaque psoriasis in June 2015, of adult patients with moderate to severe Crohn's disease in November 2016, of adult patients with moderately to severely active UC in September 2019 and of paediatric patients (age ≥6 to <12 years) with moderate to severe plaque psoriasis in January 2020.

Stelara (ustekinumab) Clinical Study CNTO1275CRD1001 (UniSTAR) was a Phase 1 study conducted primarily to evaluate the PK, safety, immunogenicity, and efficacy of ustekinumab in paediatric subjects aged 2 to <18 years with moderately to severely active Crohn's disease.

This study is included in the agreed ustekinumab PIP for Crohns disease (EMEA-000311-PIP04- 13).

2.2. Information on the pharmaceutical formulation used in the study<ies>

The following formulations were used in the CNTO1275CRD1001 study:

IV administration

- Ustekinumab 90 mg/mL LIV was supplied as a single-use sterile solution in 2 mL vialsin a dose strength of 45 mg in 0.5 mL nominal volume. This solution was diluted to an appropriate concentration using an appropriate diluent for IV infusion.
- Ustekinumab 5 mg/mL LIV was supplied as a single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume). This solution was diluted to an appropriate concentration using an appropriate diluent for IV infusion.

SC administration

- Ustekinumab 90 mg/mL LIV was supplied as a single-use sterile solution in a dose strength of 45 mg in 0.5 mL nominal volume.
- Ustekinumab 90 mg/mL pre-filled syringe was supplied as a single-use, sterile solution (ie, 90 mg in 1 mL nominal volume).

Ustekinumab was supplied in bulk batch numbers HGS1I, 16H032, HJS1Q, 17B042, 17J012, IFS08, GHS4J, 15K142, GCS2G, GJS6D_2, GAS5H, FGS6P, and 16B012.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

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

  Protocol No.: CNTO1275CRD1001

Description

Study CNTO1275CRD1001 (UniSTAR) was a Phase 1 study conducted primarily to evaluate the PK, safety, immunogenicity, and efficacy of ustekinumab in paediatric subjects aged 2 to <18 years with moderately to severely active Crohn's disease. The study consisted of a main study through Week 16 followed by an LTE up to Week 268. Paediatric subjects from the main study who were receiving benefit from ustekinumab maintenance therapy, as determined by the investigator, (through Week 16) were eligible to enter the LTE (Figure 1). Results through Week 16 were already reported in the CNTO1275CRD1001 16-Week CSR. In the LTE, Last Patient Last Visit was 18 March 2022, and the final CNTO1275CRD1001 CSR has been completed (01 August 2022).

Subjects were randomised at Week 0 in a 1:1 ratio into 1 of 2 treatment groups stratified by weight (<40 kg, ≥40 kg) and by previous TNFα antagonist exposure status (Yes, No).

Subjects in each treatment group received a single IV administration of ustekinumab at Week 0.

The induction dosage regimens were:

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

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

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

At Week 16, all subjects were eligible to enter the LTE and continued receiving maintenance doses of SC ustekinumab q8w at a dose of 2 mg/kg for subjects <40 kg or 90 mg for subjects ≥40 kg provided that the subject was receiving benefit from ustekinumab maintenance therapy through Week 268 as determined by the investigator. Subjects who had not received benefit at Week 16 as determined by the investigator completed the Week 16 visit requirements, did not receive additional SC dosing, and returned at Week 28 for a final safety assessment. Starting at Week 208, subjects who might benefit from continued treatment were eligible to enrol in CNTO1275ISD3001.

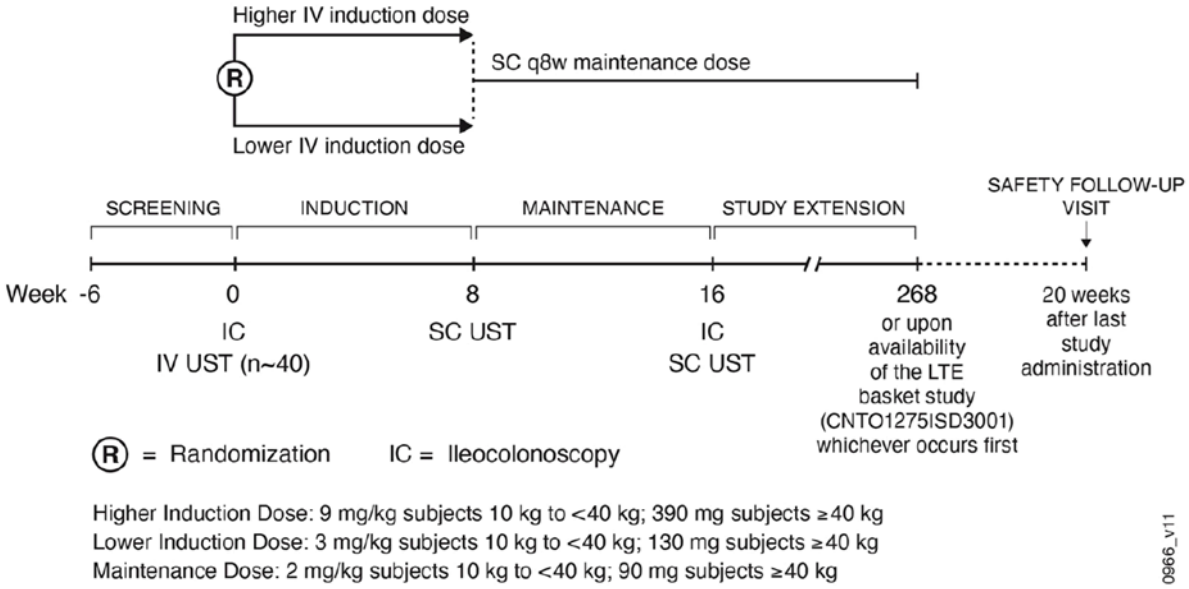
Subjects were permitted to receive the following concomitant medications for Crohn's disease in this study: oral 5-ASAs, the immunomodulators AZA, 6-MP, and MTX, oral corticosteroids, total parental or enteral nutrition, and/or antibiotics for the treatment of Crohn's disease provided the subject was receiving a stable dose for a specified period prior to baseline (as defined in the inclusion criteria). Enrolled subjects were not to initiate or increase the dose of any of the following concomitant Crohn's

disease-specific medical therapies including 5-ASAs, corticosteroids, immunomodulators (ie, AZA, 6-MP, or MTX), and/or total parental or enteral nutrition up to Week 16. Subjects who were receiving immunomodulators (ie, AZA, 6-MP, or MTX) or oral corticosteroids at baseline could discontinue them at any time during the study, and corticosteroids could be tapered beginning at Week 3. During the LTE, Crohn's disease-specific therapies including 5-ASAs, corticosteroids, immunomodulators (ie, AZA, 6-MP, or MTX), and/or total parental or enteral nutrition were permitted to be administered at the discretion of the investigator.

The first DBL occurred after all subjects had either completed their Week 16 visit or terminated study participation prior to Week 16. The second DBL occurred at the end of the LTE.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of Study CNTO1275CRD1001



Methods

Study participants

Eligible subjects were to be 2 to <18 years old in the United States, 6 to <18 years old elsewhere, of either gender with a body weight of ≥10 kg. Subjects must have had a diagnosis of Crohn's disease or fistulising Crohn's disease of at least 3 months with active colitis, ileitis or ileocolitis confirmed at any time in the past by radiography, histology, and/or endoscopy. Subjects must have moderately to severely active Crohn's disease defined as a baseline Paediatric Crohns Disease Activity Index (PCDAI) score of >30 and at least an abnormal C-reactive protein (CRP) value (>0.3 mg/dL or 3.0 mg/L) at screening, or faecal calprotectin of >250 mg/kg or >250 μg/g at screening, or an ileocolonoscopy with evidence of active Crohn's disease (defined as ulcerations in the ileum and/or colon) during screening/baseline visit. Subjects must have received prior or current medication for Crohn's disease with at least one of the following therapies: oral corticosteroids, the immunomodulators azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX])., or currently have or have had a history of corticosteroid dependency (ie, an inability to successfully taper corticosteroids without a return of the symptoms of Crohn's disease); or have a history of failure to respond to, or tolerate, at least 1 of the

following therapies: oral or IV corticosteroids, the immunomodulators AZA, 6-MP, or MTX; or required more than 3 courses of oral or IV corticosteroids in the past year. Subjects who have failed or are intolerant to anti-TNF therapy are eligible for participation but must meet at least one of the requirements for prior or current medication use for Crohn's disease.

Treatments

Subjects in each treatment group received a single IV administration of ustekinumab at Week 0. Following their single IV induction dose at Week 0, all subjects received a SC maintenance dose of ustekinumab at Week 8. Subjects who had not received benefit at Week 16 as determined by the investigator completed the Week 16 visit requirements, including ileocolonoscopy, but did not receive additional SC dosing, and returned at Week 28 for a final safety assessment.

Objectives

Through Week 16

The objectives of this study were to:

1. Evaluate the PK of ustekinumab in subjects from 2 through <18 years old and determine if it is similar to that observed in adults with moderately to severely active Crohns disease.

2. Assess the safety and immunogenicity of ustekinumab in this population.

3. Assess the efficacy of ustekinumab in the treatment of moderately to severely active Crohns disease, including assessment of improvement in the endoscopic appearance of the mucosa.

Outcomes/endpoints

Primary Endpoint

The primary focus of the study is to assess the PK of ustekinumab over time. Therefore, there is no primary efficacy endpoint, and no formal hypothesis testing was performed.

Key Clinical Efficacy Endpoints

- Clinical response through Week 16
- Clinical remission through Week 16
- Baseline and postbaseline values and the change from baseline through Week 16 in PCDAI score
- Baseline and the change from baseline at Week 8 and at Week 16 in IMPACT-III score
- Crohn's disease-related hospitalizations or surgeries through Week 16
- Clinical remission and clinical response at Week 16 by baseline weight (<40 kg, ≥40 kg)

This study also examined endpoints associated with CRP and faecal markers and endoscopic endpoints.

From Week 16 through End of Study

The objective of the LTE period of Study CNTO1275CRD1001 was to evaluate the PK, efficacy, safety and immunogenicity of ustekinumab in paediatric subjects 2 to <18 years old with moderately to severely active Crohn's disease.

During the LTE, efficacy endpoints included clinical response and remission assessed with the PCDAI, corticosteroid-free clinical remission, height, weight, and BMI status, inflammatory markers (CRP, fecal calprotectin, and fecal lactoferrin), and the IMPACT-III questionnaire (at Week 48).

Sample size

A sample size of 40 subjects was chosen empirically based on experience from previous PK studies of other biologics in paediatric subjects, including studies of golimumab in paediatric subjects with UC and paediatric subjects with juvenile idiopathic arthritis. Given the moderate variability associated with ustekinumab PK parameters in subjects with adult Crohns disease and assuming comparable PK variability between adults and paediatric subjects, a sample size of 40 was deemed sufficient to provide adequate PK data in paediatric subjects with Crohns disease.

Randomisation and blinding (masking)

Central randomisation was implemented in this study. Subjects were randomly assigned to 1 of 2 IV dose groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Permuted block randomization with stratification variables of weight (<40 kg, ≥40 kg) and previous TNFα-antagonist exposure status (Yes, No) were used).

Sponsor personnel remained blinded to induction treatment assignment until the Week 16 DBL. To maintain the study blind, a label on the study agent container containing the study name, study agent number, reference number, study agent identity, and dose was available only to unblinded study staff. However, if it was necessary for a subject's safety, the study blind could be broken by blinded staff and the dose of the study agent ascertained.

Data that could potentially unblind the treatment assignment (ie, study agent serum concentrations, anti-ustekinumab antibodies, and treatment allocation) were to be handled with special care to ensure that the integrity of the blind was maintained and the potential for bias was minimised.

Statistical Methods

All randomised subjects who received at least 1 administration of ustekinumab were included in the efficacy and safety analyses. All enrolled subjects who received at least 1 administration of ustekinumab and who had one or more PK/immunogenicity blood samples obtained after the first ustekinumab dose were included in the PK and immunogenicity data sets.

There will be no formal hypothesis testing performed. *Rather, the PK of ustekinumab in paediatric subjects with moderately to severely active CD will be evaluated using descriptive statistics and population PK analyses, and assessed for similarities to the PK of ustekinumab in adult subjects with moderately to severely active CD.*

Results

Participant flow

Subject Disposition and Study Completion/Withdrawal Information

Through Week 16

A total of 44 subjects were randomized and treated with ustekinumab: 23 in the low dose group (ustekinumab 3 mg/kg IV or 130 mg IV), and 21 in the high dose group (ustekinumab 9 mg/kg IV or 390 mg IV). A total of 4/44 (9.1%) subjects discontinued study agent through Week 16: 1 subject in the low dose group and 3 subjects in the high dose group. The most common reason for discontinuation of study agent was worsening Crohns disease.

From Week 16 through Final Safety Follow-up Visit

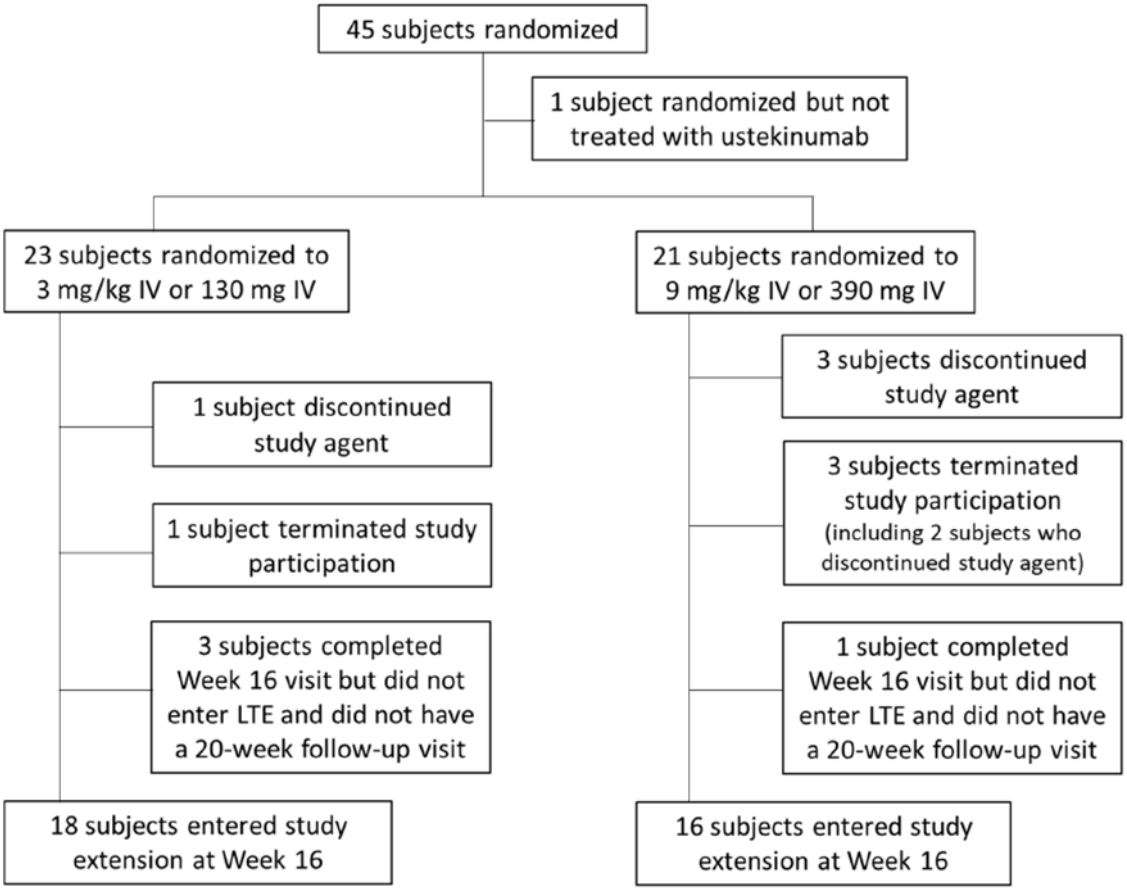
Of the 40 subjects who completed participation through Week 16, 34 subjects participated in the LTE: 18 subjects from the low dose group and 16 subjects from the high dose group. In total, 26/34 (76.5%) of the subjects remained on ustekinumab though the first year of treatment (ie, up to Week 48; including the IV induction dose at Week 0, followed by SC maintenance doses starting at Week 8 and continuing in the LTE).

Over the course of the approximately 4 years of LTE, a total of 28/34 (82.4%) subjects discontinued study agent and 26/34 (76.5%) subjects terminated study participation from Week 16 through the final safety follow-up visit. The most frequently reported reasons for study agent discontinuation were lack of efficacy and an AE of worsening Crohn’s disease (these 2 reasons together accounted for 14/34 [41.2%] subjects), withdrawal by the subject, and ‘other’ reasons.

The reasons reported for termination of study participation were withdrawal by the subject and ‘other’ reasons, which included a switch to commercial STELARA (4 subjects), lack of efficacy, and Crohn’s disease-related events (such as surgery and worsening of the disease). None of the subjects terminated study participation because of COVID-19-related reasons.

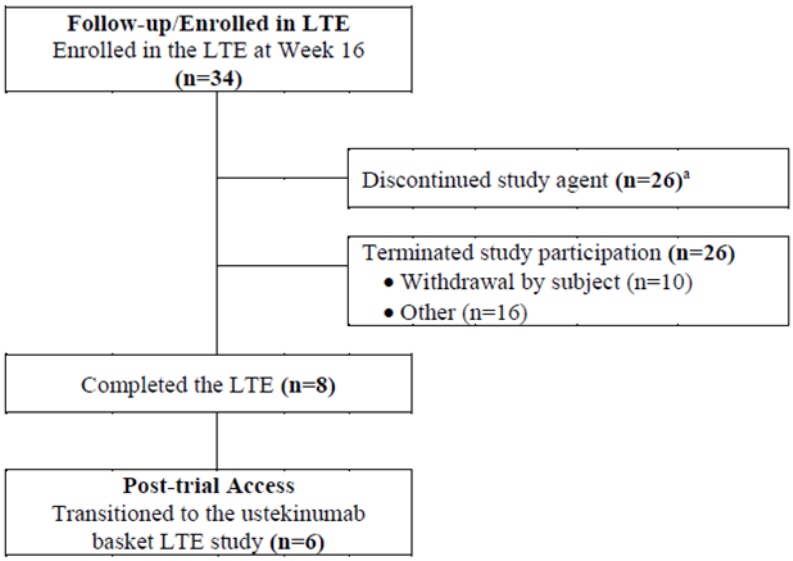
The disposition of subjects through Week 16 and through the study extension is presented in Figure 2 and Figure 3, respectively.

Figure 2: Disposition Flow Chart;[a] Main Study Efficacy Analysis Set (Study CNTO1275CRD1001)



a One additional subject was randomized but not treated; this subject was not included in any of the analyses.

Figure 3: Disposition Flow Chart; Study Extension Efficacy Analysis Set (Study CNTO1275CRD1001)



[a] Two subjects who transitioned to the basket LTE study were erroneously captured in the database as discontinuing study agent. In this flow chart, these subjects are not included in the count of subjects who discontinued study agent.

Recruitment

Baseline data

Demographic and Baseline Characteristics

Through Week 16

The baseline demographics were generally similar across both treatment groups except that there was a greater proportion of female subjects in the low dose group compared with the high dose group. The baseline demographics for the combined treatment groups are provided below.

- 59.1% (26/44 subjects) were female.
- 81.8% (36/44 subjects) were white.
- Median age of subjects was 13.0 years.

22.7% (10/44 subjects) were between the ages of 6 to 11 years.

77.3% (34/44 subjects) were between the ages of 12 to 17 years.

- Median body weight was 42.9 kg.

40.9% (18/44 subjects) had a body weight <40 kg; 7 subjects were <30 kg including 1 subject with a body weight <20 kg

59.1% (26/44 subjects) had a body weight ≥40 kg.

Baseline disease characteristics were representative of a population of subjects with moderately to severely active Crohn's disease and were similar across the treatment groups; however, baseline median CRP concentrations, baseline median fecal lactoferrin, median fecal calprotectin concentrations, and median SES-CD values were greater for subjects in the low dose group compared with subjects in the high dose group; thus the inflammatory burden was greater in the low dose group compared with the high dose group.

Among treated subjects:

- The median duration of disease was 3.6 years.
- The median PCDAI score was 42.5.
- 66.7% of subjects had severe disease (PCDAI score >40).
- The median SES-CD score was 15.0.

The proportions of subjects who had abnormal levels of inflammatory markers at baseline were as follows:

- CRP (>3 mg/L): 72.7%
- Faecal calprotectin (>250 mg/kg): 88.1%
- Faecal lactoferrin (>7.24 μg/mL): 97.7%

Prior to study enrolment:

- 88.6% (39 subjects) had used immunomodulators.
- 63.6% (28 subjects) had used corticosteroids.
- 90.9% (40 subjects) had used biologic therapy.

The proportions of subjects who were receiving each type of concomitant Crohn's disease medication were generally similar across both treatment groups except that there was a greater proportion of subjects receiving immunomodulators in the high dose group compared with the low dose group. Among treated subjects:

- 38.6% (17 subjects) were receiving immunomodulators.
- 20.5% (9 subjects) were receiving oral aminosalicylates.
- 31.8% (14 subjects) were receiving oral corticosteroids (including budesonide).

From Week 16 through End of Study

A summary of demographics at baseline for the study extension efficacy analysis set is provided below:

- 61.8% (21/34 subjects) were female.
- 85.3% (29/34 subjects) were white.
- Median (range) age of subjects was 13.0 (6.0; 17.0) years.

23.5% (8/34 subjects) were between the ages of 6 to 11 years.

76.5% (26/34 subjects) were between the ages of 12 to 17 years.

- Median (range) body weight was 41.05 (19.5; 70.1) kg.

47.1% (16/34 subjects) had a body weight <40 kg, including 1 subject with a body weight <20 kg.

52.9% (18/34 subjects) had a body weight ≥40 kg.

- Median (range) BMI was 17.23 (12.8; 25.1) kg/m2.

The Crohns disease characteristics at baseline among treated subjects are summarized below:

- The median (range) duration of disease was 3.59 (0.7; 12.4) years.
- The median (range) PCDAI score was 42.50 (12.5; 60.0).

59.4% (19/34 subjects) had severe disease (PCDAI score >40).

By Week 16 (ie, the start of the LTE period of the study), the proportions of subjects receiving concomitant medications for Crohns disease had decreased to 7/34 (20.6%). The most frequently reported concomitant medications at the start of the LTE period were oral corticosteroids (including budesonide) and antibiotics. No subjects were taking immunomodulatory drugs at Week 16.

Number analysed

Pharmacokinetics and Immunogenicity Results

Through Week 16

A summary of serum ustekinumab concentrations through Week 16 by induction treatment group in the overall paediatric CD population is presented in Table 1:

Table 1 Summary of Serum Ustekinumab Concentrations (micrograms/mL) Through Week 16; PK Analysis Set (Study CNTO1275CRD1001)

	Ustekinumab	
	3 mg/kg IV or 130 mg IV →2 mg/kg SC or 90 mg SC	9 mg/kg IV or 390 mg IV →2 mg/kg SC or 90 mg SC
Analysis set: PK analysis set	23	21
Week 0, preadministration		
N	23	21
Mean (SD)	0.05 (0.193)	0.00 (0.000)
Median	0.00	0.00
IQ range	(0.00; 0.00)	(0.00; 0.00)
Range	(0.0; 0.9)	(0.0; 0.0)
Week 0, 1 hour postadministration		
N	22	20
Mean (SD)	51.25 (9.627)	148.71 (21.250)
Median	50.51	150.22
IQ range	(46.34; 54.75)	(133.86; 168.99)
Range	(28.9; 78.9)	(114.8; 182.1)
Week 3		
N	20	20
Mean (SD)	7.66 (4.377)	23.72 (13.691)
Median	6.36	20.99
IQ range	(4.75; 11.30)	(12.80; 36.37)
Range	(1.4; 17.8)	(2.6; 51.8)
Week 6		
N	22	19
Mean (SD)	2.99 (2.637)	9.08 (8.066)
Median	2.29	5.11
IQ range	(0.98; 5.26)	(3.26; 14.85)
Range	(0.0; 10.0)	(0.3; 26.8)
Week 8		
N	21	18
Mean (SD)	1.56 (1.600)	4.76 (4.857)
Median	1.18	2.53
IQ range	(0.58; 2.09)	(1.35; 8.69)
Range	(0.0; 5.9)	(0.0; 14.6)
Week 12		
N	20	17
Mean (SD)	4.40 (2.946)	5.89 (4.479)
Median	3.67	3.32
IQ range	(2.31; 6.10)	(2.55; 9.22)
Range	(0.3; 10.9)	(1.5; 14.5)
Week 16		
N	17	13
Mean (SD)	1.47 (1.323)	1.80 (2.356)
Median	1.04	0.59
IQ range	(0.58; 2.28)	(0.20; 1.92)
Range	(0.0; 4.3)	(0.0; 6.6)

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- After a single IV administration of the low dose (3 mg/kg or 130 mg) or the high dose (9 mg/kg or 390 mg) of ustekinumab, mean and median serum ustekinumab concentrations were approximately dose-proportional at all sampling timepoints through Week 8.
- Median peak serum ustekinumab concentrations 1 hour after the Week 0 IV induction dose were 50.51 μg/mL and 150.22 μg/mL for the low and high doses, respectively. At the end of

induction at Week 8, median serum ustekinumab concentrations were 1.18 μg/mL and 2.53 μg/mL for the low and high doses, respectively.

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

The dose regimens evaluated in this study were designed to deliver comparable ustekinumab exposure in paediatric subjects with those observed in the corresponding reference adult CD population (ie, CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 studies). The following results compare ustekinumab concentrations over time between the overall paediatric population and paediatric body weight subgroups, with those in the corresponding adult reference population.

A comparison of serum ustekinumab concentration between overall paediatric and adult subjects with Crohn's disease is presented in Table 2. Of note, the 130 mg and the ~6 mg/kg treatment groups in the adult study represents the adult reference groups for the low-induction (3 mg/kg or 130 mg) and high-induction (9 mg/kg or 390 mg) dose groups in the paediatric study, respectively.

Table 2 Summary of Paediatric vs Adult Serum Ustekinumab Concentrations (Excluding Those Enrolled Prior to Study Re-Start) (micrograms/mL) Through Week 16; PK Analysis Set (Study CNTO1275CRD1001)

	CNTO1275CRD1001		CNTO1275CRD3001 and CNTO1275CRD3002 Combined → CNTO1275CRD3003[b]	
	3 mg/kg IV or 130 mg IV →2 mg/kg SC or 90 mg SC	9 mg/kg IV or 390 mg IV →2 mg/kg SC or 90 mg SC	130 mg IV →90 mg SC	approx. 6 mg/kg IV →90 mg SC
Analysis set: PK analysis set	23	21	458	456
Week 0, preadministration				
N	23	21	455	454
Mean (SD)	0.05 (0.193)	0.00 (0.000)	0.28 (2.635)	0.44 (5.806)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 0.00)	(0.00; 0.00)	(0.00; 0.00)	(0.00; 0.00)
Range	(0.0; 0.9)	(0.0; 0.0)	(0.0; 41.1)	(0.0; 109.8)
Week 0, 1 hour postadministration				
N	22	20	434	440
Mean (SD)	51.25 (9.627)	148.71 (21.250)	41.85 (12.767)	125.20 (33.634)
Median	50.51	150.22	41.86	126.06
IQ range	(46.34; 54.75)	(133.86; 168.99)	(34.60; 49.99)	(106.07; 146.16)
Range	(28.9; 78.9)	(114.8; 182.1)	(0.0; 83.0)	(0.0; 224.8)
Week 3				
N	20	20	419	420
Mean (SD)	7.66 (4.377)	23.72 (13.691)	8.35 (3.461)	25.17 (10.587)
Median	6.36	20.99	8.72	24.50
IQ range	(4.75; 11.30)	(12.80; 36.37)	(5.97; 10.42)	(17.38; 32.53)
Range	(1.4; 17.8)	(2.6; 51.8)	(0.0; 21.9)	(0.0; 72.7)
Week 6				
N	22	19	397	398
Mean (SD)	2.99 (2.637)	9.08 (8.066)	3.82 (2.390)	11.12 (6.588)
Median	2.29	5.11	3.37	9.96
IQ range	(0.98; 5.26)	(3.26; 14.85)	(2.07; 5.22)	(6.77; 15.16)
Range	(0.0; 10.0)	(0.3; 26.8)	(0.0; 10.6)	(0.0; 45.0)

Week 16[a]				
N	17	13	219	222
Mean (SD)	1.47 (1.323)	1.80 (2.356)	2.13 (1.704)	3.09 (2.631)
Median	1.04	0.59	1.74	2.41
IQ range	(0.58; 2.28)	(0.20; 1.92)	(0.84; 3.09)	(1.20; 4.32)
Range	(0.0; 4.3)	(0.0; 6.6)	(0.0; 9.6)	(0.0; 15.9)

[a] Week 12 is Week 4 of CRD3003. Week 16 is Week 8 of CRD3003.
[b] CRD3003 contains both q8 week q12 week treatment group.

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- Serum ustekinumab concentrations observed in the overall paediatric Crohns disease population were generally comparable to those observed in the reference adult CD population. However, a pattern towards lower median serum ustekinumab concentrations was observed in subjects in the <40 kg body weight subgroup compared with subjects in the ≥40 kg body weight subgroup and compared with the reference adult Crohn's disease population. Median serum ustekinumab concentrations in the ≥40 kg body weight subgroup were generally comparable with those in the reference adult population.
- Of 42 ustekinumab-treated subjects with appropriate samples, none was positive for antibodies to ustekinumab through Week 16.

From Week 16 through End of Study

After maintenance treatment with SC ustekinumab q8w starting at Week 8 and continuing in the LTE for up to 4 years, mean serum ustekinumab concentrations were generally consistent over time during the LTE period (Table 3). Most subjects had detectable drug levels through Week 200, but it should be noted that a small number of subjects remained in the study at this time.

Table 3 Summary of Serum Ustekinumab Concentrations (micrograms/mL) from Week 16 Through Final Safety Follow-up Visit; Treated Subjects in Extension Study (Study CNTO1275CRD1001)

Analysis set: Treated Subjects in the Study Extension	34
Week 16	
N	28
Mean (SD)	1.72 (1.836)
Median	0.98
IQ range	(0.42; 2.35)
Range	(0.0; 6.6)
Week 24	
N	24
Mean (SD)	1.87 (1.750)
Median	1.31
IQ range	(0.38; 2.92)
Range	(0.0; 5.6)
Week 32	
N	17
Mean (SD)	1.84 (1.807)
Median	1.26
IQ range	(0.33; 2.54)
Range	(0.0; 6.6)
Week 40	
N	16
Mean (SD)	1.58 (1.463)
Median	1.16
IQ range	(0.32; 2.69)
Range	(0.0; 4.2)
Week 48	
N	16
Mean (SD)	1.82 (1.930)
Median	1.23
IQ range	(0.32; 2.45)
Range	(0.0; 6.4)
Week 56	
N	14
Mean (SD)	2.03 (1.847)
Median	1.86
IQ range	(0.34; 3.29)
Range	(0.0; 5.9)
Week 80	
N	9
Mean (SD)	2.35 (1.968)
Median	2.24
IQ range	(0.54; 3.87)
Range	(0.0; 5.6)
Week 104	
N	6

Mean (SD)	2.98 (2.329)
Median	2.90
IQ range	(1.12; 4.11)
Range	(0.2; 6.7)
Week 128	
N	3
Mean (SD)	2.29 (0.731)
Median	2.45
IQ range	(1.50; 2.94)
Range	(1.5; 2.9)
Week 152	
N	5
Mean (SD)	1.89 (1.287)
Median	1.80
IQ range	(1.47; 3.04)
Range	(0.0; 3.1)
Week 176	
N	1
Mean (SD)	2.38 (-)
Median	2.38
IQ range	(2.38; 2.38)
Range	(2.4; 2.4)
Week 200	
N	3
Mean (SD)	3.83 (2.005)
Median	4.31
IQ range	(1.63; 5.56)
Range	(1.6; 5.6)
Week 224	
N	1
Mean (SD)	7.01 (-)
Median	7.01
IQ range	(7.01; 7.01)
Range	(7.0; 7.0)
Safety Follow-up	
N	13
Mean (SD)	3.23 (2.995)
Median	2.52
IQ range	(0.84; 4.76)
Range	(0.0; 8.5)

Adapted from Mod5.3.5.1/CNTO1275CRD1001/LTE/AttTPKCONC01

Of the 34 subjects with appropriate samples who were treated with ustekinumab during the LTE period, 1/34 (2.9%) subject was positive for antibodies to ustekinumab through the final safety visit with a peak titre of 1:100. The subject was positive for NAb.

Efficacy results

This study had no formal hypothesis testing conducted and there was no placebo control group.

The results should be interpreted with caution due to the small number of subjects, combined with the declining number of subjects over time. As the study was not designed to make any statistical comparisons, results are descriptive and are presented here for information purposes.

Through Week 16

Intravenous ustekinumab at Week 0 and an SC maintenance dose of ustekinumab at Week 8 induced improvements in clinical and endoscopic disease activity through Week 16 in paediatric subjects with Crohn's disease across the efficacy outcome measures evaluated:

- Numerically higher proportions of subjects in clinical response and clinical remission were seen in the high-induction dose group than in the low-induction dose group at earlier time points (ie Week 3 for clinical response; Week 3 and Week 6 for clinical remission).
- Reductions in the PCDAI score from baseline to Week 16 was observed in both the low induction dose group and high-induction dose group. Greater reductions were seen in the high-induction dose group than in the low-induction dose group, at Week 3
- Reductions in objective biomarkers of inflammation (eg, CRP, fecal calprotectin, and fecal lactoferrin) were observed in both dose groups.
- Improvement in the SES-CD score from baseline to Week 16 was observed in both the low induction dose group and high-induction dose group.
- Similar proportions of subjects in both dose groups had endoscopic response, endoscopic remission and clinically meaningful endoscopic improvement and endoscopic healing at Week 16.
- Improvement from baseline to Week 16 in the HRQOL measured by IMPACT III were observed in both the low-induction dose group and high-induction dose group.

From Week 16 through End of Study

Subcutaneous q8w maintenance doses of ustekinumab during the LTE period appeared to maintain the improvements in clinical and endoscopic disease activity observed up to Week 16. Among the subjects who remained in the study:

- The proportions of those in clinical response and clinical remission remained high throughout the LTE period.
- Reductions in the PCDAI score from baseline were maintained during the LTE period.
- Improvements in height and weight z-scores were maintained during the LTE period. BMI z-scores improved at Week 48 and improvements were maintained over time during the LTE period.
- Reductions from baseline in objective biomarkers of inflammation (CRP, fecal calprotectin, and fecal lactoferrin) were maintained during the LTE period.
- Improvement from baseline in HRQOL, as measured by IMPACT-III, was maintained during the LTE period.
- No clear exposure-response relationship was evident between either improvement in PCDAI score, clinical response, or clinical remission, and serum ustekinumab concentrations at Week 48.

Safety results

Through Week 16

Both single IV ustekinumab induction doses at Week 0 and the SC maintenance dose of ustekinumab at Week 8 were generally well tolerated through Week 16 in the paediatric CD population.

- 2 subjects discontinued study agent due to an AE: 1 subject in each treatment group. Discontinuation of study agent due to AEs through Week 16 was generally attributed to unsatisfactory response to ustekinumab or worsening of Crohns disease.

- Seven subjects (6 in the low dose group and 1 in the high dose group) reported SAEs through Week 16; the majority of which were associated with worsening of Crohn’s disease.
- No opportunistic infections including TB were reported through Week 16.
- No malignancies or deaths were reported through Week 16.
- There was 1 serious infection (intestinal abscess) reported in the low dose group.
- There were 17 infections (9 in the low group and 8 in the high dose group) reported through Week 16.
- One subject in the low dose group reported a transient AE of pyrexia during or within 1 hour of an infusion.
- No subjects reported injection-site reactions through the final safety visit.
- Haematology and chemistry laboratory values were generally within normal limits, infrequent abnormalities were not generally considered to be clinically important.
- The safety profile of ustekinumab was generally consistent across age and weight subgroups.

From Week 16 through End of Study

- Through the final safety follow-up visit, 5/34 (14.7%) subjects discontinued study agent because of 1 or more AEs. Among the AEs resulting in study agent discontinuation the PT Crohns disease (worsening Crohn's disease) was most frequently reported.
- Through the final safety follow-up visit, 11/34 (32.4%) subjects reported 1 or more SAEs. The most frequently reported SAE was the PT Crohn's disease (worsening Crohn's disease). The remaining SAEs were singular events commonly related to Crohn’s disease (PTs Anal ulcer, Large intestinal stenosis, Malnutrition, Vomiting) or other singular events (PTs Constipation, Pancreatitis [due to AZA], Appendicitis).
- No malignancies or deaths were reported.
- No serious infections or opportunistic infections (including TB) were reported. Through the final safety follow-up visit, 28/34 (82.4%) of subjects reported 1 or more non-serious infections. Among the AEs of infection, the PTs Upper respiratory tract infection and Nasopharyngitis were most frequently reported.
- No injection-site reactions were reported.
- There were no reports of possible anaphylactic or delayed hypersensitivity reactions.
- The majority of the observed haematology or clinical chemistry laboratory parameter abnormalities were grade 1 in severity. No grade 4 abnormalities were observed. A grade 3 abnormality (absolute lymphocytes decreased) was observed in 1/34 (2.9%) subject. Grade 2 or higher abnormalities of decreased haemoglobin, decreased absolute neutrophils, and decreased absolute lymphocytes were observed through the final safety follow-up visit. Clinical chemistry parameter abnormalities of grade 2 were sporadic in nature. Few laboratory parameter abnormalities were reported as AEs, and all were singular events.

2.3.2. Discussion on clinical aspects

The MAH has submitted a completed paediatric study for Stelara (ustekinumab) in subjects aged aged 2 to <18 with Moderately to Severely active CD, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This was a multicenter, randomised, double-blind PK study of IV ustekinumab induction treatment followed by SC ustekinumab maintenance treatment in paediatric subjects with moderately to severely active Crohn's disease. Subjects were aged 2 to <18 years old in the United States, 6 to <18 years old elsewhere, with a diagnosis of moderately to severely active Crohns disease (defined by a PCDAI score >30). Subjects had to have an inadequate response and/or intolerance to biologic therapy and/or conventional therapies or be dependent upon corticosteroids.

The purpose of study CNTO1275CRD1001 was to assess the PK of ustekinumab over time. There was no primary efficacy endpoint, and no formal hypothesis testing was performed.

A total of 44 paediatric subjects were analysed; 23 in the low-induction dose group (ustekinumab 3mg/kg IV or 130 mg IV), and 21 in the high-induction dose group (ustekinumab 9 mg/kg IV or 390 mg IV).

Overall 22.7% (10/44 subjects) were between the ages of 6 to 11 years and 77.3% (34/44 subjects) were between the ages of 12 to 17 years (median age was 13.0 years). Baseline demographic and disease characteristics were generally similar across the treatment groups.

A total of 4 of the 44 subjects (9.1%) discontinued study agent through Week 16: 1 subject in the low-induction dose group and 3 subjects in the high-induction dose group. The most common reason for discontinuation of study agent was worsening Crohns disease. A total of 34 subjects entered the study extension at Week 16.

Analysis of PK data through to Week 16 showed that:

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

Median peak serum ustekinumab concentrations 1 hour after the Week 0 IV induction dose were 50.51 µg/mL and 150.22 µg/mL for the low and high doses, respectively. At the end of induction at Week 8, median serum ustekinumab concentrations were 1.18 µg/mL and 2.53 µg/mL for the low and high doses, respectively.

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

Serum ustekinumab concentrations observed in the overall paediatric CD population were generally comparable to those observed in the reference adult CD population. However, a pattern towards lower median serum ustekinumab concentrations was observed in subjects in the <40 kg body weight subgroup compared with subjects in the ≥40 kg body weight subgroup and compared with the reference adult CD population.

Median serum ustekinumab concentrations in the ≥40 kg body weight subgroup were generally comparable with those in the reference adult population.

Of the 34 subjects with appropriate samples who were treated with ustekinumab during the LTE period, 1/34 (2.9%) subject was positive for antibodies to ustekinumab through the final safety visit with a peak titre of 1:100. The subject was positive for NAb.

Since results from this study suggested that the mg/kg dose adjustment strategy used did not consistently result in similar exposures in the lowest body weight subgroups this information was used to inform the design and dosing of the follow-up CNTO1275CRD3004 Phase 3 paediatric study. That study subsequently implemented a BSA-based dose adjustment strategy for paediatric participants with lower body weight (<40 kg) to minimize the variability of ustekinumab exposure across the lower paediatric weight band. The results from this study are seen as informing current and future ustekinumab paediatric studies.

This study had no formal hypothesis testing. However, measures of clinical response and clinical remission (including PCDAI scores, biomarkers of inflammation, SES-CD scores and other endoscopic measures) through Week 48 were suggestive of clinical improvements in disease activity.

Safety results from this study suggest that the safety profile of ustekinumab in the paediatric CD population was generally consistent with the established safety profile of ustekinumab in the adult Crohns disease population. No deaths were reported through the final safety visit.

There are several limitations of this study; firstly, although this was a randomised study, there was no placebo control group, so no comparisons can be made between the ustekinumab group and a placebo group. Secondly, the results should be interpreted with caution due to the small number of subjects, combined with the declining number of subjects over time. As the study was not designed to make any statistical comparisons, results are descriptive and are limited in value in terms of clinical value.

Despite these limitations the study does provide an understanding of the pharmacokinetic profile of ustekinumab in paediatric subjects and subsequently provided information to inform dose design for other ustekinumab paediatric CD studies. The results also appear to suggest a benefit in terms of clinical efficacy for paediatric CD patients treated with ustekinumab.

3. CHMP overall conclusion and recommendation

In the context of this PAM for a completed paediatric study for Stelara (ustekinumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, the MAH has met their obligations.

Due to the design of the study no conclusions on safety and efficacy of ustekinumab in paediatric subjects could be made.

Stelara, at this time, does not have an indication for treatment of paediatric patients with CD, no updates to PI are proposed.

☒ Fulfilled:

No regulatory action required.