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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/P46/051

Note

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

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1. Introduction

On 30 March 2021, the MAH submitted a completed paediatric study for Stelara (ustekinumab), 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 neutralizes 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.

The current Article 46 submission summarizes the efficacy and safety data from the long-term extension (LTE) period of the completed CNTO1275PSO3013 or CADMUS Junior (hereafter referred to as PSO3013). PSO3013 was an open-label, multicenter study to evaluate the efficacy, safety, PK, and immunogenicity of ustekinumab in children aged from ≥6 to <12 years with moderate to severe chronic plaque psoriasis which allowed paediatric subjects who have demonstrated clinical benefit through week 52 of the main study to continue receiving ustekinumab

The results of the main study (through Week 56) have been submitted previously (EMEA/H/C/000958/II/0073), and formed the basis of the extension of indication to children aged 6 to 12 years with moderate to severe psoriasis.

2.2. Information on the pharmaceutical formulation used in the study

Ustekinumab was supplied as a liquid in vial for administration by subcutaneous injection. There was a single drug concentration (ie, 45 mg in 0.5 mL volume). Each 0.5 mL of ustekinumab solution contains 45 mg ustekinumab, L-histidine, sucrose, and polysorbate 80 at pH 6.0. Four ustekinumab lot numbers were used in the LTE of the study (4374328, 4375688, 4376094, 4378527).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final long-term extension clinical study report for:

- Study CNTO1275PSO3013y , A Phase 3 Open-label Study to Assess the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Ustekinumab in the Treatment of Moderate to Severe Chronic Plaque Psoriasis in Paediatric Subjects ≥6 to <12 Years of Age.

2.3.2. Clinical study

CNTO1275PSO3013 CADMUS Jr

Description

The CNTO1275PSO3013 study was designed to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of ustekinumab during up to 5 years of continuous treatment in paediatric subjects ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis.

This open-label study consisted of a main study through Week 56 (previously assessed under EMEA/H/C/000958/II/0073) followed by a long-term extension (LTE) through Week 264 to allow paediatric subjects who have demonstrated clinical benefit through Week 52 of the main study to continue receiving ustekinumab. The LTE is the focus of this assessment.

Methods

Objectives

The objective of the LTE of the study was to allow paediatric subjects who demonstrated clinical benefit through Week 52 of the main study to continue receiving ustekinumab and to evaluate the efficacy and safety of ustekinumab in paediatric subjects aged ≥6 through <12 years with moderate to severe chronic plaque psoriasis.

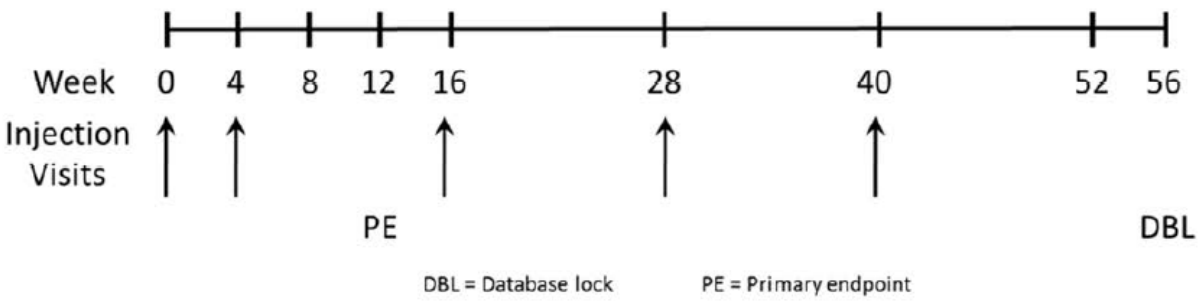
The endpoints evaluated during the LTE of the study were:

- the proportion of subjects achieving a PGA score of cleared (0) over time.
- the proportion of subjects achieving a PGA score of cleared (0) or minimal (1) over time.
- the proportion of subjects achieving a PGA score of mild or better (≤2) over time.

Study design

PSO3013 was an open-label multicenter study conducted at multiple sites in Europe, US, and Canada that evaluated the safety, efficacy, and PK of ustekinumab in pediatric subjects ≥6 to <12 years of age, with moderate to severe chronic plaque psoriasis.

Study Schema through Week 56



As outlined earlier in this report, the main study was the focus of Procedure No. EMEA/H/C/000958/II/0073. Both study design and results to week 56 were previously assessed and so will not be described in detail in this assessment report.

After the main study through Week 56, subjects who met entry criteria (had a beneficial response from ustekinumab treatment as determined by the investigator, and who had not yet reached the age of 12 years or older in countries where marketing authorization for ustekinumab had been granted for the treatment of psoriasis in adolescent patients ≥12 to <18 years of age), were allowed to enter the LTE.

The LTE was considered completed when all subjects had either terminated participation according to the above criteria or completed their follow-up at Week 264.

CHMP's comment

The MAH is requested to confirm that the LTE was part of the agreed EMA paediatric investigation plan, which received a positive opinion from EMA Paediatric Committee on compliance with a PIP, as presented under EMEA/H/C/000958/II/0073.

The MAH has clarified has clarified that the LTE of CNTO1275PSO3013 was part of the overall study design but was not part of the key binding elements of the PIP.

Study population /Sample size

The subject population was comprised of paediatric subjects ≥6 to <12 years of age with a diagnosis of plaque psoriasis for at least 6 months prior to first study drug administration and with moderate to severe disease defined by PASI ≥12, PGA ≥3, and body surface area (BSA) ≥10%. The planned total sample size for the main study was approximately 40 subjects. A total of 44 subjects were enrolled in the main study. Of the 39 subjects who completed participation in the main study through Week 56, 28 subjects participated in the LTE.

Treatments

Details about the dosing regimen and administration of ustekinumab through Week 40 were previously presented under EMEA/H/C/000958/II/0073. Briefly, all subjects enrolled in the study were to receive subcutaneous (SC) ustekinumab at Weeks 0 and 4 followed by a maintenance dose every 12 weeks thereafter, with the last dose at Week 40.

Subject dosing was based on body weight measured at each visit and the dose of ustekinumab was adjusted accordingly as follows:

- 0.75 mg/kg in subjects weighing <60 kg
- 45 mg in subjects weighing ≥60 kg to ≤100 kg
- 90 mg in subjects weighing >100 kg

Eligible subjects who entered the LTE received ustekinumab q12w beginning at Week 56 and continued treatment according to criteria defined in Section 3.1.1.

Endpoints

Efficacy

The efficacy evaluations of the LTE consisted of PGA assessments, which occurred every 24 weeks from week 80. The endpoints evaluated during the LTE of the study were:

- the proportion of subjects achieving a PGA score of cleared (0) over time.
- the proportion of subjects achieving a PGA score of cleared (0) or minimal (1) over time.
- the proportion of subjects achieving a PGA score of mild or better (≤2) over time

Pharmacokinetic and immunogenicity

No PK or immunogenicity assessments were performed during the LTE.

Safety

Safety was evaluated based on:

- Adverse events
- Clinical laboratory tests (hematology, serum chemistry)
- Vital sign measurements
- Physical examinations
- Concomitant medication review
- Injection-site reactions
- Allergic reactions
- TB evaluations

Table 2 below details the study drug administration, ongoing subject reviews, and safety and efficacy assessments in subjects who enter the LTE starting at the Week 56 study visit.

Table 2: Time and Events Schedule for the Long-term Extension (Week 56 to Week 264)

	Long-term Extension[f]																	
Week	56	68	80	92	104	116	128	140	152	164	176	188	200	212	224	236	248	264[g]
Study Procedures																		
Study Drug Administration																		
Study drug administration[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Assessments																		
Physical examination					X				X				X				X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height					X				X				X				X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test, qualitative[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full chemistry[e]					X				X				X				X	
Hematology[e]					X				X				X				X	
Ongoing Subject Review																		
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event (AE) review[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments																		
Physician's Global Assessment (PGA)[d]			X		X		X		X		X		X		X		X	

[a] All procedures and evaluations are to be completed prior to study drug injection. For subjects in the LTE who decide to withdraw from study participation, or who discontinue treatment, the assessments (excluding study drug injection) for the Week 248 study visit will be performed.
[b] Urine pregnancy test to be conducted for girls of childbearing potential.
[c] Includes TB evaluation. Refer to the Early Detection Of Active Tuberculosis text in Section 9.6.
[d] Efficacy assessments (PGA) should be performed by the investigator or any qualified healthcare provider at the study site.
[e] All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled. Details will be provided in the Laboratory Manual.
[f] Subjects who discontinue study drug but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for approximately 16 weeks (4 months) following the last dose of study drug. At the subject's last study visit for the LTE prior to Week 248, the procedures and evaluations (excluding study drug injection) for Week 248 will be followed. If a subject discontinues study drug and terminates study participation, the procedures and evaluations (excluding study drug injection) for Week 248 will be performed at the current visit.
[g] Final LTE visit. The Week 264 visit is a follow-up safety visit that will be handled as a phone call.

Statistical Methods

Observed data were summarised and no imputation rules were applied. In addition to the summaries over time, line plots were created displaying proportions and exact 95% confidence intervals of subjects achieving a PGA score of cleared (0), and of cleared (0) or minimal (1) over time.

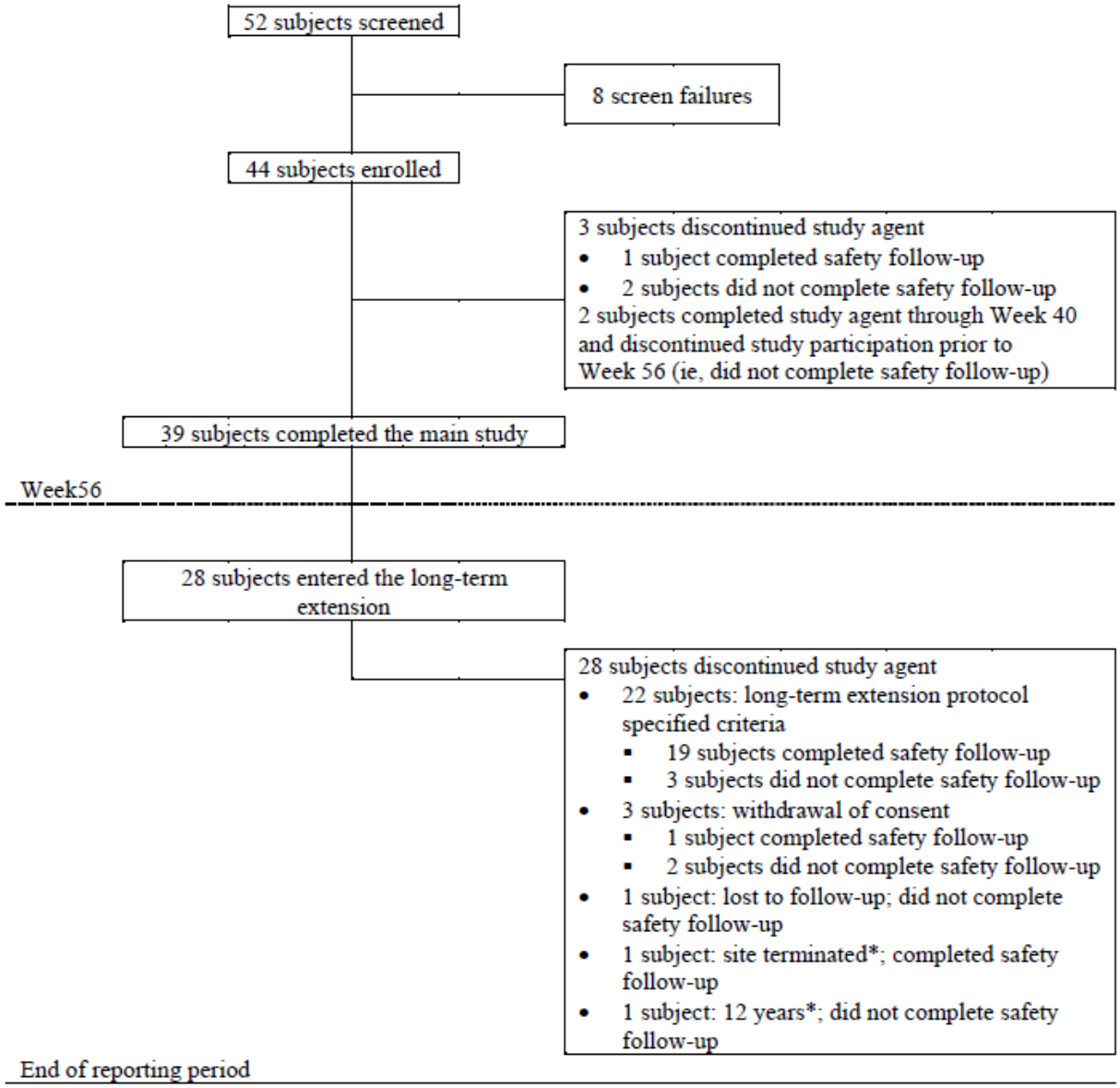
Results

Recruitment/ Number analysed

A total of 28 subjects participated in the LTE. All 28 (100%) subjects discontinued study participation before reaching Week 264, of whom 21 (75.0%) subjects completed the protocol-required safety follow-up and 7 (25.0%) subjects did not complete safety follow-up after the last study agent administration. Analysis of the PGA response rates during the LTE was based on the full analysis set.

The disposition of subjects through the end of the reporting period is presented below in Figure 1.

Figure 1: Subject Disposition Through the End of the Reporting Period



* For both subjects marked with an asterisk above, the reason for study agent discontinuation was reported incorrectly and should have been documented as LONG TERM EXTENSION PROTOCOL-SPECIFIED CRITERIA 9.1.5". For one patient discontinuation was documented as "SITE TERMINATED BY SPONSOR and for another the reason for study agent discontinuation was reported incorrectly as "OTHER - SUBJECT TURNED 12".

CHMP's comments

A total of 28 patients were included in the LTE and 100% of these discontinued study agent before Week 264. The majority of these (24) discontinued due to protocol specified criteria 9.1.5:

- The subject turns 12 years of age and resides in a country where marketing authorisation has been granted for ustekinumab treatment of psoriasis in adolescent patients
- Marketing authorisation is obtained for ustekinumab for treatment of plaque psoriasis for patients ≥6 to <12 years of age in the subject's country of residence
- Marketing authorisation is denied for ustekinumab for the treatment of plaque psoriasis for

patients ≥6 to <12 years of age in the subject's country of residence

- A company decision is made to no longer pursue an indication in plaque psoriasis in the paediatric population (≥6 to <12 years of age) in the subject's country of residence

The longest treatment duration was 176 weeks. Based on the above discontinuation criteria, it is not unexpected that patients who entered the LTE discontinued from the study before week 264, however the small numbers of patients evaluated during the LTE, with only 13 and 3 subjects evaluated at Week 152 and Week 176, respectively limits the usefulness of the observations.

Baseline data

Demographic and baseline characteristics were previously presented in Mod5.3.5.1/CNTO1275PSO3013/CSR/Sec4.2.

CHMP's comments

Demographic and disease characteristics of subjects in PSO3013 were previously described and assessed under EMEA/H/C/000958/II/0073, essentially the rapporteur considers the population studied to be representative of the target treatment population in the EEA.

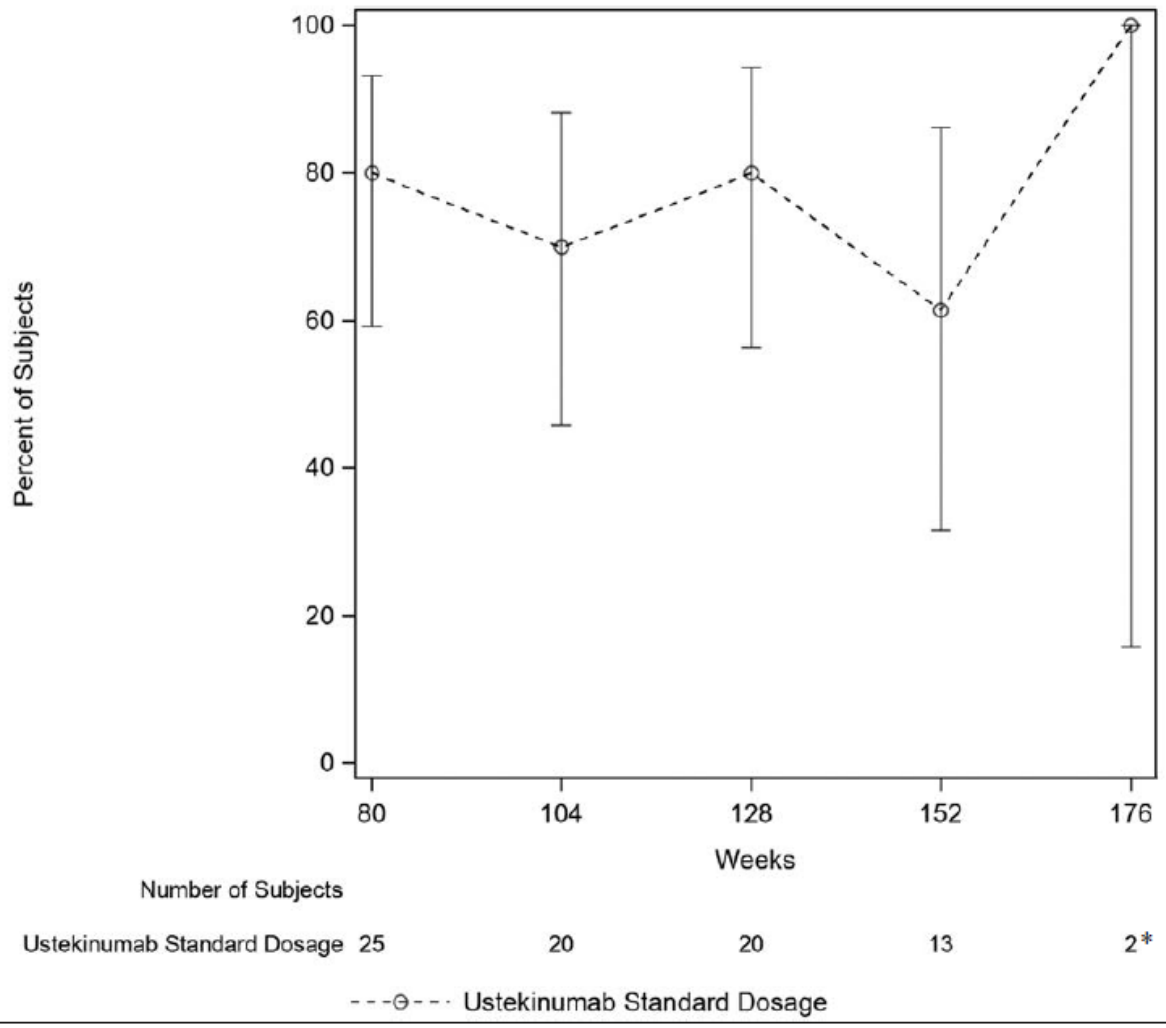
Pharmacokinetic results

No PK or immunogenicity assessments were performed during the LTE.

Efficacy results

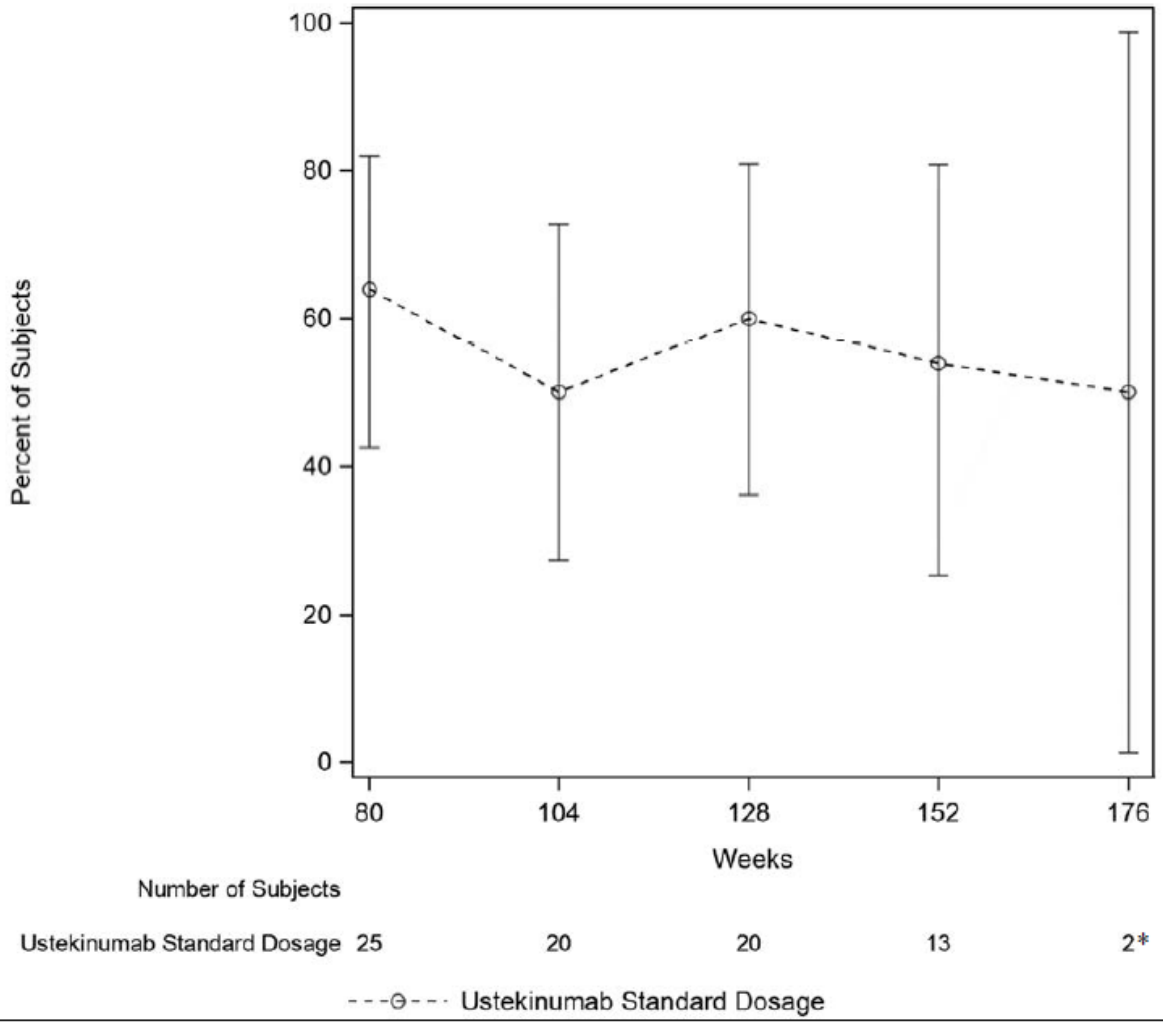
The efficacy evaluations of the LTE consisted of PGA assessments, which occurred every 24 weeks. The first LTE efficacy assessment was performed at Week 80. Overall, the PGA response rates of cleared (0) or minimal (1) (Figure 2), and PGA response rates of cleared (0) (Figure 3) were maintained from Week 80 through Week 176. Over all visits within this period, the proportion of subjects with a PGA score of mild or better (≤2) was ≥95%.

Figure 2: **Percent of Subjects Achieving a PGA Score of Cleared (0) or Minimal (1) From Week 80 Through Week 176 by Visit; Full Analysis Set With Subjects Participating in the Long-term Extension (Study CNTO1275PSO3013)**



Note: 95% confidence intervals were based on the exact method.
*An additional subject was dosed and assessed for PGA at Week 176; however, the PGA assessment (score of 2) was mapped incorrectly to the Week 164 unscheduled visit and is therefore missing from the Week 176 timepoint in this figure.

Figure 3: **Percent of Subjects Achieving a PGA Score of Cleared (0) From Week 80 Through Week 176 by Visit; Full Analysis Set With Subjects Participating in the Long-term Extension (Study CNTO1275PSO3013)**



Note: 95% confidence intervals were based on the exact method.
*An additional subject was dosed and assessed for PGA at Week 176; however, the PGA assessment (score of 2) was mapped incorrectly to the Week 164 unscheduled visit and is therefore missing from the Week 176 timepoint in this figure.

CHMP's comments

During the LTE, the PGA response rates of cleared (0) or minimal (1) were 80% at week 80, 70% at week 104, 80 % at week 128, 61.5% at week 152 and 100% at week 176. PGA response rates of cleared (0) were 64% at week 80, 50% at week 104, 60% at week 128, 54% at week 152 and 50% at week 179) Over all visits within this period, the proportion of subjects with a PGA score of mild or better (≤2) was ≥95%.

As such, the MAHs position that PGA response rates of cleared (0) (Figure 3) were maintained from Week 80 through Week 176 is accepted (in the main study the proportion (95% confidence interval [CI]) of subjects who achieved a PGA 0/1 score at week 12 was 77.3% (62.2%; 88.5%)). However, the small patient numbers in this LTE (with 13 and 3 subjects evaluated at Week 152 and Week 176, respectively) provide a very limited sample size. CDLQI and PSAI, which formed key secondary

endpoints in the main study, were not measured as part of the LTE.

Safety results

Safety was evaluated based on:

- Adverse events
- Clinical laboratory tests (hematology, serum chemistry)
- Vital sign measurements
- Physical examinations
- Concomitant medication review
- Injection-site reactions
- Allergic reactions
- TB evaluations

Summaries of AEs and other safety data are presented from Week 56 onwards based on the 28 subjects enrolled in the LTE who received at least an injection of ustekinumab at Week 56 (partial or complete), ie, the safety analysis set.

From Week 56 through the end of the reporting period, 19 (67.9%) subjects reported 1 or more AEs as shown in Table 2. There were no severe AE reported from week 56 to end of reporting period.

Table 2: Number of Subjects With Treatment-emergent Adverse Events With Frequency of at Least 5% From Week 56 Through the End of the Reporting Period by System Organ Class and Preferred Term; Safety Analysis Set With Subjects Participating in the Long-Term Extension (Study CNTO1275PSO3013)

	Ustekinumab Standard Dosage
Analysis set: Safety analysis set with subjects participating in the long-term extension	28
Avg duration of follow-up (weeks)	83.05
Avg exposure (number of administrations)	6.68
Subjects with 1 or more AEs	19 (67.9%)
System organ class Preferred term	
Infections and infestations	15 (53.6%)
Nasopharyngitis	8 (28.6%)
Gastroenteritis	3 (10.7%)
Otitis media	2 (7.1%)
Respiratory tract infection	2 (7.1%)
Upper respiratory tract infection	2 (7.1%)
Viral upper respiratory tract infection	2 (7.1%)
Respiratory, thoracic and mediastinal disorders	6 (21.4%)
Cough	3 (10.7%)
Oropharyngeal pain	3 (10.7%)
Musculoskeletal and connective tissue disorders	4 (14.3%)
Arthralgia	3 (10.7%)
General disorders and administration site conditions	3 (10.7%)
Injection site erythema	2 (7.1%)
Gastrointestinal disorders	2 (7.1%)
Vomiting	2 (7.1%)

Key: AE = adverse event, Avg = average
Note: Subjects are counted only once for any given event, regardless of the number of times that they actually experienced the event. Adverse events are coded using MedDRA Version 22.0.

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Related Adverse Events

From Week 56 through the end of the reporting period, 8 (28.6%) subjects reported 1 or more

related AEs:

TSFAE07B: Number of Subjects With Related Treatment-emergent Adverse Events From Week 56 Through the End of the Reporting Period by System Organ Class and Preferred Term; Safety Analysis Set With Subjects Participating in the Long-Term Extension (Study CNTO1275PSO3013)

	Ustekinumab Standard Dosage
Analysis set: Safety analysis set with subjects participating in the long-term extension	28
Avg duration of follow-up (weeks)	83.05
Avg exposure (number of administrations)	6.68
Subjects with 1 or more related AEs	8 (28.6%)
System organ class Preferred term	
Infections and infestations	6 (21.4%)
Nasopharyngitis	4 (14.3%)
Respiratory tract infection	1 (3.6%)
Sinusitis	1 (3.6%)
Viral upper respiratory tract infection	1 (3.6%)
Respiratory, thoracic and mediastinal disorders	3 (10.7%)
Oropharyngeal pain	2 (7.1%)
Cough	1 (3.6%)
Nasal congestion	1 (3.6%)
General disorders and administration site conditions	2 (7.1%)
Injection site erythema	2 (7.1%)
Injection site pain	1 (3.6%)
Injection site reaction	1 (3.6%)
Skin and subcutaneous tissue disorders	1 (3.6%)
Skin hyperpigmentation	1 (3.6%)

Key: AE = adverse event, Avg = average
Note: Subjects are counted only once for any given event, regardless of the number of times that they actually experienced the event. Adverse events are coded using MedDRA Version 22.0.

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Deaths/Serious Adverse Events

There we not deaths and one SAE during the reporitng period. The subject was hospitalized for the evaluation of left ankle pain and the SAE arthralgia was reported. The SAE was of mild intensity and was assessed by the investigator as unrelated to the study agent

Discontinuations due to Adverse Events

From Week 56 through Week 176 (ie, the longest treatment duration in this study), no subjects discontinued study agent due to an AE.

Injection site reactions

There (out of 187; 1.6%) injections were associated with injection-site reactions in 2 (7.1%).

Infections Requiring antimicorbial treatment

TSFINFE03B: Number of Subjects With Treatment-emergent Infections Requiring Oral or Parenteral Antimicrobial Treatment From Week 56 Through the End of the Reporting Period by System Organ Class and Preferred Term; Safety Analysis Set With Subjects Participating in the Long-Term Extension (Study CNTO1275PSO3013)

	Ustekinumab Standard Dosage
Analysis set: Safety analysis set with subjects participating in the long-term extension	28
Avg duration of follow-up (weeks)	83.05
Avg exposure (number of administrations)	6.68
Subjects with 1 or more infections requiring treatment	6 (21.4%)
System organ class Preferred term	
Infections and infestations	6 (21.4%)
Otitis media	2 (7.1%)
Upper respiratory tract infection	2 (7.1%)
Bronchitis	1 (3.6%)
Pharyngitis	1 (3.6%)
Pharyngitis streptococcal	1 (3.6%)
Sinusitis	1 (3.6%)

Key: Avg = average
Note: Subjects are counted only once for any given event, regardless of the number of times that they actually experienced the event. Adverse events are coded using MedDRA Version 22.0.

Adverse events of clinical interest

From Week 56 through the end of the reporting period, there were no reports of TB or opportunistic infection. Neither were there any reports of malignancies or reports of cardiovascular events, thought there was one report of skin papilloma:

TSFAE01B: Number of Subjects With Treatment-emergent Adverse Events From Week 56 Through the End of the Reporting Period by System Organ Class and Preferred Term; Safety Analysis Set With Subjects Participating in the Long-Term Extension (Study CNTO1275PSO3013)

	Ustekinumab Standard Dosage
Analysis set: Safety analysis set with subjects participating in the long-term extension	28
Avg duration of follow-up (weeks)	83.05
Avg exposure (number of administrations)	6.68
Subjects with 1 or more AEs	19 (67.9%)
System organ class Preferred term	
Infections and infestations	15 (53.6%)
Nasopharyngitis	8 (28.6%)
Gastroenteritis	3 (10.7%)
Otitis media	2 (7.1%)
Respiratory tract infection	2 (7.1%)
Upper respiratory tract infection	2 (7.1%)
Viral upper respiratory tract infection	2 (7.1%)
Bronchitis	1 (3.6%)
Conjunctivitis	1 (3.6%)
Impetigo	1 (3.6%)
Pharyngitis	1 (3.6%)
Pharyngitis streptococcal	1 (3.6%)
Sinusitis	1 (3.6%)
Viral infection	1 (3.6%)
Respiratory, thoracic and mediastinal disorders	6 (21.4%)
Cough	3 (10.7%)
Oropharyngeal pain	3 (10.7%)
Nasal congestion	1 (3.6%)
Musculoskeletal and connective tissue disorders	4 (14.3%)
Arthralgia	3 (10.7%)
Growing pains	1 (3.6%)
Osteochondrosis	1 (3.6%)
Pain in extremity	1 (3.6%)
General disorders and administration site conditions	3 (10.7%)
Injection site erythema	2 (7.1%)
Injection site pain	1 (3.6%)
Injection site reaction	1 (3.6%)
Non-cardiac chest pain	1 (3.6%)
Pyrexia	1 (3.6%)
Gastrointestinal disorders	2 (7.1%)
Vomiting	2 (7.1%)
Abdominal pain upper	1 (3.6%)
Diarrhoea	1 (3.6%)
Nausea	1 (3.6%)
Injury, poisoning and procedural complications	2 (7.1%)
Arthropod bite	1 (3.6%)
Skin laceration	1 (3.6%)

TSFAE01B: Number of Subjects With Treatment-emergent Adverse Events From Week 56 Through the End of the Reporting Period by System Organ Class and Preferred Term; Safety Analysis Set With Subjects Participating in the Long-Term Extension (Study CNTO1275PSO3013)	
	Ustekinumab Standard Dosage
Nervous system disorders	2 (7.1%)
Amnestic disorder	1 (3.6%)
Disturbance in attention	1 (3.6%)
Headache	1 (3.6%)
Skin and subcutaneous tissue disorders	2 (7.1%)
Acne	1 (3.6%)
Skin hyperpigmentation	1 (3.6%)
Eye disorders	1 (3.6%)
Dry eye	1 (3.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.6%)
Skin papilloma	1 (3.6%)

Key: AE = adverse event, Avg = average
Note: Subjects are counted only once for any given event, regardless of the number of times that they actually experienced the event. Adverse events are coded using MedDRA Version 22.0.

Changes in Haematology

From Week 56 through the end of the reporting period, 2 (7.7%) subjects presented with abnormally low lymphocyte levels (defined as <1.5 x 109/L and at least 33% decrease from the baseline value). For 1 subject, the abnormally low lymphocyte level was observed approximately 13 weeks after the last ustekinumab administration (which occurred at Week 152). For the other subject, the abnormally low lymphocyte level was observed from the Week 104 assessment. This was a transient abnormality and subsequently resolved without interruption of ustekinumab treatment.

Changes in Clinical Chemistry

From Week 56 through the end of the reporting period, no subjects presented with markedly abnormal clinical chemistry values.

Vital Signs and Physical Findings

From Week 104 through Week 152, weight, height, and BMI increased slightly, consistent with the age of the subjects and expected growth over this period.

CHMP's comments

The safety profile observed in the LTE appears consistent with that observed in the main study and generally similar to that identified across the clinical development program, though the limitations of the very small patient numbers in the LTE must be born in mind.

Given that both IL-12 and IL-23 mediate inflammation and modulate cellular immune responses, immune suppression affecting host defences against infections and malignancies are potential risks. Section 4.4 of the SmPC outlines that ustekinumab may have the potential to increase the risk of infections and reactivate latent infections as well as to increase the risk of malignancy.

Nasopharyngitis was the most frequently reported AE in this LTE (8 [28.6%] subjects), followed by gastroenteritis, cough, oropharyngeal pain, and arthralgia (3 [10.7%] subjects each.

The pattern of AEs is agreed to be similar to that in the main study where 19 (43.2%) subjects reported 1 or more related AEs and the SOC with the highest incidence of related AEs was Infections

and infestations (12 [27.3%] subjects), followed by General disorders and administration site conditions (6 [13.6%] subjects). In the main study nasopharyngitis and injection site erythema were the most frequently reported related AEs through Week 56 (6 [13.6%] subjects each), followed by pharyngitis (3 [6.8%] subjects) and tonsillitis (2 [4.5%] subjects).

There were no serious infections in the LTE period, though 6 patients did require antimicrobial treatment. There are extensive warnings in section 4.4 concerning the risk of infections, including warnings that patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur and that if a patient develops a serious infection, the patient should be closely monitored and STELARA should not be administered until the infection resolves.

The MAH is requested to provide further details in relation to the AE of skin papilloma.

The company should confirm whether patients generally remained within expected range of their baseline centiles for weight, height and BMI.

Additional safety data for the population will be garnered from the ongoing post-marketing study to confirm the long-term safety profile and monitor any potential effect on growth and development in paediatric patients aged which was extended so as to include children aged 6 to less than 12 years of age, in addition to those aged 12 to <18 years of age under EMEA/H/C/000958/II/0073.

In response to RSI the MAH provided additional details in relation to the AE of skin papilloma and relating to whether patients generally remained within expected range of their baseline centiles for weight, height and BMI.

It is noted that the event of skin papilloma of left foot occurred while the female patient was apparently 9 years of age. The patient is described as having a history of warts and previous treatment for psoriasis is listed as being limited to topical treatments. The patient experienced non-serious, mild AR of "viral wart of left foot" which was treated with monochloroacetic acid and which resolved after 2 months. The assessment as not related to study treatment is considered reasonable.

The MAH provided shift tables from baseline to Weeks 52, 104, and 152 for the weight, height, and BMI centiles for subjects in Study CNTO1275PSO3013. On review of the data presented, it can be agreed that no patterns are observed in centile shifts from baseline in weight, height, or BMI at each time point and that the shifts observed are in general consistent with the variations in growth rates expected in a paediatric population of 6 to 12 year olds.

2.3.3. Discussion on clinical aspects

The current Article 46 submission summarizes the efficacy and safety data from the long-term extension (LTE) period of the completed CNTO1275PSO3013 or CADMUS Junior (hereafter referred to as PSO3013). PSO3013 was an open-label, multicenter study to evaluate the efficacy, safety, PK, and immunogenicity of ustekinumab in children aged from ≥6 to <12 years with moderate to severe chronic plaque psoriasis which allowed pediatric subjects who have demonstrated clinical benefit through week 52 of the main study to continue receiving ustekinumab. The open-label, single arm design was in accordance with the EMA paediatric investigation plan.

The results of the main study (through Week 56) have been submitted previously (EMEA/H/C/000958/II/0073), and formed the basis of the extension of indication to children aged 6 to 12 years with moderate to severe psoriasis.

A total of 28 patients were included in the LTE and 100% of these discontinued study agent before Week 264. The majority of these (24) discontinued due to protocol specified criteria 9.1.5:

- The subject turns 12 years of age and resides in a country where marketing authorization has been granted for ustekinumab treatment of psoriasis in adolescent patients
- Marketing authorization is obtained for ustekinumab for treatment of plaque psoriasis for patients ≥6 to <12 years of age in the subject's country of residence
- Marketing authorization is denied for ustekinumab for the treatment of plaque psoriasis for patients ≥6 to <12 years of age in the subject's country of residence
- A company decision is made to no longer pursue an indication in plaque psoriasis in the paediatric population (≥6 to <12 years of age) in the subject's country of residence

The longest treatment duration was 176 weeks. Based on the above discontinuation criteria it is not unexpected that patients who entered the LTE discontinued from the study before week 264, however the small numbers of patients evaluated during the LTE, with only 13 and 3 subjects evaluated at Week 152 and Week 176, respectively limits the usefulness of the observations.

Demographic and disease characteristics of subjects in PSO3013 were previously described and assessed under EMEA/H/C/000958/II/0073, essentially the rapporteur considers the population studied to be representative of the target treatment population in the EEA.

During the LTE, the PGA response rates of cleared (0) or minimal (1) were 80% at week 80, 70% at week 104, 80 % at week 128, 61.5% at week 152 and 100% at week 176. PGA response rates of cleared (0) were 64% at week 80, 50% at week 104, 60% at week 128, 54% at week 152 and 50% at week 179) Over all visits within this period, the proportion of subjects with a PGA score of mild or better (≤2) was ≥95%.

As such, the MAHs position that PGA response rates of cleared (0) (Figure 3) were maintained from Week 80 through Week 176 is accepted (in the main study the proportion (95% confidence interval [CI]) of subjects who achieved a PGA 0/1 score at week 12 was 77.3% (62.2%; 88.5%)). However, the small patient numbers in this LTE (with 13 and 3 subjects evaluated at Week 152 and Week 176, respectively) provide a very limited sample size. CDLQI and PSAI, which formed key secondary endpoints in the main study, were not measured as part of the LTE.

The safety profile observed in the LTE appears consistent with that observed in the main study and generally similar to that identified across the clinical development program, though the limitations of the very small patient numbers in the LTE must be born in mind.

Given that both IL-12 and IL-23 mediate inflammation and modulate cellular immune responses, immune suppression affecting host defences against infections and malignancies are potential risks. Section 4.4 of the SmPC outlines that ustekinumab may have the potential to increase the risk of infections and reactivate latent infections as well as to increase the risk of malignancy

Nasopharyngitis was the most frequently reported AE in this LTE (8 [28.6%] subjects), followed by gastroenteritis, cough, oropharyngeal pain, and arthralgia (3 [10.7%] subjects each.

The pattern of AEs is agreed to be similar to that in the main study where 19 (43.2%) subjects reported 1 or more related AEs and the SOC with the highest incidence of related AEs was Infections and infestations (12 [27.3%] subjects), followed by General disorders and administration site conditions (6 [13.6%] subjects). In the main study nasopharyngitis and injection site erythema were the most frequently reported related AEs through Week 56 (6 [13.6%] subjects each), followed by pharyngitis (3 [6.8%] subjects) and tonsillitis (2 [4.5%] subjects).

There were no serious infections in the LTE period, though 6 patients did require antimicrobial treatment. There are extensive warnings in section 4.4 concerning the risk of infections, including warnings that patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur and that if a patient develops a serious infection, the patient should be closely monitored and STELARA should not be administered until the infection resolves.

The MAH is requested to provide further details in relation to the AE of skin papilloma. OC

The company should confirm whether patients generally remained within expected range of their baseline centiles for weight, height and BMI. OC

Additional safety data for the population will be garnered from the ongoing post-marketing study to confirm the long-term safety profile and to monitor any potential effect on growth and development in paediatric patients which was extended so as to include children aged 6 to less than 12 years of age, in addition to those aged 12 to <18 years of age under EMEA/H/C/000958/II/0073.

3. Rapporteur's current conclusion and recommendation

As per section 4, the Rapporteur has raised a number of clarification requests in relation to the data presented.

☒ **Fulfilled:**

☐ **Not fulfilled:**

Based on the data submitted, the MAH should provide clarification to points raised in section 4 as part of this procedure, see section "Additional clarification requested".

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH is requested to confirm that the LTE was part of the agreed EMA paediatric investigation plan, which received a positive opinion from EMA Paediatric Committee on compliance with a PIP, as presented under EMEA/H/C/000958/II/0073.
2. The MAH is requested to provide further details in relation to the AE of skin papilloma.
3. The company should confirm whether patients generally remained within expected range of their baseline centiles for weight, height and BMI.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

1. The MAH is requested to confirm that the LTE was part of the agreed EMA paediatric investigation plan, which received a positive opinion from EMA Paediatric Committee on compliance with a PIP, as presented under EMEA/H/C/000958/II/0073.

Applicant Response

The MAH confirms that Study CNTO1275PSO3013 was part of the agreed EMA paediatric investigation plan (PIP; EMEA-C-000311-PIP01-08-M04), which received a positive opinion from the EMA Paediatric Committee (PDCO) in compliance with a PIP, as presented under EMEA/H/C/000958/II/0073. While the LTE of CNTO1275PSO3013 was part of the overall study design, it was not part of the key binding elements of the PIP.

CHMP Comment

The applicant has clarified that the LTE of CNTO1275PSO3013 was part of the overall study design but was not part of the key binding elements of the PIP. This clarification is noted in the AR.

Query is considered to be resolved.

2. The MAH is requested to provide further details in relation to the AE of skin papilloma.

Applicant Response

Available details regarding the adverse event (AE) of skin papilloma reported in Subject 000050 are provided in Attachment 1.

Subject 000050 was a 6 year-old female subject who enrolled in the Study CNTO1275PSO3013 and received her first dose of open-label ustekinumab on 10 Aug 2017. The subject's medical history included a history of warts. In April 2019 (day not specified), the subjected experienced a non-serious AE of skin papilloma (verbatim term: viral wart of left foot) that was mild in intensity and considered not related to study treatment by the investigator. The event was treated with Vericaust (monochloroacetic acid) and the event resolved in June 2019 (day not specified). No change to the subject's ustekinumab dose was made, and the subject continued in the study.

CHMP Comment

The MAH was requested to provide additional details in relation to the AE of skin papilloma. It is noted that the event of skin papilloma of left foot occurred while the female patient was apparently 9 years of age. The patient is described as having a history of warts and previous treatment for psoriasis is listed as being limited to topical treatments. The patient experienced nonserious, mild AR of "viral wart of left foot" which was treated with monochloroacetic acid and which resolved after 2 months. The assessment as not related to study treatment is considered reasonable.

Response acceptable.

3. The company should confirm whether patients generally remained within expected range of their baseline centiles for weight, height and BMI.

Applicant Response

Child growth dynamic standards were analyzed using the World Health Organization (WHO) Reference 2007 (5-19 years) SAS macro package. This package covers height-for-age (5-19 years), weight-for-age (5-10 years), and body mass index (BMI)-for-age (5-19 years) in children and adolescents. In children over 10 years of age, weight-for-age is not considered by

the WHO to be a good growth indicator as these children are experiencing pubertal growth and may appear to have excess weight, which cannot be distinguished from height in tall children. The WHO recommends using the BMI-for-age indicator for evaluation of appropriate weight in children 10-19 years of age (WHO 2009). Thus, weight-for-age analyses were only performed for subjects up to 10 years of age.

The subject population in Study CNTO1275PSO3013 included 44 subjects in the main study; these subjects had height and weight measurements collected at baseline (Week 0). Of the 44 subjects in the main study, 40 subjects had height and weight measurements collected at Week 52, and 28 of these subjects entered into the LTE. Subjects in the LTE discontinued from the study when they met the protocol-specified discontinuation criteria at any time between Week 52 and Week 264; therefore, the population of subjects in the LTE decreased over time and the number of subjects with height and weight measurements at Week 104 and Week 152 are fewer than the numbers at Week 0 and Week 52.

Shift tables from baseline to Weeks 52, 104, and 152 for the weight (Attachment 2, Attachment 3, and Attachment 4, respectively), height (Attachment 5, Attachment 6, and Attachment 7,respectively), and BMI (Attachment 8, Attachment 9, and Attachment 10, respectively) centiles for subjects in Study CNTO1275PSO3013 were calculated by every 10% centile interval in the Safety Analysis Set.

In general, subjects in Study CNTO1275PSO3013 remained within their baseline centiles for weight, height, and BMI at Weeks 52, 104, and 152. No patterns were observed in centile shifts from baseline in weight, height, or BMI at each time point and the shifts observed were consistent with the variations in growth rates expected in a paediatric population of 6 to 12 year olds.

Attachment 2: Shift Table of Weight (kg) at Week 52 by 10 Percentile Interval; Safety Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab									
	Baseline Status									
	≤10	>10 to ≤20	>20 to ≤30	>30 to ≤40	>40 to ≤50	>50 to ≤60	>60 to ≤70	>70 to ≤80	>80 to ≤90	>90
Baseline	-	-	4	1	2	3	2	1	1	13
Week 52										
N[a]	-	-	2	1	1	-	2	-	1	7
≤10 percentile	-	-	0	0	0	-	0	-	0	0
>10 percentile to ≤20 percentile	-	-	1 (50.0%)	0	0	-	0	-	0	0
>20 percentile to ≤30 percentile	-	-	0	0	0	-	0	-	0	0
>30 percentile to ≤40 percentile	-	-	1 (50.0%)	1 (100.0%)	0	-	0	-	0	0
>40 percentile to ≤50 percentile	-	-	0	0	1 (100.0%)	-	0	-	0	0
>50 percentile to ≤60 percentile	-	-	0	0	0	-	0	-	0	0
>60 percentile to ≤70 percentile	-	-	0	0	0	-	0	-	0	0
>70 percentile to ≤80 percentile	-	-	0	0	0	-	2 (100.0%)	-	0	1 (14.3%)
>80 percentile to ≤90 percentile	-	-	0	0	0	-	0	-	1 (100.0%)	0
>90 percentile	-	-	0	0	0	-	0	-	0	6 (85.7%)

Note: Percentiles are based on WHO 2007 SAS macro package.
[a] The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement.
[TSVS01.RTF] [CNTO1275\PSO3013\DBR_LTE\RE_CHMP\PROD\TSVS01.SAS] 21JUN2021, 16:16

Attachment 3: Shift Table of Weight (kg) at Week 104 by 10 Percentile Interval; Safety Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab									
	Baseline Status									
	≤10	>10 to ≤20	>20 to ≤30	>30 to ≤40	>40 to ≤50	>50 to ≤60	>60 to ≤70	>70 to ≤80	>80 to ≤90	>90
Baseline	-	-	4	1	2	3	2	1	1	13
Week 104										
N[a]	-	-	1	1	1	-	1	-	1	7
≤10 percentile	-	-	0	0	0	-	0	-	0	0
>10 percentile to ≤20 percentile	-	-	1 (100.0%)	0	0	-	0	-	0	0
>20 percentile to ≤30 percentile	-	-	0	0	0	-	0	-	0	0
>30 percentile to ≤40 percentile	-	-	0	1 (100.0%)	0	-	0	-	0	0
>40 percentile to ≤50 percentile	-	-	0	0	1 (100.0%)	-	0	-	0	0
>50 percentile to ≤60 percentile	-	-	0	0	0	-	0	-	0	0
>60 percentile to ≤70 percentile	-	-	0	0	0	-	0	-	0	0
>70 percentile to ≤80 percentile	-	-	0	0	0	-	1 (100.0%)	-	0	0
>80 percentile to ≤90 percentile	-	-	0	0	0	-	0	-	1 (100.0%)	2 (28.6%)
>90 percentile	-	-	0	0	0	-	0	-	0	5 (71.4%)

Note: Percentiles are based on WHO 2007 SAS macro package.
[a] The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement.

Attachment 4: Shift Table of Weight (kg) at Week 152 by 10 Percentile Interval; Safety Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab									
	Baseline Status									
	≤10	>10 to ≤20	>20 to ≤30	>30 to ≤40	>40 to ≤50	>50 to ≤60	>60 to ≤70	>70 to ≤80	>80 to ≤90	>90
Baseline	-	-	4	1	2	3	2	1	1	13
Week 152										
N[a]	-	-	1	-	1	-	1	-	-	2
≤10 percentile	-	-	0	-	0	-	0	-	-	0
>10 percentile to ≤20 percentile	-	-	1 (100.0%)	-	0	-	0	-	-	0
>20 percentile to ≤30 percentile	-	-	0	-	0	-	0	-	-	0
>30 percentile to ≤40 percentile	-	-	0	-	0	-	0	-	-	0
>40 percentile to ≤50 percentile	-	-	0	-	1 (100.0%)	-	0	-	-	0
>50 percentile to ≤60 percentile	-	-	0	-	0	-	0	-	-	0
>60 percentile to ≤70 percentile	-	-	0	-	0	-	0	-	-	0
>70 percentile to ≤80 percentile	-	-	0	-	0	-	1 (100.0%)	-	-	0
>80 percentile to ≤90 percentile	-	-	0	-	0	-	0	-	-	0
>90 percentile	-	-	0	-	0	-	0	-	-	2 (100.0%)

Note: Percentiles are based on WHO 2007 SAS macro package.
[a] The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement.

Attachment 5: Shift Table of Height (cm) at Week 52 by 10 Percentile Interval; Safety Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab									
	Baseline Status									
	≤10	>10 to ≤20	>20 to ≤30	>30 to ≤40	>40 to ≤50	>50 to ≤60	>60 to ≤70	>70 to ≤80	>80 to ≤90	>90
Baseline	4	2	-	3	4	1	9	4	7	10
Week 52										
N[a]	4	2	-	3	4	-	8	4	5	10
≤10 percentile	0	0	-	0	0	-	0	0	0	0
>10 percentile to ≤20 percentile	1 (25.0%)	1 (50.0%)	-	0	0	-	0	0	0	0
>20 percentile to ≤30 percentile	0	0	-	0	0	-	0	0	0	0
>30 percentile to ≤40 percentile	2 (50.0%)	0	-	0	0	-	0	0	0	0
>40 percentile to ≤50 percentile	0	0	-	1 (33.3%)	2 (50.0%)	-	0	1 (25.0%)	0	0
>50 percentile to ≤60 percentile	0	1 (50.0%)	-	1 (33.3%)	1 (25.0%)	-	1 (12.5%)	0	0	0
>60 percentile to ≤70 percentile	0	0	-	0	0	-	1 (12.5%)	1 (25.0%)	0	0
>70 percentile to ≤80 percentile	0	0	-	1 (33.3%)	1 (25.0%)	-	1 (12.5%)	0	3 (60.0%)	1 (10.0%)
>80 percentile to ≤90 percentile	0	0	-	0	0	-	3 (37.5%)	2 (50.0%)	1 (20.0%)	1 (10.0%)
>90 percentile	1 (25.0%)	0	-	0	0	-	2 (25.0%)	0	1 (20.0%)	8 (80.0%)

Note: Percentiles are based on WHO 2007 SAS macro package.
[a] The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement.

Attachment 6: Shift Table of Height (cm) at Week 104 by 10 Percentile Interval; Safety Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab									
	Baseline Status									
	≤10	>10 to ≤20	>20 to ≤30	>30 to ≤40	>40 to ≤50	>50 to ≤60	>60 to ≤70	>70 to ≤80	>80 to ≤90	>90
Baseline	4	2	-	3	4	1	9	4	7	10
Week 104										
N[a]	2	1	-	2	2	-	5	2	1	4
≤10 percentile	0	0	-	0	0	-	0	0	0	0
>10 percentile to ≤20 percentile	1 (50.0%)	0	-	0	0	-	0	0	0	0
>20 percentile to ≤30 percentile	1 (50.0%)	0	-	0	0	-	0	0	0	0
>30 percentile to ≤40 percentile	0	0	-	0	0	-	0	0	0	0
>40 percentile to ≤50 percentile	0	0	-	0	1 (50.0%)	-	1 (20.0%)	0	0	0
>50 percentile to ≤60 percentile	0	0	-	0	0	-	0	0	0	0
>60 percentile to ≤70 percentile	0	0	-	0	1 (50.0%)	-	1 (20.0%)	1 (50.0%)	0	0
>70 percentile to ≤80 percentile	0	1 (100.0%)	-	2 (100.0%)	0	-	1 (20.0%)	1 (50.0%)	1 (100.0%)	0
>80 percentile to ≤90 percentile	0	0	-	0	0	-	2 (40.0%)	0	0	0
>90 percentile	0	0	-	0	0	-	0	0	0	4 (100.0%)

Note: Percentiles are based on WHO 2007 SAS macro package.
[a] The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement.

Attachment 7: Shift Table of Height (cm) at Week 152 by 10 Percentile Interval; Safety Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab									
	Baseline Status									
	≤10	>10 to ≤20	>20 to ≤30	>30 to ≤40	>40 to ≤50	>50 to ≤60	>60 to ≤70	>70 to ≤80	>80 to ≤90	>90
Baseline	4	2	-	3	4	1	9	4	7	10
Week 152										
N[a]	2	-	-	1	1	-	1	2	1	5
≤10 percentile	1 (50.0%)	-	-	0	0	-	0	0	0	0
>10 percentile to ≤20 percentile	1 (50.0%)	-	-	0	0	-	0	0	0	0
>20 percentile to ≤30 percentile	0	-	-	0	0	-	0	0	0	0
>30 percentile to ≤40 percentile	0	-	-	0	1 (100.0%)	-	0	0	0	0
>40 percentile to ≤50 percentile	0	-	-	0	0	-	0	0	0	0
>50 percentile to ≤60 percentile	0	-	-	0	0	-	1 (100.0%)	0	0	0
>60 percentile to ≤70 percentile	0	-	-	0	0	-	0	0	1 (100.0%)	0
>70 percentile to ≤80 percentile	0	-	-	1 (100.0%)	0	-	0	1 (50.0%)	0	1 (20.0%)
>80 percentile to ≤90 percentile	0	-	-	0	0	-	0	1 (50.0%)	0	0
>90 percentile	0	-	-	0	0	-	0	0	0	4 (80.0%)

Note: Percentiles are based on WHO 2007 SAS macro package.
[a] The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement.

Attachment 8: Shift Table of BMI (kg/m2) at Week 52 by 10 Percentile Interval; Safety Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab									
	Baseline Status									
	≤10	>10 to ≤20	>20 to ≤30	>30 to ≤40	>40 to ≤50	>50 to ≤60	>60 to ≤70	>70 to ≤80	>80 to ≤90	>90
Baseline	2	2	1	2	3	2	3	3	7	19
Week 52										
N[a]	2	2	1	1	3	2	3	3	7	16
≤10 percentile	2 (100.0%)	0	0	0	0	0	0	0	0	0
>10 percentile to ≤20 percentile	0	1 (50.0%)	0	1 (100.0%)	0	0	0	0	0	0
>20 percentile to ≤30 percentile	0	0	0	0	0	1 (50.0%)	1 (33.3%)	0	1 (14.3%)	0
>30 percentile to ≤40 percentile	0	1 (50.0%)	1 (100.0%)	0	0	0	0	0	0	0
>40 percentile to ≤50 percentile	0	0	0	0	0	0	0	1 (33.3%)	0	0
>50 percentile to ≤60 percentile	0	0	0	0	1 (33.3%)	0	0	0	1 (14.3%)	0
>60 percentile to ≤70 percentile	0	0	0	0	1 (33.3%)	0	1 (33.3%)	0	0	0
>70 percentile to ≤80 percentile	0	0	0	0	1 (33.3%)	1 (50.0%)	1 (33.3%)	0	2 (28.6%)	1 (6.3%)
>80 percentile to ≤90 percentile	0	0	0	0	0	0	0	2 (66.7%)	0	1 (6.3%)
>90 percentile	0	0	0	0	0	0	0	0	3 (42.9%)	14 (87.5%)

Note: Percentiles are based on WHO 2007 SAS macro package.
[a] The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement.

Attachment 9: Shift Table of BMI (kg/m2) at Week 104 by 10 Percentile Interval; Safety Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab									
	Baseline Status									
	≤10	>10 to ≤20	>20 to ≤30	>30 to ≤40	>40 to ≤50	>50 to ≤60	>60 to ≤70	>70 to ≤80	>80 to ≤90	>90
Baseline	2	2	1	2	3	2	3	3	7	19
Week 104										
N[a]	1	1	1	1	1	-	2	-	5	7
≤10 percentile	0	0	0	0	0	-	0	-	0	0
>10 percentile to ≤20 percentile	1 (100.0%)	1 (100.0%)	0	1 (100.0%)	0	-	0	-	0	0
>20 percentile to ≤30 percentile	0	0	0	0	0	-	0	-	0	0
>30 percentile to ≤40 percentile	0	0	1 (100.0%)	0	0	-	0	-	1 (20.0%)	0
>40 percentile to ≤50 percentile	0	0	0	0	0	-	0	-	0	0
>50 percentile to ≤60 percentile	0	0	0	0	0	-	0	-	0	0
>60 percentile to ≤70 percentile	0	0	0	0	0	-	0	-	1 (20.0%)	0
>70 percentile to ≤80 percentile	0	0	0	0	0	-	2 (100.0%)	-	1 (20.0%)	1 (14.3%)
>80 percentile to ≤90 percentile	0	0	0	0	0	-	0	-	1 (20.0%)	2 (28.6%)
>90 percentile	0	0	0	0	1 (100.0%)	-	0	-	1 (20.0%)	4 (57.1%)

Note: Percentiles are based on WHO 2007 SAS macro package.
[a] The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement.

CHMP Comment

The MAH was requested to confirm whether patients generally remained within expected range of their baseline centiles for weight, height and BMI. As part of the response, the applicant provided shift tables from baseline to Weeks 52, 104, and 152 for the weight, height, and BMI centiles for subjects in Study CNTO1275PSO3013. While the low numbers of patients in the LTE limit the ability to draw conclusions of effects on growth, on review of the data presented, it can be agreed that no patterns are observed in centile shifts from baseline in weight, height, or BMI at each time point and that the shifts observed are in general consistent with the variations in growth rates expected in a paediatric population of 6 to 12 year olds.

Query resolved.