14 January 2020
EMA/12150/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stelara

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/000958/II/0073

Note

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

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List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	averse event
BMI	body mass index
BQL	below the lowest quantifiable sample concentration of the assay (<lower limit of quantification x minimum required dilution)
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Report
DKMA	Danish Medicines Agency
ECLIA	electrochemiluminescent immunoassay
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HPRA	Health Products Regulatory Authority
ICH	International Council on Harmonisation
IL	interleukin
IQ	interquartile
LIV	liquid in vial
LTE	long-term extension
MACE	major adverse cardiovascular events
MHRA	Medicines and Healthcare Products Regulatory Agency
MSD	Meso Scale Discovery
PASI	Psoriasis Area and Severity Index
PFS	pre-filled syringe
PGA	Physician's Global Assessment
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PDCO	Paediatric Committee
PHOENIX	A Phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of CNTO1275 in the treatment of subjects with moderate to severe plaque-type psoriasis followed by long-term extension
PSOLAR	Psoriasis Longitudinal Assessment and Registry
PSUR	Periodic Safety Update Report
q12w	every 12 weeks
RMP	Risk Management Plan
SAE	serious adverse event
SC	Subcutaneous(ly)
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	standard deviation
SmPC	Summary of Product Characteristics
TNFα	tumor necrosis factor alpha
URTI	upper respiratory tract infection
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 25 June 2019 an application for a variation.

The following variation was requested:

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

Extension of Indication to include a new population for Stelara solution for injection in children aged 6 to 12 years with moderate to severe psoriasis based on the results of study CNTO1275PSO3013. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated accordingly. The Package Leaflet is updated in accordance. Section 4.8 for Stelara concentrate for solution for infusion is also updated in accordance.
Minor editorial changes are made to Section 4.5 for both formulations.
In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The RMP version 15.0 has also been submitted. The MAH took the opportunity to add "follow-up of pregnancy registry" in Part III.1 of the RMP in line with the existing information in Part V.3 of the RMP.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0003/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0003/2016 was completed.

The PDCO issued an opinion on compliance for the PIP P/0003/2016.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jayne Crowe Co-Rapporteur: Mark Ainsworth

Timetable	Actual dates
Submission date	25 June 2019
Start of procedure:	20 July 2019
CHMP Rapporteur Assessment Report	13 September 2019
CHMP Co-Rapporteur Assessment Report	13 September 2019
PRAC Rapporteur Assessment Report	20 September 2019
PRAC members comments	25 September 2019
Updated PRAC Rapporteur Assessment Report	26 September 2019
PRAC Outcome	3 October 2019
CHMP members comments	7 October 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2019
Request for supplementary information (RSI)	17 October 2019
PRAC Rapporteur Assessment Report	18 November 2019
PRAC members comments	n/a
CHMP Rapporteur Assessment Report	26 November 2019
PRAC Outcome	28 November 2019
CHMP members comments	02 December 2019
Updated CHMP Rapporteur Assessment Report	05 December 2019
Opinion	12 December 2019

An opinion was adopted by the CHMP on 12 December 2019.

A revised opinion was adopted by the CHMP on 14 January 2020 in order to correct the information on paediatric requirements.

2. Scientific discussion

2.1. Introduction

Ustekinumab (CNTO1275) is a fully human immunoglobulin G1 kappa monoclonal antibody to human interleukin (IL)-12/23p40 that binds with high affinity to human IL-12 and IL-23.

Since the first approval of ustekinumab in Canada (12 December 2008), it has received marketing approval in countries worldwide for the treatment of adult patients with moderate to severe plaque-type psoriasis, psoriatic arthritis, and moderate to severe Crohn's disease. In many countries, including in the EEA, STELARA has also received marketing approval for the treatment of psoriasis in adolescent patients ≥12 to <18 years of age (variation II/42, EC decision on 22 June 2015).

The approved ustekinumab subcutaneous (SC) dose regimen for psoriasis in adults is 45 mg (for patients ≤100 kg) or 90 mg (for patients >100 kg) at Weeks 0 and 4, followed by maintenance doses every 12 weeks (q12w). In countries where the adolescent indication is approved, the dose regimen for psoriasis in adolescents ≥12 to <18 years of age is 0.75 mg/kg (for patients <60 kg), 45 mg (for patients ≥60 kg to ≤100 kg), or 90 mg (for patients >100 kg) at Weeks 0 and 4, followed by maintenance doses q12w.

The approval for the treatment of moderate to severe plaque-type psoriasis in adolescent patients ≥12 to <18 years of age was based upon results from CNTO1275PSO3006 (CADMUS or PSO3006), a Phase 3, randomized, double-blind, placebo-controlled, multicentre study in 110 paediatric subjects ⩾12 to <18 years of age with plaque-type moderate to severe psoriasis.

Analyses in the adolescent submission showed that the approved weight-based dosage provided serum ustekinumab concentrations in subjects ≥12 to <18 years of age which were generally comparable to those in the adult psoriasis population treated with the approved ustekinumab dosage for adult psoriasis. In addition, other analyses in the adolescent submission showed that the efficacy, safety, and exposure-response profiles of the weight-based standard dosage of ustekinumab in adolescents were comparable to those seen in adults with psoriasis. The bridge between paediatric and adult psoriasis populations was therefore established for ustekinumab by the analyses included in the adolescent application.

As there is no distinction between psoriasis occurring in younger children and adolescents, the application is built upon the bridge established in the adolescent submission to support the extension of the current paediatric indication and posology to include patients ≥6 to <12 years of age. The application included results from Study (CNTO1275PSO3013 [CADMUS Jr] or PSO3013), an open-label multicentre study of ustekinumab in paediatric subjects ≥6 to <12 years of age with moderate to severe chronic plaque-type psoriasis. The primary focus of PSO3013 was to collect pharmacokinetic (PK), efficacy, and safety data to determine if a body weight adjusted dosage (identical to the approved adolescent dosage) is appropriate for paediatric subjects ≥6 to <12 years of age. A side by side comparisons of the efficacy data from PSO3013 and PSO3006 was presented to demonstrate comparability between paediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years of age.

In addition, a summary of relevant endpoints from the pivotal Phase 3 adult studies (C0743T08, and C0743T09) were presented to bridge the efficacy observed in paediatric subjects ages ≥6 to <12 years of age with that observed in adult subjects.

2.2. Quality aspects

No new pharmaceutical data were provided in this application.

The applicant justified suitability of the formulation for use in children from 6 years of age and older formulation in accordance with the guideline on Pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2). The needle thickness and length in relation to the use of the PFS presentation in the paediatric population is suitable for use in children from 6 years of age. Target pH and Osmolality have been selected to minimise pain and irritation. Recommendations on needle thickness and length when using the vial presentation are added in the SmPC Section 6.6. In addition, justification has been provided on the excipients and level of exposure. Considering that the formulation has been used in adolescents and adults, potential for toxicity unique to younger paediatric patients from 6 years of age is unlikely. Overall, the formulation is considered acceptable by the CHMP for use in paediatric patients from 6 years of age.

2.3. Non-clinical aspects

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

2.3.1. Ecotoxicity/environmental risk assessment

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

2.3.2. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant has provided a statement to the effect that clinical trials (CNTO1275PSO3013) conducted outside the European Union (Canada and United States) were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Overview of Ustekinumab Phase 3 Paediatric Psoriasis Study in children (⩾6 to <12 years of age)	
Design Elements	**CNTO1275PSO3013**
Study Population	Paediatric subjects (⩾6 to <12 years of age) with moderate to severe plaque-type psoriasis (defined by PASI score ⩾12, PGA ⩾3, and BSA involvement ⩾10%)
Study Regions	Europe, Canada, and US
Last Efficacy Assessment	52 Weeks
Subjects enrolled/randomized	44
Treatment groups (n)	• Ustekinumab - Standard dosage[a] (n=44)
Primary Endpoint	PGA score of cleared (0) or minimal (1) at Week 12
Major Secondary Efficacy Endpoints	• PASI 75 response at Week 12 • Change in CDLQI score from baseline at Week 12 • PASI 90 response at Week 12

Abbreviations: BSA=body surface area; CDLQI=Children's Dermatology Life Quality Index; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment.

[a] weight-adjusted dose of 0.75 mg/kg for subjects weighing <60 kg, fixed dose of 45 mg for those weighing ⩾60 kg to ⩽100 kg, and a fixed dose of 90 mg for those weighing >100 kg

2.4.2. Pharmacokinetics

The proposed extension of the psoriasis indication to the younger age group (children ≥6 to <12 years of age) was based primarily on data from study PSO3013. Population PK modelling and simulation were also employed to verify that the proposed dosage for paediatric patients (≥6 to <12 years of age) resulted in systemic drug exposure comparable to that seen in the adolescent population (≥12 to <18 years of age) and led to similar exposure-response relationships.

Adolescent data are based on study CNTO1275PSO3006 or CADMUS (hereafter referred to as PSO3006) from a previous submission.

Study PSO3013 – Children ≥6 to <12 years of age

Methods

Study design: PSO3013 was a Phase 3, open-label, multicenter, single-arm study in paediatric subjects ≥6 to <12 years of age who had a diagnosis of plaque psoriasis.

Inclusion Criteria: Paediatric subjects ≥6 to <12 years of age were eligible for this study if they had moderate to severe plaque-type psoriasis with or without PsA as defined by PASI ≥12, PGA ≥3, and BSA involvement ≥10%. Subjects were also required to be candidates for phototherapy or systemic treatment of psoriasis (either naïve or history of previous treatment) or had psoriasis not adequately controlled by topical therapies, specifically, those subjects who, in the opinion of the investigator, were inadequately controlled with topical therapy after an adequate dose and duration of therapy.

Dosing: The weight-based standard ustekinumab dosage was used: 0.75 mg/kg for subjects <60 kg, 45 mg for subjects ≥60 kg to ≤100 kg, and 90 mg for subjects >100 kg. Subjects received SC

injections of ustekinumab with the weight-based standard dosage at Weeks 0 and 4 followed by dose administrations q12w through Week 40.

PK and immunogenicity sampling: In study PSO3013, PK samples were collected at screening, and Weeks 4, 12, 16, 28, 40, and 52. Serum samples for the detection of antibodies to ustekinumab were collected at screening, and at Weeks 12, 28, and 52. A sample was also collected at the final visit from subjects who terminated study participation early.

Pharmacokinetic Parameters: The apparent clearance (CL/F) and apparent volume of distribution (V/F) were estimated using a nonlinear mixed effects modeling (NONMEM) approach.

Bioanalytical methods

Serum ustekinumab concentrations were measured by a validated electrochemiluminescent immunoassay (ECLIA) method using the Meso Scale Discovery (MSD®) platform. The below the lowest quantifiable sample concentration of the assay (BQL) was <0.1688 µg/mL.

In both PSO3013 and PSO3006, the presence of anti-drug antibodies (ADA) against ustekinumab in serum was determined by a newer validated sensitive, drug- and target-tolerant ECLIA method using the MSD® platform. This ADA assay was developed to reduce ustekinumab interference in the detection of antibodies to ustekinumab in human serum samples. The maximum observed sensitivity of the serum ADA ECLIA was 1.97 ng/mL in human serum. It was verified that the presence of drug in serum at the concentration level studied did not interfere with the ADA ECLIA, and 50 ng/mL of an ADA could be detected in the presence of up to 100 µg/mL of ustekinumab in serum.

To characterize neutralizing antibodies (NAbs) in both PSO3013 and PSO3006, serum samples that were confirmed to contain antibodies to ustekinumab were further characterized for the ability of those antibodies to neutralize the bioactivity of ustekinumab using a validated sensitive, drug- and target-tolerant competitive MSD ECLIA NAb method.

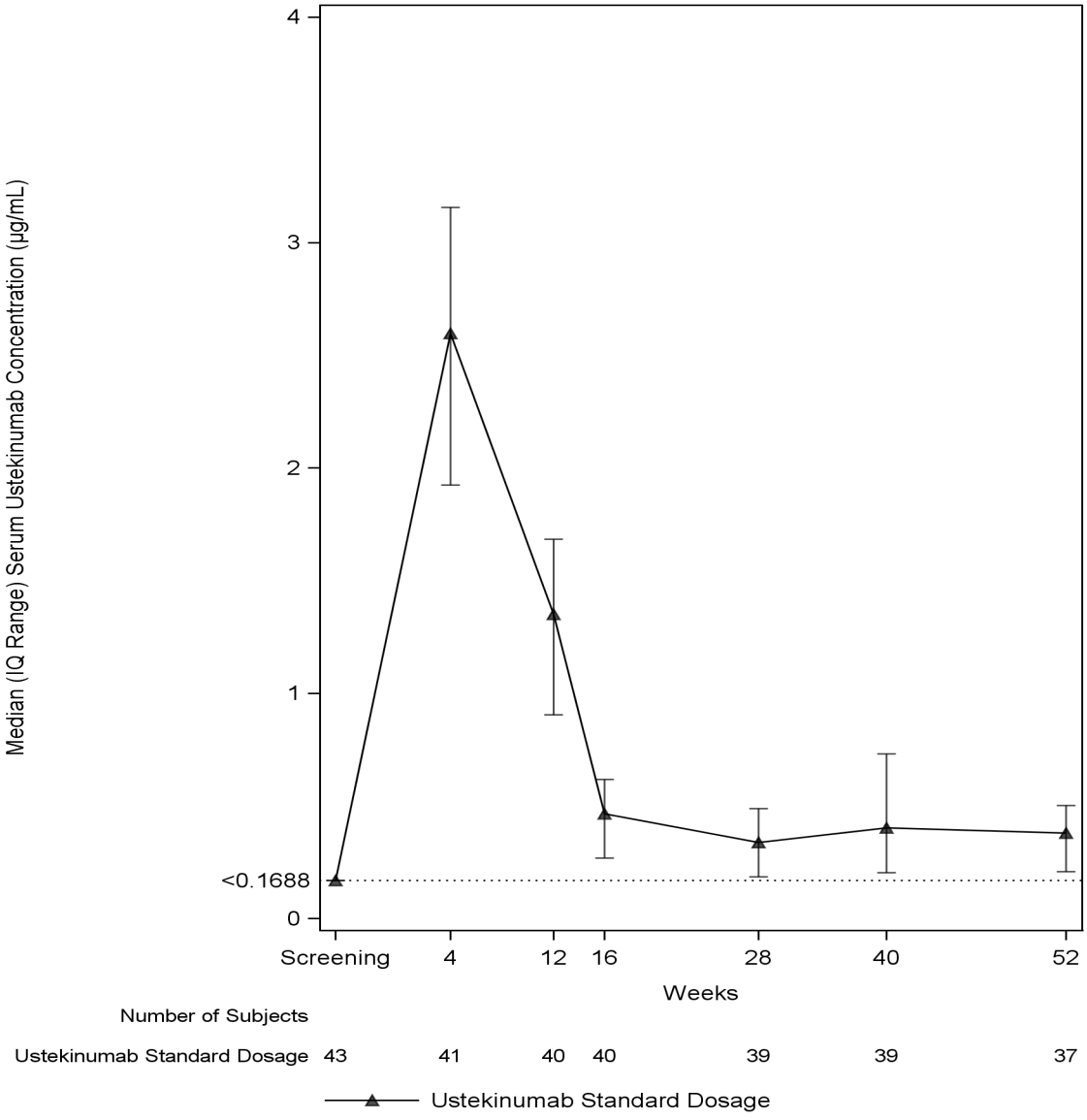
Results

A total of 44 subjects were enrolled and treated in this study. Most subjects were female (61.4%) and white (90.9%). The median body weight was 33.3 kg, with the majority of subjects (90.9%) having a body weight of <60 kg. The median BMI was 18.0 kg/m^2. Of these 44 subjects, only 4 subjects had a baseline body weight in the range of ≥60 to ≤100 kg and no subject had a baseline body weight >100 kg. The median age was 9.5 years, with 50.0% of subjects <10 years of age. All ages across the age range (≥6 to <12 year of age) were represented in the study population.

Ustekinumab serum concentrations

Median trough serum ustekinumab concentrations at Weeks 28, 40, and 52 were 0.34 µg/mL, 0.40 µg/mL, and 0.38 µg/mL, respectively. Following multiple subcutaneous doses of ustekinumab, mean or median trough serum ustekinumab concentrations were maintained at a steady state from Week 28 through Week 52. There was no evidence of accumulation of serum ustekinumab concentrations over time. Median and interquartile (IQ) ranges of serum ustekinumab concentrations by visit through Week 52 are presented for the overall population in Figure 1.

Figure 1: Median and IQ Range of Serum Ustekinumab Concentration (micrograms/mL) Through Week 52; Pharmacokinetics Analysis Set (Study CNTO1275PSO3013)



Serum ustekinumab below the lowest quantifiable concentration

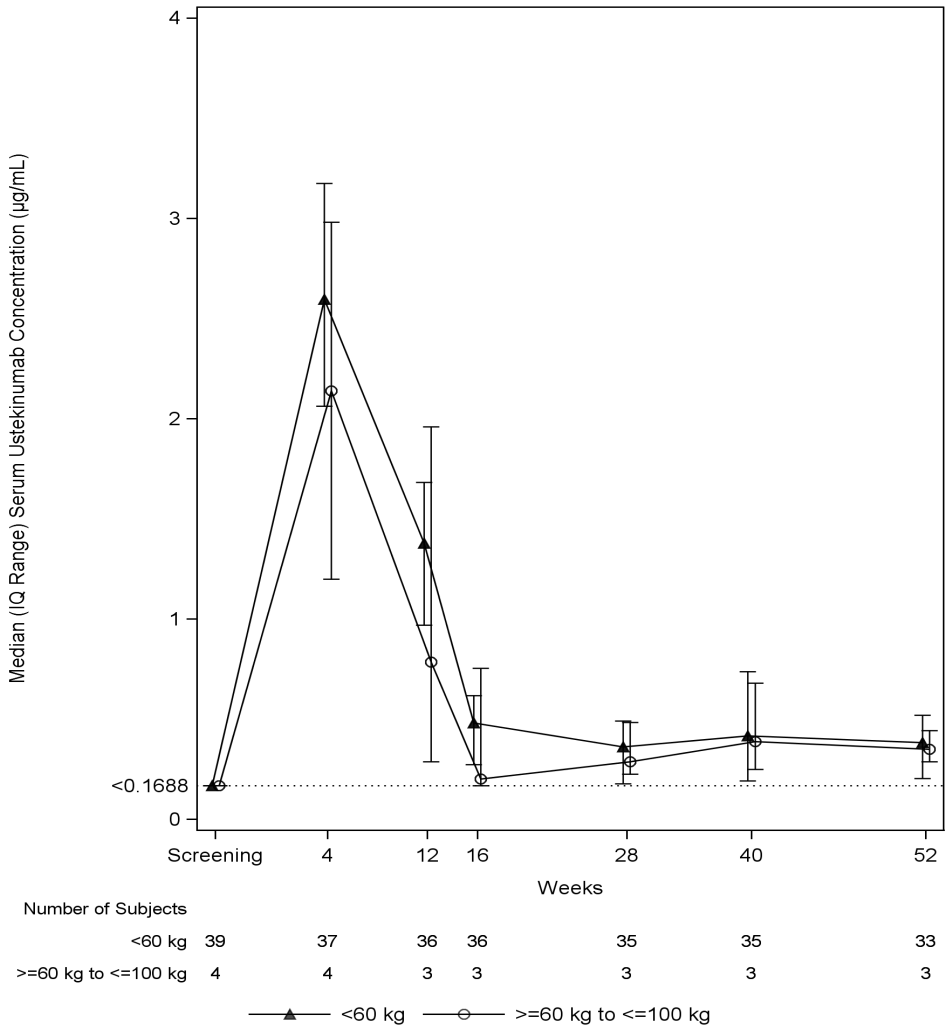
At Weeks 28, 40, and 52, the proportions of subjects with BQL trough serum ustekinumab concentrations were 17.9%, 15.4%, and 16.2%, respectively.

Ustekinumab serum concentrations by body weight

Similar serum ustekinumab concentrations were observed for subjects with body weight <60 kg at baseline treated with the weight-based 0.75 mg/kg dosage and subjects with body weight ≥60 kg to ≤100 kg at baseline treated with the fixed 45 mg dosage, as evidenced by the generally comparable median trough serum ustekinumab concentrations and substantial overlap of the corresponding IQ ranges of trough serum ustekinumab concentrations at Weeks 28, 40, and 52 between the 2 body

weight subgroups (**Figure 2**). However, only a limited number of subjects (n=4) had a baseline weight ≥60 kg to ≤100 kg.

Figure 2 Median and IQ Range of Serum Ustekinumab Concentration (micrograms/mL) Through Week 52 by Weight at Baseline; Pharmacokinetics Analysis Set (Study CNTO1275PSO3013)



Immunogenicity

Of the 44 subjects treated with ustekinumab, 42 subjects had 1 or more post-treatment serum samples that were evaluable for antibodies to ustekinumab. The incidence of antibodies to ustekinumab was 9.5% (n=4). Of the 4 ADA-positive subjects, 2 (50.0%) were positive for NAbs. Two of the 4 subjects who were positive for antibodies to ustekinumab achieved PGA scores of cleared (0) or minimal (1) and PASI 75 responses at Week 52.

Study PSO3006 – Adolescents ≥12 to <18 Years

Study design: PSO3006 was a Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter, 3-arm study in adolescent subjects (≥12 to <18 years of age) who had a diagnosis of moderate to severe plaque-type psoriasis.

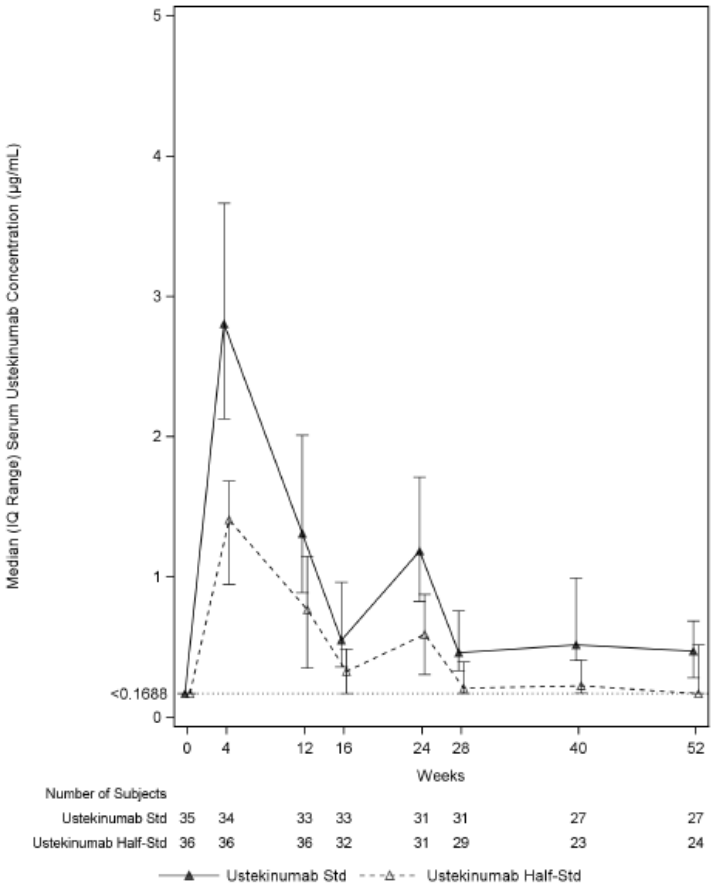
Inclusion criteria: Adolescent subjects ≥12 to <18 years of age were eligible for this study if they had moderate to severe plaque-type psoriasis (defined by PASI ≥12, PGA ≥3, and BSA involvement ≥10%) and were candidates for phototherapy or systemic treatment of psoriasis or had psoriasis considered by the investigator as poorly controlled with topical therapy after an adequate dose and duration of therapy.

Dosage: Two doses were investigated, the standard weight based dose (0.75 mg/kg for subjects ≤60 kg, 45 mg for subjects >60 kg but ≤100 kg, and 90 mg for subjects >100 kg) and half-standard dose.

Results: Dose-proportionality in serum ustekinumab concentrations was observed when comparing mean or median serum ustekinumab concentrations between the half-standard dosage and standard dosage groups. Steady state was achieved at Week 28 with median steady-state trough serum ustekinumab concentration 0.46 µg/mL at Week 28 for the standard dosage group. Mean or median trough serum ustekinumab concentrations were generally maintained at steady state from Week 28 through Week 52. There was no evidence of accumulation in serum ustekinumab concentrations over time.

Plasma-concentrations for standard and half-standard doses are presented in Figure 3.

Figure 3 Median Serum Ustekinumab Concentration (micrograms/mL) Through Week 52; Subjects Treated with Ustekinumab Who were Randomized to Ustekinumab Groups at Week 0 (Study CNTO1275PSO3006)



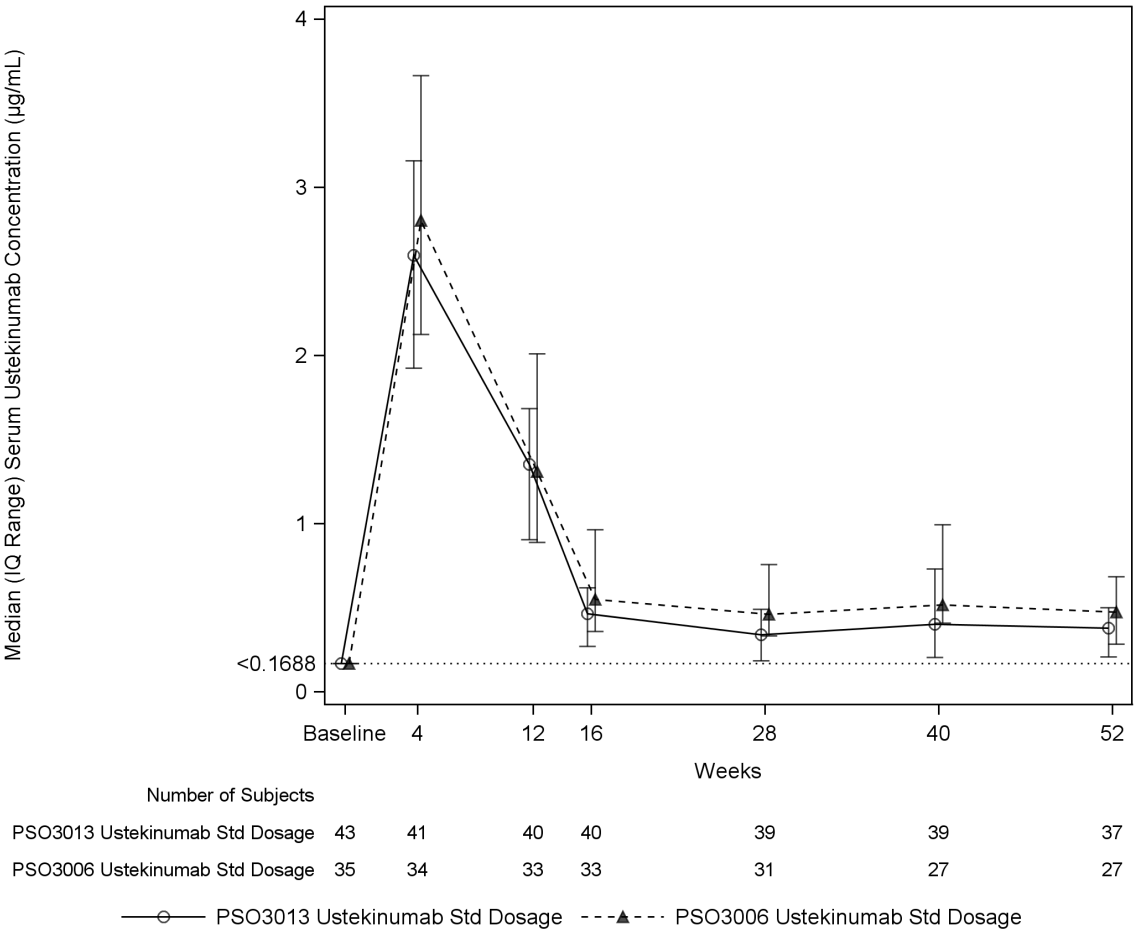
At week 24, 16.1 % of subjects treated with standard dose, had BQL trough serum ustekinumab concentrations. At week 40 and 52, 14.8 % of subjects treated with standard dose had BQL trough serum ustekinumab concentrations.

Comparison of PK and immunogenicity between paediatric and adolescent patients

Pharmacokinetics

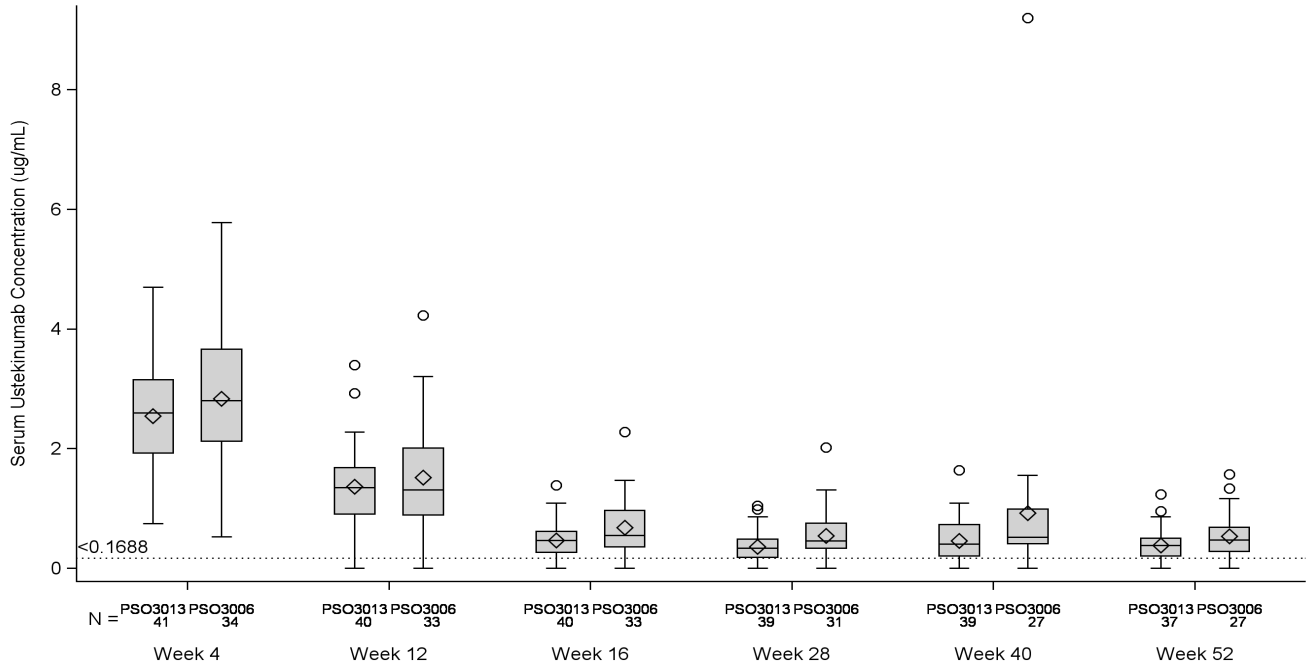
A comparison of serum ustekinumab concentrations by visit through Week 52 in paediatric subjects ≥6 to <12 years of age in study PSO3013 and adolescent subjects ≥12 to <18 years of age in study PSO3006 treated with the weight-based standard dosage are presented in **Figure 4**, **Figure 5**.

Figure 4: Median and IQ Range of Serum Ustekinumab Concentration (micrograms/mL) Through Week 52; Subjects Treated With Standard Dosage (CNTO1275PSO3013 and CNTO1275PSO3006)



Key: IQ=interquartile; Std=standard

Figure 5: Boxplot of Serum Ustekinumab Concentrations (µg/mL) Through Week 52 by Visit; Subjects Treated With Standard Dosage (CNTO1275PSO3013 and CNTO1275PSO3006)

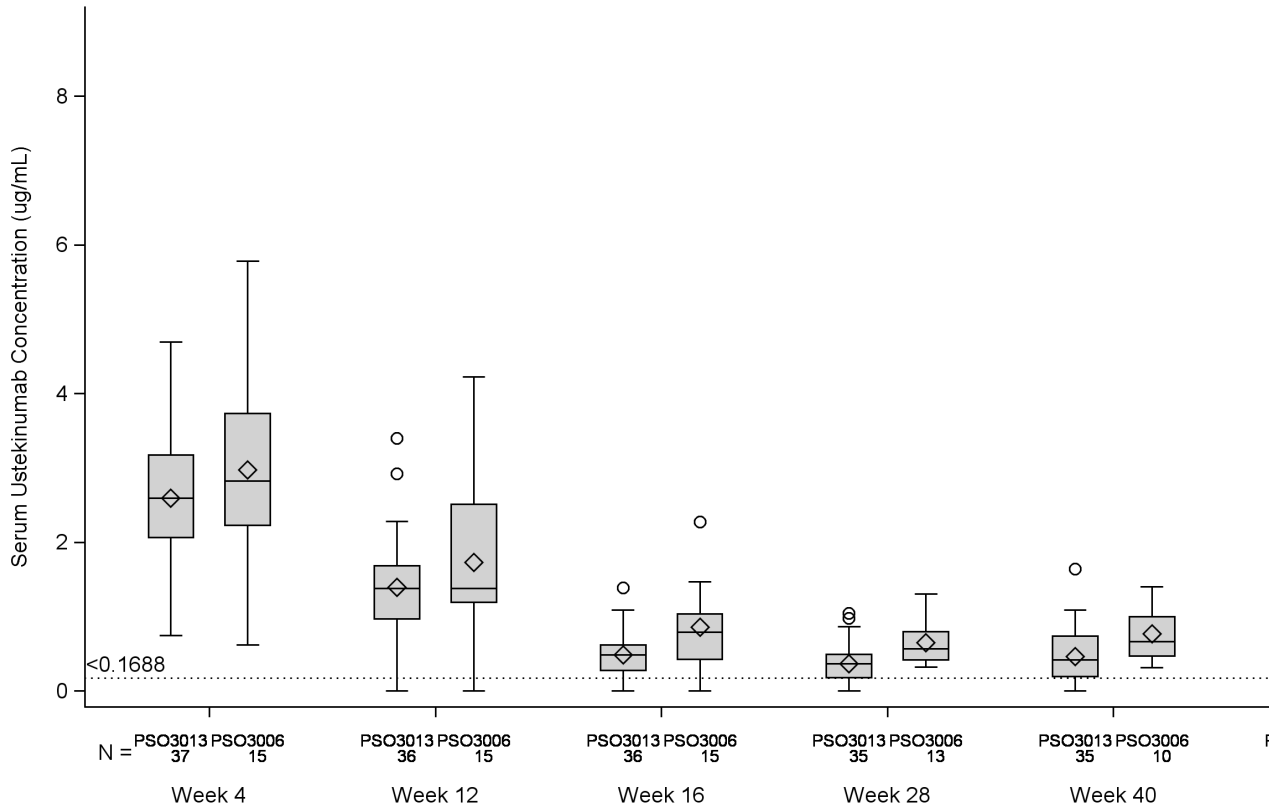


Note: The line inside the box represents the median value. The symbol inside the box represents the mean value. The outer box borders represent the lower and upper quartiles (25th and 75th percentiles of the data). The interquartile range is the difference between the upper and lower quartiles. The upper whisker represents the largest observation between the upper quartile and 1.5 times the interquartile range plus the upper quartile. The lower whisker represents the lowest observation between the lower quartile and the lower quartile minus 1.5 times the interquartile range. Outliers are any observations greater than or lower than the upper and lower whiskers and are represented as circles on the plot.

The comparisons of ustekinumab concentrations in paediatric subjects with bodyweight <60 kg and ≥60 kg to ≤100 kg treated with the standard dosage in study PSO3013 and adolescent subjects with body weight <60 kg and ≥60 kg to ≤100 kg treated with the standard dosage in study PSO3006 are presented below.

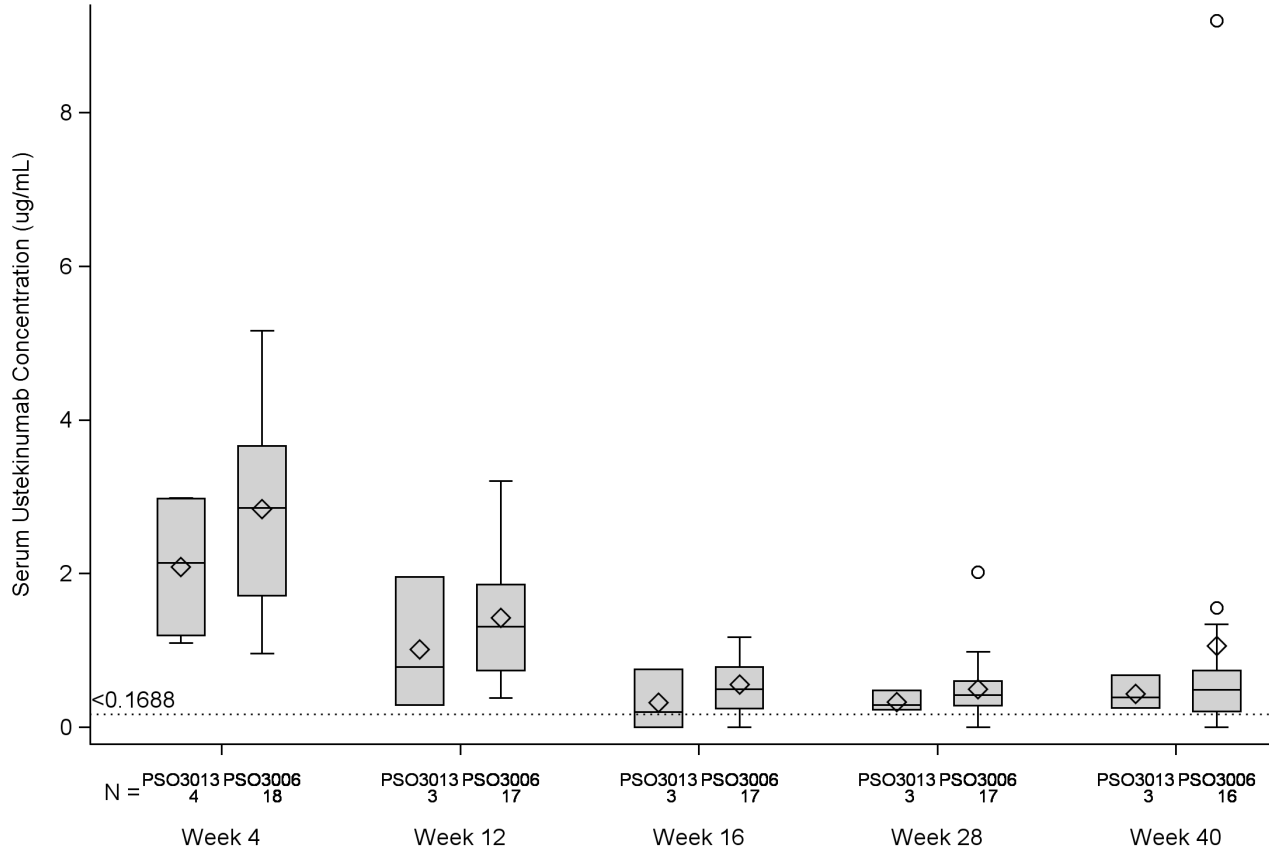
Figure 6 Graphical Presentation of Serum Ustekinumab Concentrations (micrograms/mL) Through Week 52 by Body Weight at Baseline

6a: Boxplot of Serum Ustekinumab Concentrations (micrograms/mL) Through Week 52 by Visit; Subjects in Pharmacokinetics Analysis Set and Baseline Weight <60 kg



Note: The line inside the box represents the median value. The symbol inside the box represents the mean value. The outer box borders represent the lower and upper quartile (25th and 75th percentiles of the data). The interquartile range is the difference between the upper and lower quartiles. The upper whisker represents the largest observation between the upper quartile and 1.5 times the interquartile range plus the upper quartile. The lower whisker represents the lowest observation between the lower quartile and the lower quartile minus 1.5 times the interquartile range. Outliers are any observations greater than or lower than the upper and lower whiskers and are represented as circles on the plot.

6b: Boxplot of Serum Ustekinumab Concentrations (micrograms/mL) Through Week 52 by Visit; Subjects in Pharmacokinetics Analysis Set and Baseline Weight >=60 kg to <=100 kg



Note: The line inside the box represents the median value. The symbol inside the box represents the mean value. The outer box borders represent the lower and upper quartile (25th and 75th percentiles of the data). The interquartile range is the difference between the upper and lower quartiles. The upper whisker represents the largest observation between the upper quartile and 1.5 times the interquartile range plus the upper quartile. The lower whisker represents the lowest observation between the lower quartile and the lower quartile minus 1.5 times the interquartile range. Outliers are any observations greater than or lower than the upper and lower whiskers and are represented as circles on the plot.

The weight-based standard dosage used in the PSO3013 and PSO3006 studies provided similar ustekinumab exposure in paediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years of age.

Immunogenicity

In study PSO3013, 4 paediatric subjects (9.5%) had samples positive for ADA post-baseline after treatment with the weight-based standard dosage. In study PSO3006, 5 adolescent subjects (6.8%) had samples positive for ADA post-baseline (**Table 1**). Although the identical assay method was utilized to detect antibodies to ustekinumab in serum for both the PSO3013 and PSO3006 studies, a change in the assay specificity cut point was implemented for the paediatric study (PSO3013) to comply with updated regulatory guidelines.

Table 1: Summary of Anti-ustekinumab Antibodies Status Through the End of the Reporting Period; Immunogenicity Analysis Set

	PSO3013 Standard Dosage	PSO3006 Standard Dosage	PSO3006 Half-Standard Dosage	Combined
Analysis set: Immunogenicity analysis set	42	36	37	73
Subjects with appropriate samples[a]	42	36	37	73
Subjects with baseline positive samples[b,c]	2 (4.8%)	0	0	0
Subjects postbaseline positive for anti-ustekinumab antibodies[c,d]	4 (9.5%)	1 (2.8%)	4 (10.8%)	5 (6.8%)
Peak titers				
1:200	1	0	1	1
1:400	1	1	0	1
1:800	0	0	1	1
1:1600	1	0	0	0
1:12800	1	0	1	1
1:204800	0	0	1	1
Subjects postbaseline negative for anti-ustekinumab antibodies[c,e]	38 (90.5%)	35 (97.2%)	33 (89.2%)	68 (93.2%)

[a] Subjects with appropriate samples had 1 or more evaluable samples obtained after their first ustekinumab administration.
[b] Subjects had samples positive for anti-ustekinumab antibodies at baseline, regardless of antibody status after their first ustekinumab administration.
[c] Denominator is number of subjects with appropriate samples for antibodies to ustekinumab.
[d] Subjects positive for anti-ustekinumab antibodies includes all subjects who had positive sample (treatment-boosted or treatment-induced) at any time after their first ustekinumab administration through the end of the reporting period. In the instance that a subject had a positive sample at baseline (predose), the subject was considered as positive only if the peak titer of the posttreatment samples was at least a 2-fold higher (ie, ≥2-fold) than the titer of the baseline sample.
[e] Includes all subjects whose last sample was negative, and excludes subjects who were positive for anti-ustekinumab antibodies through the end of the reporting period.

The combined incidence of antibodies to ustekinumab was 8.2% (n=9) across all ustekinumab-treated subjects (PSO3013 and PSO3006).

Population pharmacokinetic analyses

A population PK modeling approach was used to describe the PK characteristics of ustekinumab in paediatric subjects ≥6 to <12 years of age and comparing them with those in adolescent subjects ≥12 to <18 years of age, after accounting for differences in body weight.

Methods

Dataset

A total of 15,349 serum ustekinumab concentration-time records (283 from paediatric subjects, 928 from adolescent subjects, and 14,138 from adults) were available for PopPK analysis, of which 2,034 (13.3%) records were pre-dose samples with BQL concentrations, and 2,488 (16.2%) records were post-dose samples with BQL concentrations. All pre-dose records were excluded from all analyses. For models where the likelihood based (M3) method was implemented, the post-dose BQL values were included in the analyses.

PopPK model development

The PopPK analyses were performed using NONMEM (version 7.4.1). The first-order conditional estimation with interaction (FOCE-I) method was employed for all model runs.

Two modeling approaches were implemented:

- Pooled Paediatric Model: this modeling approach is referred to as Pooled Paediatric Model in later sections, which includes data from PSO3013 and PSO3006 studies.
- Pooled Paediatric and Adult Model: this modeling approach is referred to as Pooled Paediatric and Adult Model in later sections, which includes data from PSO3013, PSO3006, 0743T08 and C0743T09 studies.

It was known *a priori* that body weight would be an important covariate for PK of ustekinumab. As such, body weight effects on both the apparent clearance (CL/F) and apparent volume of distribution (V/F) estimates were included in the base structural model *a priori*, in which two complementary methodologies were employed with respect to the body weight effects. In the primary analysis (the fixed body weight effect [FBW] approach), the exponents for body weight effects on CL/F and V/F were fixed to 0.75 and 1, respectively. For the supplemental analysis (the estimated body weight effect [EBW] approach), the exponents for weight effects on CL/F and V/F were estimated by NONMEM along with other model parameters.

Serum ustekinumab concentration-time profiles in paediatric subjects with psoriasis were adequately described by the one-compartment linear model with first-order absorption and first-order elimination. Random effects with an estimated covariance term on CL/F and V/F were included. Given the prior knowledge that body weight is a significant covariate on the PK of ustekinumab, two alternative modeling methodologies, FBW and EBW, were utilized with respect to the modeling of body weight effects on CL/F and V/F. Given the potential of clinical relevance, one additional covariate (immune response positive [IRP]) was retained in both models.

Simulations were conducted using the final population PK model, which focused on the FBW effect on CL/F and V/F. Body weight values for paediatric subjects ≥6 to <12 years of age and adolescents ≥12 to <18 years of age were sampled with replacement from the Third National Health and Nutrition Examination Survey (NHANES III) growth database. The exposure parameters at steady state (area under the serum ustekinumab concentrations versus time curve over one dosing interval period of 12 weeks [AUC], C_{peak}, and C_{trough}) were obtained through simulations with the developed population PK model. All simulations were based on 1,000 simulated subjects in the different dosage weight-based or fixed dose regimens.

Results

Pooled Paediatric Model

For the Pooled Paediatric Model, a total of 889 (73.4%) non-BQL observations were included in the base structural model development. The combined paediatric and adolescent serum ustekinumab concentration-time data were well described by a one-compartment model with first-order absorption and elimination. The exponents for body weight effects on CL/F and V/F were fixed to 0.75 and 1, respectively. One additional covariate, Immune Response Positive, was retained in the final model.

The PK estimates of the final model are provided in Table 2.

Table 2 Parameter Estimates from the Final FBW Pooled Paediatric Model

Parameter (Units)	Estimate	RSE (%)	IIV (%CV)	RSE (%)	Shrinkage (%)	Nonparametric bootstrap Median (2.5th and 97.5th percentiles)
CL/F (L/day)	0.204	4.53	38.9	10.9	5.83	0.204 (0.185, 0.224)
V/F (L)	6.77	4.12	30.2	14.2	26.3	6.80 (6.20, 7.37)
Ka (1/day)	0.371	30.2				0.352 (0.225, 1.75)
IRP on CL	1.32	9.02				1.32 (1.07, 1.61)
Prop Err (%CV)	0.242	10.0				0.240 (0.194, 0.291)

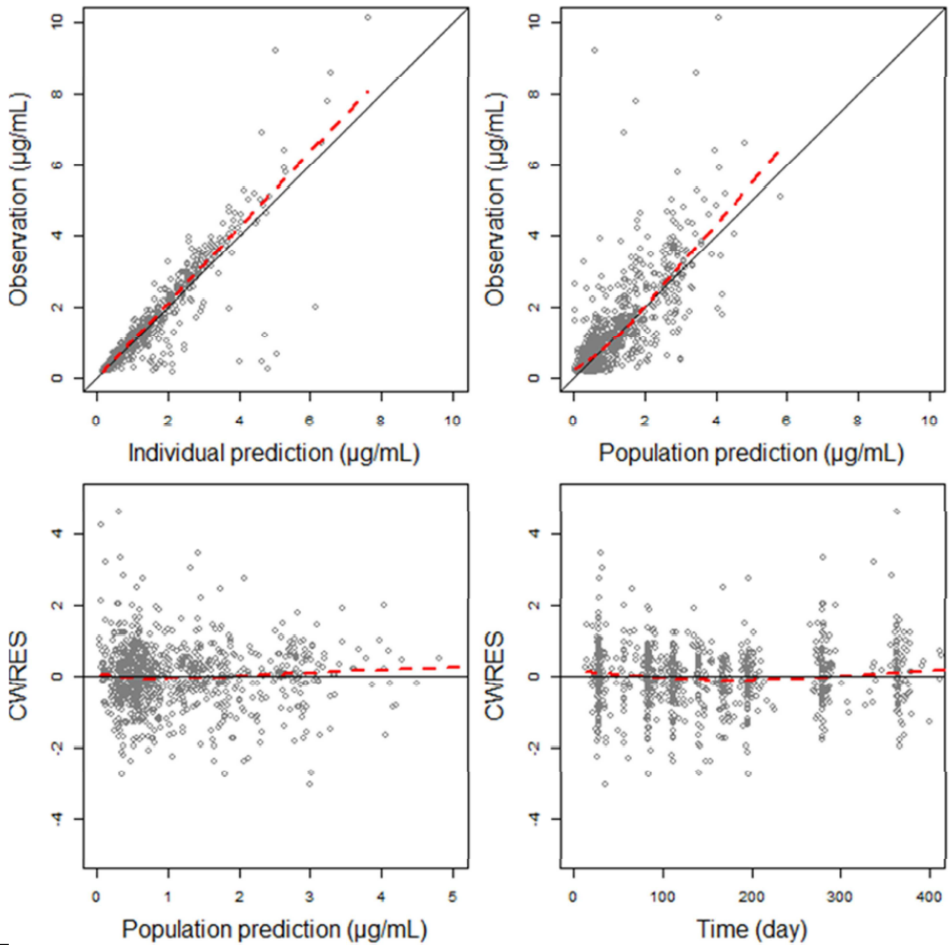
Parameter estimates were based on a typical subject with body weight equals to 56 kg. FBW, fixed body weight effects on CL/F and V/F as exponents of 0.75 and 1, respectively.
CL/F, apparent clearance; V/F, apparent volume of distribution; Ka, absorption rate constant; IRP, immune response positive (positive = 1, negative = 0); RSE, relative standard error; IIV, inter-individual random effects; Prop Err, proportional error; %CV, percentage coefficient of variation.
The covariance between CL/F and V/F was 40.1% and the RSE was 41.5%;

$$CL_i = CL_0 \times \left(\frac{WT}{56}\right)^{0.75} \times \left(\theta_{IRP_{CL}}\right)^{IRP} \times \exp(\eta_{CL,i})$$

$$V_i = V_0 \times \left(\frac{WT}{56}\right)^{1} \times \exp(\eta_{V,i})$$

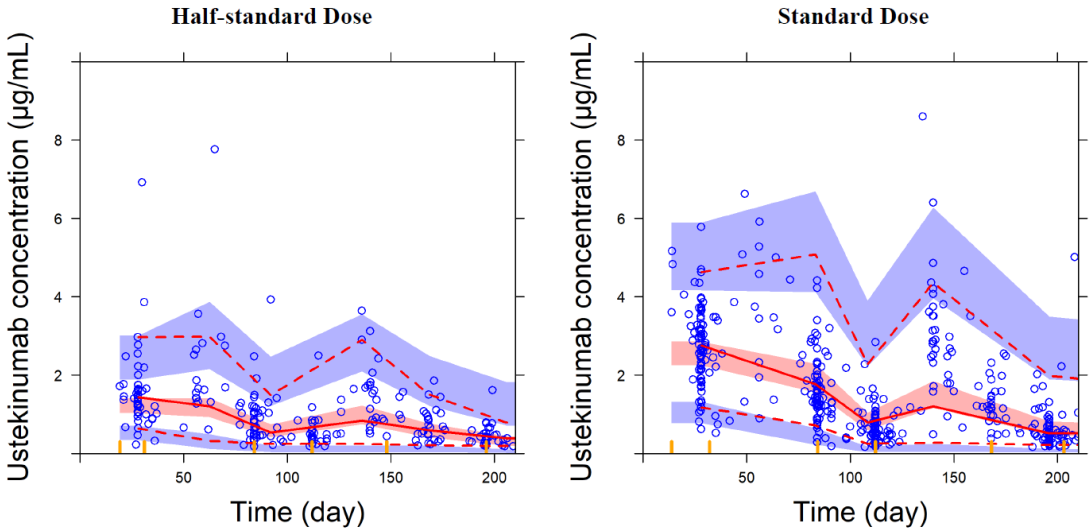
The goodness-of-fit plots for the final Pooled Paediatric Model are presented in Figure 7. VPCs with stratifications by dose levels are presented in Figure 8.

Figure 7 Goodness of fit Plots for Final FBW Pooled Paediatric Model



The black solid line is the line of identity or the zero line, and the red solid line is the trend line. The grey circles are the observations.
Key: CWRES=conditional weighted residuals.

Figure 8 VPC Stratified by Dose Levels for Final FBW Pooled Paediatric Model



Pooled Paediatric and Adult Model

For the Pooled Paediatric and Adult Model, a total of 10,827 (70.5%) non-BQL observations were included in the base structural model development. A one-compartment model with first-order absorption and elimination also well described the pooled dataset from paediatric and adult studies, and the exponents for body weight effects on CL/F and V/F were fixed to 0.75 and 1, respectively. Immune Response Positive was not retained in the model since different immunogenicity assays were used across studies. Diabetic comorbidity was found to be a clinically relevant covariate on CL/F and retained in the model.

The PK parameter estimates of the final Pooled Paediatric and Adult Model are provided in Table 3.

Table 3 Parameter Estimates from the Final FBW Pooled Paediatric and Adult Model

Parameter (Units)	Estimate	RSE (%)	IIV (%CV)	RSE (%)	Shrinkage (%)	Nonparametric bootstrap Median (2.5th and 97.5th percentiles)
CL/F (L/day)	0.319	3.51	45.1	3.23	4.57	0.318 (0.297, 0.344)
V/F (L)	10.8	3.50	36.7	5.74	19.5	10.8 (10.1, 11.6)
Ka (1/day)	0.318	9.18				0.320 (0.274, 0.393)
Assay Bias	0.629	3.56				0.627 (0.586, 0.676)
DIAB on CL	0.233	14.4				0.231 (0.171, 0.298)
Prop Err1 (%CV)	0.273	1.67				0.273 (0.265, 0.283)
Prop Err2 (%CV)	0.248	11.5				0.245 (0.192, 0.305)

Parameter estimates were based on a typical subject with body weight equals to 88 kg. FBW, fixed body weight effects on CL/F and V/F as exponents of 0.75 and 1, respectively.
CL/F, apparent clearance; V/F, apparent volume of distribution; Ka, absorption rate constant; DIAB, diabetes status (positive = 1, negative = 0); RSE, relative standard error; IIV, inter-individual random effects; Prop Err1, proportional error of old assay; Prop Err2, proportional error of new assay; %CV, percentage coefficient of variation; The covariance between CL/F and V/F was 79.7% and the RSE was 5.34%; Bioanalysis assay bias was modeled as bioavailability (F1) = 1 for new assay, F1 = 0.629 for old assay.

$$CL_i = CL_0 \times \left(\frac{WT}{88}\right)^{0.75} \times (1 + \theta_{DIAB_{CL}} \times DIAB) \times \exp(\eta_{CL,i})$$

$$V_i = V_0 \times \left(\frac{WT}{88}\right)^{1} \times \exp(\eta_{V,i})$$

The goodness-of-fit plots for the final Pooled Paediatric and Adult Model are presented in Figure 9. VPCs with stratifications by dose levels are presented in Figure 10.

Figure 9 Goodness of fit Plots for Final FBW Pooled Paediatric and Adult Model

Figure 4: Goodness-of-fit Plots for Final FBW Pooled Pediatric and Adult Model (run405)

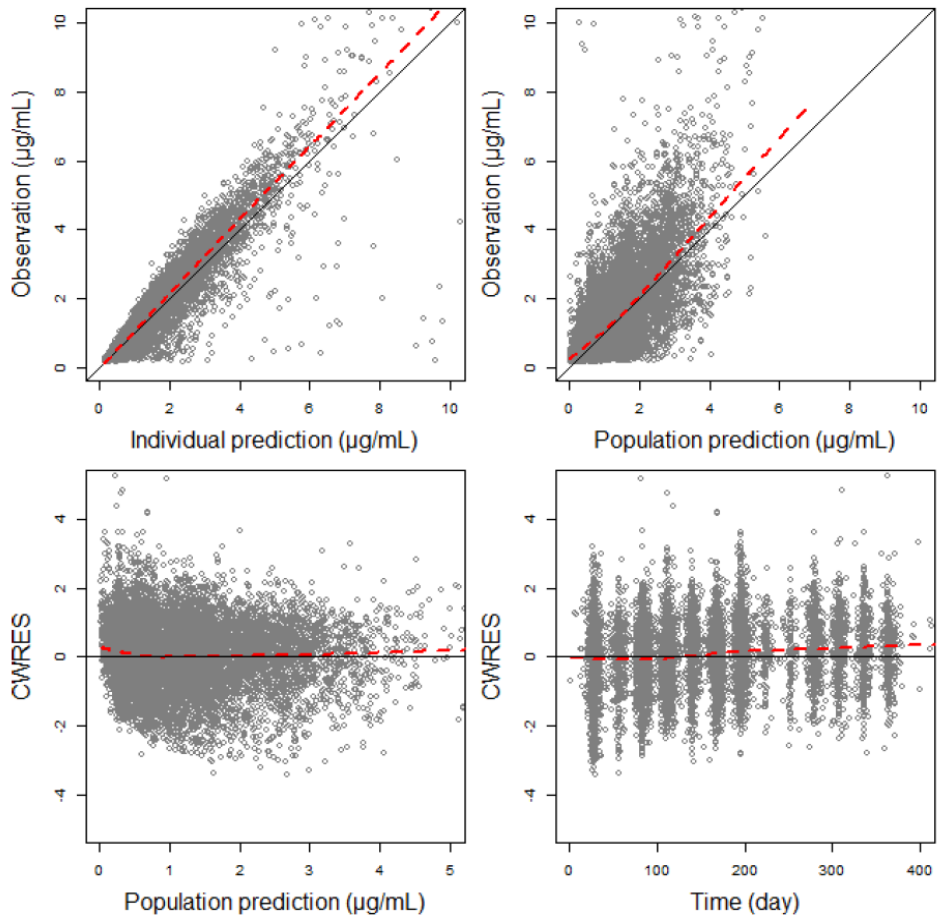
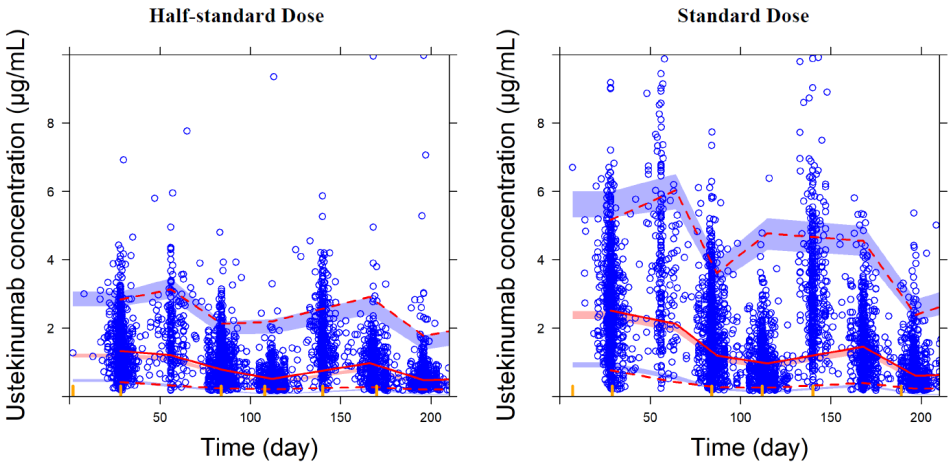


Figure 10 VPC Stratified by Dose Levels for Final FBW Pooled Paediatric and Adult Model

Figure 4: VPC Stratified by Dose Levels for Final Pooled Pediatric and Adult Model (Fixed Body Weight Approach)

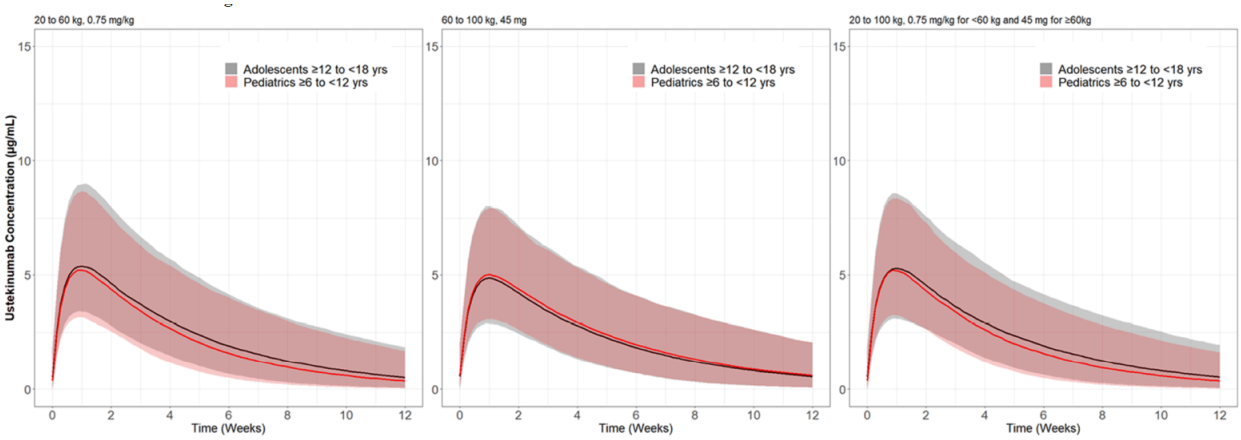


Simulations using the final PopPK models

Figure 11 provides overlay plots for median (90% prediction interval) serum concentration-time profiles of ustekinumab in paediatric and adolescent subjects in different body weight categories following the

proposed/approved dosing regimens. The simulated PK profiles for the paediatric subjects are superimposable to those in the respective reference adolescent subjects.

Figure 11 Comparison of the Final FBW Pooled Paediatric Model Predicted Serum Concentration time Profiles of Istekinumab in Paediatric Subjects ≥6 to <12 Years of Age Receiving the Proposed Fixed Ustekinumab Dosage with Respective Adolescent Reference Populations Receiving the Approved Standard Dosage



Lines represent medians of the simulated values. Shaded regions represent the 5th – 95th percentile ranges.

A summary of simulated PK exposure parameters by population and body weight group is presented in Table 4. Following SC administration of 0.75 mg/kg q12w for the 20 to 60 kg paediatric subjects, the median Ctrough was predicted to be 0.364 µg/mL (90% prediction interval: [0.0346, 1.68]), which is slightly lower than the median Ctrough (0.516 µg/mL) (90% prediction interval: [0.0596, 1.86]) for the 20 to 60 kg adolescent subjects receiving 0.75 mg/kg dose q12w. All other simulated exposure parameters in paediatric subjects with psoriasis following the proposed dosage regimens were comparable to those in adolescent subjects with psoriasis who received the approved standard dosage of ustekinumab for adolescent subjects.

Table 4 Median (90% Prediction Intervals) of Model Predicted Exposure Parameters with the Final FBW Pooled Paediatric Model by Study Population

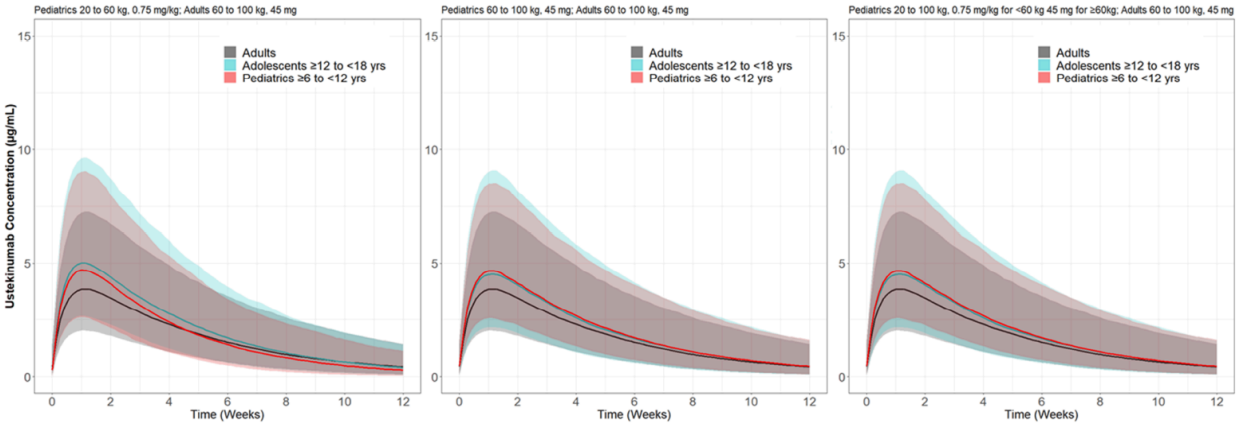
	AUC (µg·day/mL)	C_{peak} (µg/mL)	C_{trough} (µg/mL)
Pediatrics ≥6 to <12 yrs 20 to 60 kg; 0.75 mg/kg q12w	176 (88.7, 360)	5.23 (3.19,8.66)	0.364 (0.0346, 1.68)
Pediatrics ≥6 to <12 yrs 60 to 100 kg; 45 mg q12w	195 (98.0, 361)	5.03 (3.09,7.94)	0.601 (0.0728, 2.07)
Pediatrics ≥6 to <12 yrs; 0.75 mg/kg for body weight <60 kg and 45 mg for body weight ≥60kg SC q12w	174 (92.8, 340)	5.23 (3.28,8.37)	0.360 (0.0298, 1.63)
Adolescents ≥12 to <18 yrs 20 to 60 kg; 0.75 mg/kg q12w	198 (103, 381)	5.38 (3.42,9.01)	0.516 (0.0596, 1.86)
Adolescents ≥12 to <18 yrs 60 to 100 kg; 45 mg q12w	185 (94.0, 370)	4.87 (2.88,8.03)	0.550 (0.0721, 2.05)
Adolescents ≥12 to <18 yrs; 0.75 mg/kg for body weight <60 kg and 45 mg for body weight ≥60kg SC q12w	192 (101, 373)	5.29 (3.11,8.65)	0.534 (0.0530, 1.96)

AUC, area under the serum ustekinumab concentration versus time curve over one dosing interval period of 12 weeks at steady-state C_{peak}, peak serum ustekinumab concentration at steady state; C_{trough}, trough serum ustekinumab concentration at steady state

Figure 12 provides overlay plots for median (90% prediction interval) serum concentration-time profiles of ustekinumab in paediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years of age in different body weight categories following the proposed/approved dosing regimens in

comparison to 60 to 100 kg adult subjects with psoriasis receiving SC administration of 45 mg fixed dose q12w.

Figure 12 Comparison of the Final FBW Pooled Paediatric and Adult Model Predicted Serum Concentration time Profiles of Istekinumab in Paediatric Subjects ≥6 to <12 Years of Age and Adolescents Subjects ≥12 to <18 Years of Age Receiving the Proposed/Approved Standard Ustekinumab Dosage with Respective Adult Reference Populations Receiving the Approved Standard Dosage



Lines represent medians of the simulated values. Shaded regions represent the 5th – 95th percentile ranges.

A summary of simulated exposure parameters by population and body weight group is presented in Table 5. The results from simulations based on the final Pooled Paediatric and Adult Model also confirmed that the systemic exposures of ustekinumab in each of the paediatric weight groups were comparable to that in the reference adult population.

Table 5 Median (90% Prediction Intervals) of Model Predicted Exposure Parameters with the Final FBW Pooled Paediatric and Adult Model (run405) by Study Population

	AUC (µg·day/mL)	C_{peak} (µg/mL)	C_{trough} (µg/mL)
Pediatrics ≥6 to <12 yrs 20 to 60 kg; 0.75 mg/kg q12w	156 (73.7, 346)	4.71 (2.61, 9.07)	0.285 (0.0391, 1.13)
Pediatrics ≥6 to <12 yrs 60 to 100 kg; 45 mg q12w	173 (87.2, 365)	4.67 (2.56, 8.52)	0.451 (0.0996, 1.61)
Pediatrics ≥6 to <12 yrs; 0.75 mg/kg for body weight <60 kg and 45 mg for body weight ≥60kg SC q12w	159 (72.3, 341)	4.85 (2.51, 9.22)	0.285 (0.0385, 1.17)
Adolescents ≥12 to <18 yrs 20 to 60 kg; 0.75 mg/kg q12w	180 (82.6, 387)	5.03 (2.68, 9.65)	0.400 (0.0682, 1.41)
Adolescents ≥12 to <18 yrs 60 to 100 kg; 45 mg q12w	168 (71.7, 384)	4.51 (2.17, 9.10)	0.448 (0.0878, 1.56)
Adolescents ≥12 to <18 yrs; 0.75 mg/kg for body weight <60 kg and 45 mg for body weight ≥60kg SC q12w	174 (84.0, 362)	4.80 (2.56, 9.13)	0.411 (0.0852, 1.41)
Adults 60 to 100 kg; 45 mgq12w	148 (72.6, 323)	3.85 (2.01, 7.28)	0.429 (0.100, 1.43)

AUC, area under the serum ustekinumab concentration versus time curve over one dosing interval period of 12 weeks at steady-state Cpeak, peak serum ustekinumab concentration at steady state; Ctrough, trough serum ustekinumab concentration at steady state

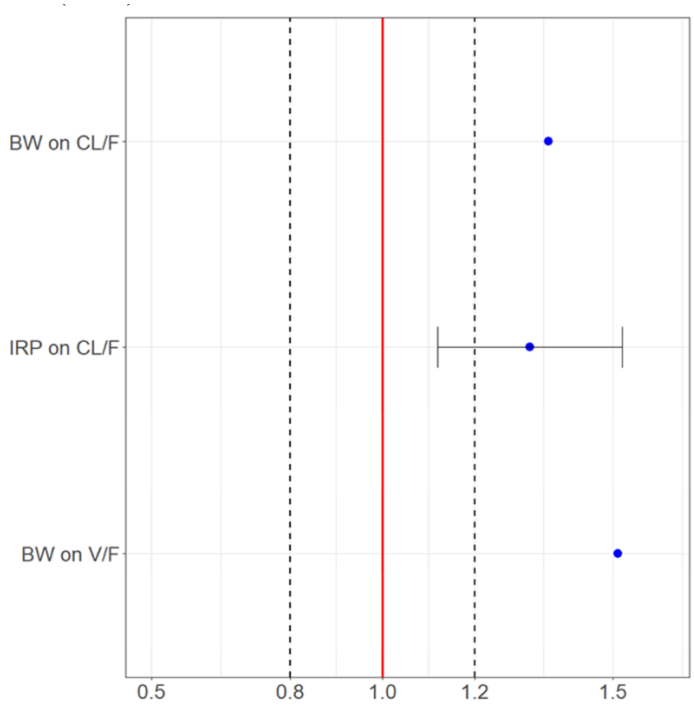
Special populations

Covariates affecting pharmacokinetics (PopPK analyses)

Pooled Paediatric PopPK Model

The CL/F estimates were 32% higher for subjects who were positive for antibodies to ustekinumab (IRP). Subjects at the upper (75th percentile, 68 kg) range of the observed weight were predicted to have 51% higher CL/F and 32% higher V/F values, respectively, than subjects at the lower (25th percentile, 45 kg) weight range. The impact of the covariates on the respective PK parameters in the final Pooled Paediatric Model is illustrated in Figure 13.

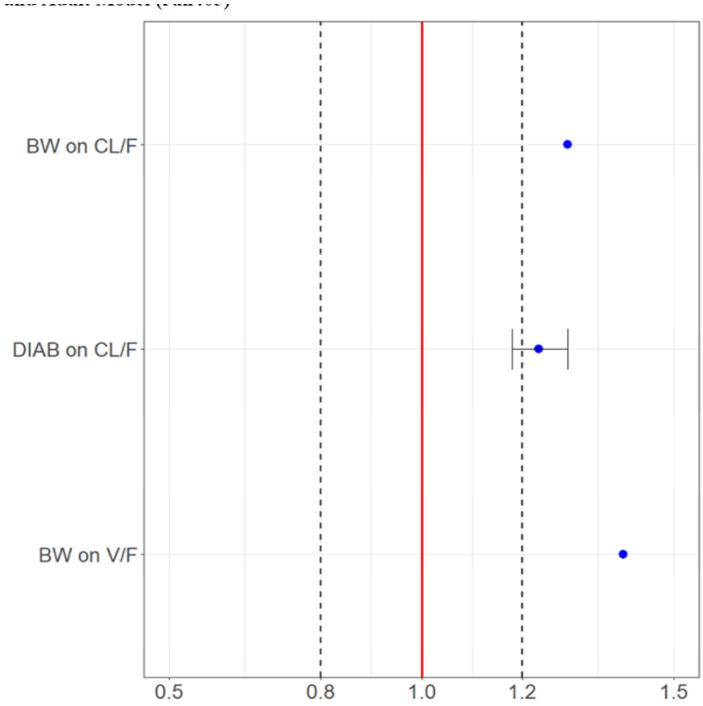
Figure 13 Effects of Covariates on the PopPK Parameters of Ustekinumab in the FBW Pooled Paediatric Model (run201)



Pooled Paediatric and Adult PopPK Model

The CL/F estimates were 23% higher for subjects who had diabetic comorbidity. Subjects at the upper (75th percentile, 104 kg) range of the observed weight were predicted to have 29% higher CL/F and 40% higher V/F values, respectively, than subjects at the lower (25th percentile, 74 kg) weight range. The impact of the covariates on the respective PK parameters in the final Pooled Paediatric Model is illustrated in Figure 14.

Figure 14 Effects of Covariates on the PopPK Parameters of Ustekinumab in the FBW Pooled Paediatric and Adult Model (run405)



2.4.3. Pharmacodynamics

Mechanism of action

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis through interruption of the Th1 and Th17 cytokine pathways, which is central to the pathology of this disease.

Primary and secondary pharmacology

Biomarker analysis (Study PSO3013)

Emerging evidence suggests that Th17 cytokines, a family of effector cytokines partly downstream of IL-23, are increased in lesional skin and blood of patients with psoriasis and respond to IL-23 targeted treatment.

In study PSO3013, the goal of the biomarker analysis was to evaluate the pharmacodynamics (PD) of ustekinumab by measuring levels of IL-17 and other inflammatory cytokines and aid in evaluating the pharmacodynamic-clinical response relationship.

The biomarker analytes in this analysis were: IL-17A, IL-17F, and IL-22, each measured in serum via the Erenna high-sensitivity immunoassay antibody-based platform.

There were 41 study participants with measurements at baseline for at least 1 of the 3 analytes, 39 at week 12, and 40 at week 52.

The set of healthy control serum samples that were run in parallel were not demographically matched to the samples from the paediatric population of CADMUS Jr, and thus only serve as a reference point for a non-psoriatic population (NHS). This NHS set represented 13 males and 11 females, with an age range of 19 to 76 years (average of 42.2 years).

Baseline biomarker comparisons

Summary statistics for the baseline biomarker profiles in the PSO3013 psoriasis study population and a healthy control cohort are presented in Table 6. Levels of each of the 3 cytokines were higher in the psoriasis samples compared to the non-psoriasis samples.

Table 6 Summary Statistics of Serum Biomarkers from Disease Baseline and Normal Healthy Control Samples.

	PSO GeoMean [pg/ml]	Number	Healthy Controls GeoMean [pg/ml]	Number	Geomean ratio	p-value
IL-17A	0.50	41	0.17	25	2.86	6.76E-08
IL-17F	1.52	41	0.67	25	2.27	0.002
IL-22	7.33	41	1.95	25	4.05	8.18E-06

Post-treatment comparisons

Differences in cytokine levels at pre-treatment and during the treatment interval were assessed using a mixed-effects model for repeated-measures analysis. IL-17A, IL-17F and IL-22 serum levels were consistently reduced during the treatment period compared with the pre-treatment samples, with reduction seen at both timepoints evaluated (weeks 12 and 52). Maximal reduction was at week 52 in all cases, although the effects were generally similar at week 12 timepoints. Comparison of analyte levels at week 12 and week 52 to those of the normal human serum (NHS) samples indicated that the difference seen with the baseline samples was no longer observed for IL-17F at week 12 or week 52, and was reduced for IL-17A and IL-22 at those timepoints (Table 7).

Table 7 Analysis of Pharmacodynamic (PD) Effects at Weeks 12 and 52 during Study Treatment.

	log2 ratio	Std. Error	DF	t-value	p-value	fold change
IL-17A						
Week 12 (vs baseline)	-0.843	0.195	76	-4.315	4.74E-05	-1.79
Week 52 (vs baseline)	-1.024	0.194	76	-5.268	1.24E-06	-2.03
IL-17F						
Week 12 (vs baseline	-1.391	0.249	75	-5.578	3.67E-07	-2.62
Week 52 (vs baseline)	-1.448	0.246	75	-5.881	1.06E-07	-2.73
IL-22						
Week 12 (vs baseline)	-0.855	0.256	74	-3.345	0.0013	-1.81
Week 52 (vs baseline)	-0.968	0.250	74	-3.869	0.0002	-1.96

2.4.4. PK/PD modelling

Exposure-Response relationship of observed serum ustekinumab concentrations and clinical efficacy in paediatric (≥6 to <12 years) subjects with psoriasis (PSO3013)

To explore the relationship between systemic exposure to ustekinumab and clinical efficacy (improvement in PGA and PASI), the proportions of subjects who achieved PGA cleared (0) or minimal (1), PGA cleared (0), PASI 75, or PASI 90 responses at Week 40 were evaluated with respect to observed steady-state trough serum ustekinumab concentration levels at Week 40.

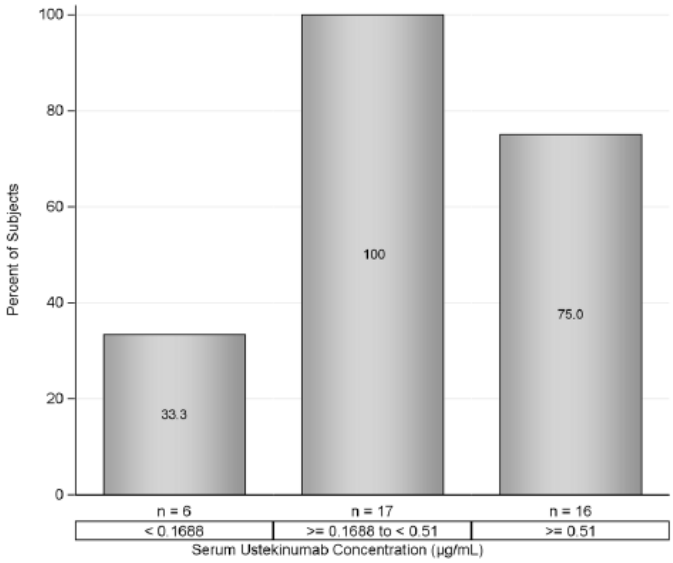
The steady-state trough serum ustekinumab concentrations at Week 40 were categorized into 3 different levels:

- BQL: <0.1688 µg/mL
- First quantifiable level: ≥0.1688 µg/mL to <0.51 µg/mL
- Second quantifiable level: ≥0.51 µg/mL

PGA responses

The proportion of subjects who achieved PGA scores of cleared (0) or minimal (1) response at Week 40 was higher in subjects with quantifiable serum ustekinumab concentrations at Week 40 when compared with subjects with BQL serum ustekinumab concentrations at Week 40 (33.3%; Figure 15). The PGA score of cleared (0) response at Week 40 also appeared to be associated with quantifiable steady-state trough serum ustekinumab concentration levels.

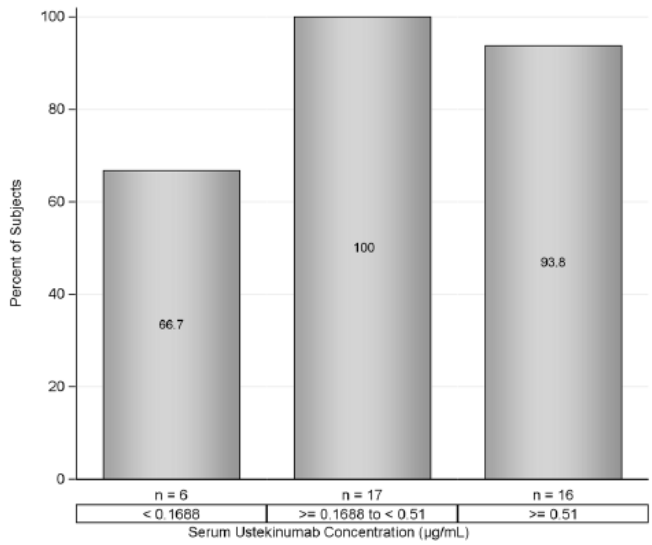
Figure 15 Percent of Subjects Achieving a PGA Score of Cleared (0) or Minimal (1) at Week 40 by Trough Serum Ustekinumab Concentrations at Week 40; Pharmacokinetics Analysis Set (Study CNTO1275PSO3013)



PASI responses

The proportion of subjects who achieved PASI 75 response at Week 40 was higher in subjects with quantifiable serum ustekinumab concentrations at Week 40 when compared with subjects with BQL concentrations at Week 40 (66.7%; Figure 16). The PASI 90 response at Week 40 also appeared to be associated with quantifiable steady-state trough serum ustekinumab concentration levels.

Figure 16 Percent of Subjects Achieving a PASI 75 Response at Week 40 by Trough Serum Ustekinumab Concentrations at Week 40; Pharmacokinetics Analysis Set (Study CNTO1275PSO3013)



Exposure-Response relationship of model-predicted serum ustekinumab concentrations and clinical efficacy in paediatric, adolescent and adult subjects with psoriasis

Graphical evaluations were performed to assess ER relationships for percentage of subjects who achieved PGA 0/1, PASI 75, and PASI 90 versus model-predicted serum ustekinumab concentration in tertile levels at Week 12 and Week 28.

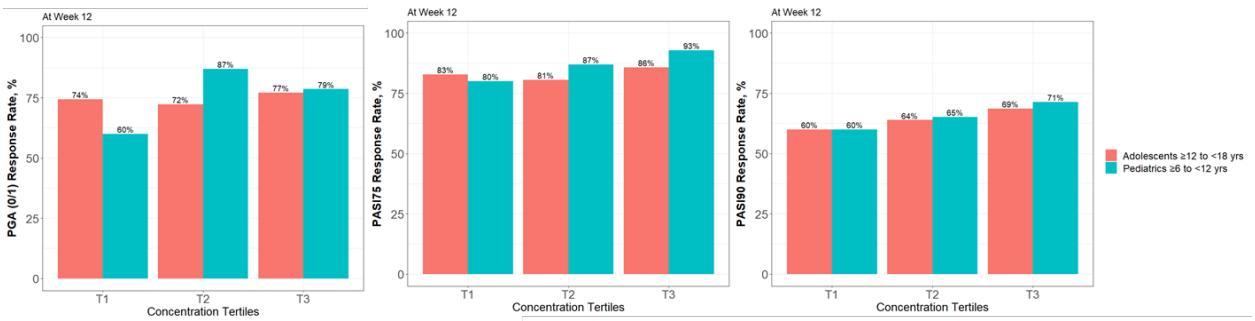
Using the final Pooled Paediatric PopPK Model, tertile levels of predicted concentrations in adolescent subjects (≥12 to <18 years of age) were determined, and the same tertile levels were applied to predicted concentrations in paediatric subjects (≥6 to <12 years of age), so that the clinical response rates could be compared directly with respect to the same exposure ranges.

Similar analyses were performed using the final Pooled Paediatric and Adult PopPK Model to compare the consistency of ER relationship between adults and the two paediatric age groups.

ER analysis between paediatrics (≥6 to <12 years) and adolescents (≥12 to <18 years)

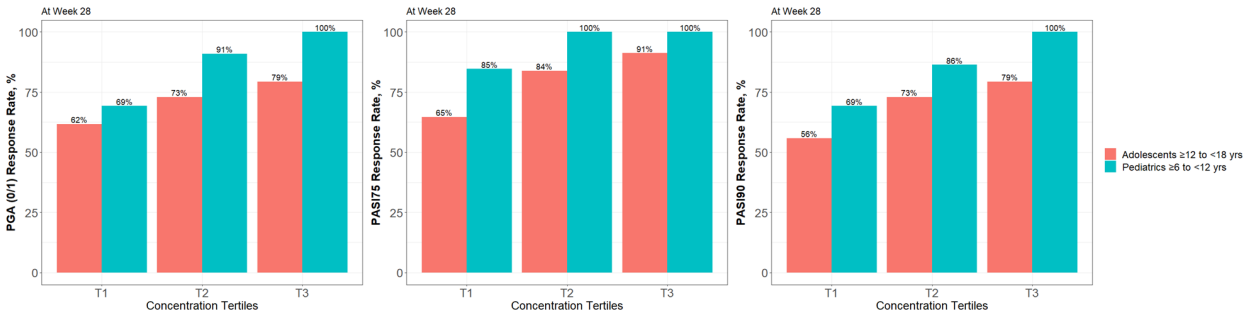
Regardless of the timepoint and clinical efficacy endpoint evaluated, the overall patterns of ER relationships were similar between paediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years of age(**Figure 17**, **Figure 18**), with higher model-predicted serum ustekinumab concentrations being associated with higher clinical response rates. Subjects with serum ustekinumab concentrations in the first tertile level had lower response rates when compared with those who had serum ustekinumab concentrations in the 2 higher tertile levels; these differences were more pronounced at Week 28. These results suggest that the exposure-response relationships are similar between paediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years of age with psoriasis, although paediatric subjects ≥6 to <12 years of age with psoriasis had slightly higher clinical efficacy as compared with the adolescent population.

Figure 17: Exposure-Response Relationships of PGA 0/1, PASI 75, or PASI 90 Responses by Model-Predicted Serum Ustekinumab Concentrations in Tertile Levels at Week 12 in Paediatric Subjects ≥6 to <12 Years of Age and Adolescent Subjects ≥12 to <18 Years of Age Receiving Ustekinumab Standard Dosage



The tertile levels of serum ustekinumab concentrations from CADMUS were ≥0.02 to ≤0.74, >0.74 to ≤1.46, and >1.46 to ≤4.73 µg/mL at Week 12; The numbers of paediatric subjects ≥6 to <12 years of age fell into each tertile level were 5, 23, and 14, respectively; The numbers of adolescent subjects ≥12 to <18 years of age fell into each tertile level were 35, 36, and 35, respectively.

Figure 18: Exposure-Response Relationships of PGA 0/1, PASI 75, or PASI 90 Responses versus Model-Predicted Serum Ustekinumab Concentrations in Tertile Levels at Week 28 in Paediatric Subjects ≥6 to <12 Years of Age and Adolescent Subjects ≥12 to <18 Years of age Receiving Ustekinumab Standard Dosage

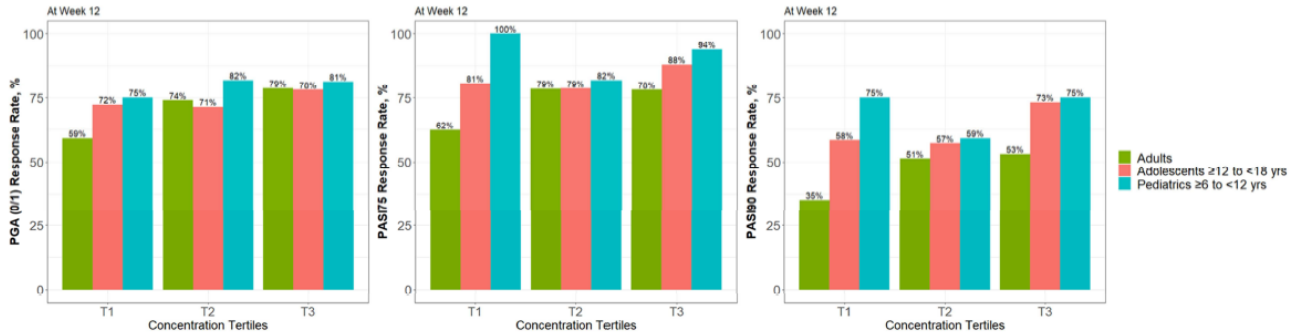


The tertile levels of serum ustekinumab concentrations from CADMUS were ≥0.01 to ≤0.28, >0.28 to ≤0.46, and >0.46 to ≤4.63 µg/mL at Week 28. The numbers of paediatric subjects ≥6 to <12 years of age fell into each tertile level were 13, 22, and 6, respectively; The numbers of adolescent subjects ≥12 to <18 years of age fell into each tertile level were 34, 37, and 34, respectively.

ER analysis between paediatrics (≥6 to <12 years), adolescents (≥12 to <18 years) and adults

Figure 19 and Figure 20 show that the overall patterns of ER relationships were comparable between paediatric subjects ≥6 to <12 years of age, adolescent subjects and adult subjects, with higher model-predicted serum ustekinumab concentrations being associated with higher clinical response rates. Consistent ER relationship was also confirmed between paediatric subjects, adolescent subjects and adults with psoriasis, although paediatric subjects ≥6 to <12 years of age with psoriasis had slightly higher clinical efficacy as compared with the adolescent and adult population.

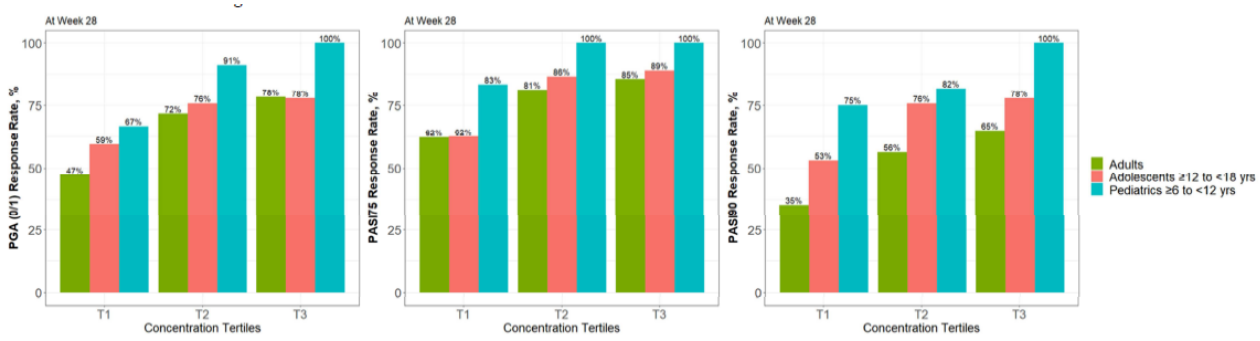
Figure 19 ER Relationships of PGA 0/1, PASI 75, or PASI 90 Responses versus Model-Predicted Serum Ustekinumab Concentrations in Tertile Levels at Week 12 in Paediatric Subjects ⩾6 to <12 Years of Age, Adolescent Subjects ⩾12 to <18 Years of Age and Adults Receiving Proposed Ustekinumab Standard Dosage



The tertile levels serum ustekinumab concentrations from CADMUS were ≥0.03 to ≤0.76, >0.76 to ≤1.39 and >1.39 to ≤23.0 µg/mL at Week 12. The number of pediatric subjects ≥6 to <12 years of age that fell into each tertile level was 4, 22, and 16, respectively; The number of adolescent subjects ≥12 to <18 years of age that fell into each tertile level was 36, 28, and 41, respectively; The number of adult subjects that fell into each tertile level was 619, 605 and 615, respectively.

Figure 20 ER Relationships of PGA 0/1, PASI 75, or PASI 90 Responses versus Model-Predicted Serum Ustekinumab Concentrations in Tertile Levels at Week 28 in Paediatric Subjects ⩾6 to

<12 Years of Age, Adolescent Subjects ⩾12 to <18 Years of Age and Adults Receiving Proposed Ustekinumab Standard Dosage



The tertile levels serum ustekinumab concentrations from CADMUS were (≥0.00 to ≤0.25), (>0.25 to ≤0.55) and (>0.55 to ≤18.0) µg/mL at Week 28. The number of pediatric subjects ≥6 to <12 years of age that fell into each tertile level was 12, 22, and 7, respectively; The number of adolescent subjects ≥12 to <18 years of age that fell into each tertile level was 32, 37, and 36, respectively; The number of adult subjects that fell into each tertile level was 468, 490 and 475, respectively.

2.4.5. Discussion on clinical pharmacology

The submission aimed to build on the bridge established for ustekinumab between adolescents and adults with psoriasis. Given that there is no known difference in the pathophysiology of psoriasis occurring in younger children (≥6 to <12 years of age) and adolescents, it was expected that younger children will have a similar clinical response to ustekinumab as adolescents. The proposed extension of the psoriasis indication to the younger paediatric age group is based primarily on data from study PSO3013. Population PK modeling and simulation were also employed to verify that the proposed dosage for younger paediatric patients (≥6 to <12 years of age) resulted in systemic drug exposure comparable to that seen in the adolescent population (≥12 to <18 years of age) and led to similar exposure-response relationships.

Bioanalytical methods

All bioanalytical methods were previously summarised in the plaque psoriasis CADMUS submission for adolescents and the more recent ulcerative colitis submission. The methods follow the regulatory guidance and requirements.

Study PSO3013

In terms of PK and immunogenicity, the methodology of the study is acceptable. A comparison of ustekinumab concentrations by body weight showed similar ustekinumab concentrations for subjects with body weight <60 kg treated with the 0.75 mg/kg dosage and subjects with body weight ≥60 kg to ≤100 kg treated with the fixed 45 mg dosage.

Median trough serum ustekinumab concentrations were slightly lower but generally comparable with the adolescent psoriasis study (PSO3006). Furthermore, the distributions of ustekinumab concentrations were comparable between study PSO3013 and study PSO3006 in each weight range, although the mean and median serum ustekinumab concentrations in study PSO3013 were numerically lower than those in study PSO3006. However, subject numbers were limited.

The overall incidence of antibodies through week 56 in the paediatric trial (PSO3013) was reasonably low (9.5%) but slightly higher than adolescent subjects overall (6.8%). The comparison of antibody incidence between paediatric and adolescent subjects is, however, limited by the low patient numbers and the different cut points for false-positive rate used for the two studies. None of the 4 paediatric subjects who were positive for antibodies to ustekinumab had any injection-site reactions after development of antibodies to ustekinumab. Two of the 4 antibody-positive paediatric subjects achieved PGA scores of cleared (0) or minimal (1) and PASI 75 responses at Week 52.

Population PK analyses

The methods used in the PopPK analyses are acceptable. Both the final Pooled Paediatric Model, and the final Pooled Paediatric and Adult Model, were based on a previously developed PopPK model in adolescent subjects with psoriasis. Body weight effects on both apparent clearance and apparent volume of distribution were included in the structural models, with exponents fixed to 0.75 and 1, respectively, in the final models, which is supported.

For the final Pooled Paediatric Model, all PK parameters were estimated with good precision, with all %RSEs <10% except for Ka with a %RSE of 30%. The IIV was also estimated with good precision (%RSE <15%). Bayesian shrinkage of CL/F and V/F was reasonably low (<30%) and bootstrap parameters were consistent with final PopPK model parameters. Along with body weight, the covariate Immune Response Positive was included in the final model given the potential for clinical relevance. However, inclusion of this covariate resulted in negligible reduction in IIV of CL/F (reduced by 0.3%). The GOF plots showed a slight trend for under-prediction at higher concentrations. The VPCs show that the model describes central tendency and variability of observed concentrations reasonably well for both half-standard dosage and standard dosage.

For the Pooled Paediatric and Adult Model, all PK parameters estimated were in good precision, with all %RSEs <10%. Bayesian shrinkage was reasonably low (<20%) and bootstrap parameters were consistent with final PopPK model parameters. Along with body weight, diabetic comorbidity was found to be a clinically relevant covariate on clearance and included in the final model. However, inclusion of this covariate resulted in negligible reduction in IIV of CL/F (reduced by 0.8%). There is a slight trend for under-prediction in the GOF plots, particularly at higher concentrations. The VPCs show that the model describes the data adequately.

Simulations by population and body weight groups showed that exposures in paediatric subjects with psoriasis receiving the proposed dosage of ustekinumab were generally comparable to adolescent and adult subjects with psoriasis receiving the approved standard dosage. This provides support for the proposed dosage regimen for paediatric subjects (6-12 years) with psoriasis.

According to the Pooled Paediatric PopPK Model, clearance of ustekinumab is 32% higher in paediatric subjects with antibodies to ustekinumab. This is consistent with results obtained in adults using the original Adult PopPK Model. Although paediatric subjects positive for antibodies to ustekinumab showed higher clearance of ustekinumab, antibody positivity did not preclude a clinical response to ustekinumab.

According to the Pooled Paediatric and Adult PopPK Model, clearance of ustekinumab is 23% higher for patients with diabetic comorbidity. However, none of the subjects in the paediatric and adolescent psoriasis studies had diabetes as a comorbidity. Therefore, the higher clearance of ustekinumab was driven by the data from adult subjects with a comorbidity of diabetes.

Biomarker analysis

The relevance of the control group (NHS, normal human serum) used in the biomarker sub-study of CADMUS Jr is not clear as the mean age of those in the control group was 42.2 years. Baseline levels of IL-17A, IL-17F and IL-22 in children aged 6-12 years cannot be assumed to be the same as those in an adult population. It can be concluded that in patients with moderate to severe plaque psoriasis aged 6-12 years, treatment with ustekinumab appeared to reduce circulating levels of IL-17A, IL-17F and IL-22 by week 12. This reduction was maintained to week 52 with ongoing ustekinumab treatment.

Exposure-response analyses

For the ER analysis using observed serum ustekinumab concentrations, the PGA and PASI responses appeared to be associated with quantifiable steady-state trough ustekinumab levels in paediatric subjects (≥6 to <12 years) with psoriasis. The proportion of subjects who achieved PGA 0/1, PGA 0, PASI 75, and

PASI 90 responses at Week 40 was higher in subjects with quantifiable trough serum ustekinumab concentrations at Week 40 when compared with subjects with BQL trough ustekinumab concentrations at Week 40.

Graphical evaluations were also performed to assess ER relationships using model-predicted serum ustekinumab concentrations. These generally showed that the proportion of subjects who achieved clinical responses (PGA 0/1, PASI 75, or PASI 90) increased with increasing ustekinumab concentrations. Overall, the ER relationships appear to be similar between paediatric (≥6 to <12 years), adolescent (≥12 to <18 years), and adult subjects with psoriasis.

2.4.6. Conclusions on clinical pharmacology

The pharmacokinetic data collected in the paediatric study is considered adequate to describe the PK in paediatric patients aged ≥6 years and <12 years and to compare to the PK data available from the adolescent and adult phase III studies. The exposure in paediatric subjects ≥6 to <12 years of age at the proposed standard dosage results in acceptably comparable exposure data to that seen in adolescents and adults with the approved dosage.

2.5. Clinical efficacy

2.5.1. Main study

Study PSO3013 (CADMUS Jr): 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.

Methods

Trial design

Open-label multi-center study conducted at multiple sites in Europe, US, and Canada that evaluated the safety, efficacy, and PK of ustekinumab in paediatric subjects ≥6 to <12 years of age.

Visits were every 4 weeks (q4w) through Week 16, then q12w through Week 52. Efficacy assessments were collected through Week 52 and subjects had a final safety follow-up at Week 56. A database lock (DBL) occurred after all subjects completed their Week 56 visit.

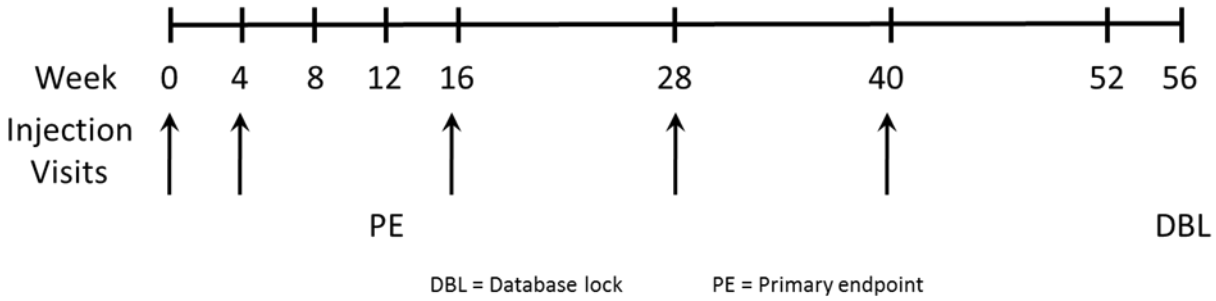
Following completion of the Week 52 visit, subjects who had a beneficial response from ustekinumab treatment as determined by the investigator, and who had not yet reached the age of 12 years or older in countries where marketing authorization for ustekinumab has been granted for the treatment of psoriasis in adolescent patients ≥12 to <18 years of age, were permitted to enter a long-term extension (LTE) of the study. Subjects are allowed to continue participation in the LTE until they reach Week 264 or:

- 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.

The LTE was ongoing during the evaluation procedure.

A diagrammatic representation of the main study design is presented in **Figure 21**.

Figure 21 Study Design of CNTO1275PSO3013 (Paediatric Subjects ≥6 to <12 years of age)



Study participants

Main inclusion criteria

Paediatric subjects ≥6 to <12 years of age were eligible for this study if they had moderate to severe plaque-type psoriasis with or without PsA as defined by PASI ≥12, PGA ≥3, and BSA involvement ≥10%. Subjects were also required to be candidates for phototherapy or systemic treatment of psoriasis (either naïve or history of previous treatment) or had psoriasis not adequately controlled by topical therapies, specifically, those subjects who, in the opinion of the investigator, were inadequately controlled with topical therapy after an adequate dose and duration of therapy.

Main exclusion criteria

Subjects were not to be enrolled into this study if they had:

- nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular) or
- drug-induced psoriasis (eg, a new onset of psoriasis or anexacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
- used topical medications/treatments that could affect psoriasis or PASI evaluation within 2 weeks of first administration of study agent, or
- received phototherapy or any systemic medications/treatments that could affect psoriasis or PASI evaluation within 4 weeks of the first administration of study agent.
- received any systemic immunosuppressants within 4 weeks of the first administration of study agent;
- received any biologic agent within the previous 3 months or 5 times the t1/2 of the agent (whichever was longer).
- used any therapeutic agent targeted at reducing interleukin-12 or interleukin-23.

Subjects with a history of the following were not eligible for enrolment into this study:

- chronic or recurrent infectious disease; serious infection;
- latent or active granulomatous infection (including tuberculosis [TB]);
- a nontuberculous mycobacterial infection or systemic opportunistic infection;
- an immune deficiency syndrome;
- or a lymphoproliferative disease;
- any known malignancy or a history of malignancy; known to be infected with human immunodeficiency virus, hepatitis B, or hepatitis C.

Treatments

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

The use of any topical corticosteroid preparations for the treatment of psoriasis was prohibited within 2 weeks prior to the first study agent administration and during the first 12 weeks of the study period.

After the Week 12 evaluation, low potency topical corticosteroids could be used on the face and groin only. Acceptable low potency corticosteroids included 2.5% concentration or less of hydrocortisone cream or equivalent.

Other non-corticosteroid topical therapies that could affect psoriasis or the PASI evaluation, such as tar, anthralin, calcipotriene, tazarotene, methoxsalen, picrolimus, or tacrolimus, were prohibited through Week 52 of the study and, as with topical corticosteroids, were to be discontinued 2 weeks prior to the first study agent administration. Through Week 52, the only allowable concomitant treatments for psoriasis were shampoos (containing tar or salicylic acid only) and topical moisturizers.

Objectives

Primary Objective
To evaluate the efficacy and safety of ustekinumab in paediatric subjects ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis.

Secondary Objectives
- Evaluate the PK of ustekinumab in paediatric subjects ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis.
- Evaluate the effect of ustekinumab on the dermatologic health-related quality of life in paediatric subjects ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis.
- Evaluate the immunogenicity of ustekinumab in paediatric subjects ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis.

Outcomes/endpoints

Primary efficacy endpoint

The primary endpoint of the study was the proportion of subjects with a PGA of cleared (0) or minimal (1) at Week 12. Subjects who met treatment failure criteria prior to Week 12 were considered non-responders at Week 12. In addition, subjects who had a missing PGA score at Week 12 were considered as not achieving the primary endpoint at Week 12.

Secondary efficacy endpoints

The major secondary efficacy endpoints for this study were:

- The proportions of subjects who achieved a ≥75% improvement in PASI from baseline at Week 12.
- The change in CDLQI from baseline at Week 12.
- The proportions of subjects who achieved a ≥90% improvement in PASI from baseline at Week 12.

Other efficacy endpoints

- The proportions of subjects achieving a PGA score of cleared (0), the proportion of subjects achieving a PGA score of cleared (0) or minimal (1), and the proportion of subjects achieving a PGA score of mild or better (≤2) over time.
- The proportions of subjects who achieve PASI 50, PASI 75, PASI 90, and PASI 100 responses over time.
- The percent improvement from baseline in PASI over time.
- The change from baseline in CDLQI over time.
- The proportion of subjects with CDLQI = 0 or 1 over time.

Sample size

The planned total sample size was approximately 40 subjects. A total of 44 subjects were enrolled and treated in this study.

The sample size of 40 was determined based on both efficacy and PK assessments. The primary objective was to evaluate the efficacy and safety of ustekinumab for paediatric subjects aged ≥6 to <12 years with moderate to severe chronic plaque psoriasis and 1 of the major secondary objectives was to evaluate the PK of ustekinumab for this population. To support these objectives, a sample size of 40 subjects was chosen. For the efficacy assessment, no formal hypothesis testing was performed. However, the observed response rates and its 95% confidence interval of PGA of cleared (0) or minimal (1) at Week 12 were provided. A sample size of 40 provides a 95% confidence interval [50%, 80%], if the observed response rate is 65%.

Randomisation

This was an open-label study; therefore, all subjects were assigned to receive active study drug (ustekinumab).

Blinding (masking)

As this was an open-label study, all subjects were assigned to receive active study drug (ustekinumab) and blinding of study drug was not applicable. However, a blinded efficacy evaluator was used to assess efficacy during the main study.

Statistical methods

No formal hypothesis testing was performed. Efficacy and safety of ustekinumab in paediatric subjects ≥6 through <12 years of age with moderate to severe chronic plaque psoriasis was evaluated using descriptive statistics.
Two-sided exact 95% confidence intervals (CI) were provided for the primary and major secondary endpoints. Subjects who discontinued study treatment due to lack of efficacy, an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could affect their psoriasis were considered as treatment failures.

In this study, the efficacy analyses were to be performed on the full analysis set, which is defined as all enrolled and treated subjects who received at least 1 injection of ustekinumab (partial or complete) during the study. The full analysis set was used for all primary and secondary efficacy analyses. In addition, the primary endpoint was also to be performed using the per protocol analysis set.

Missing data imputation
For most of the efficacy analyses (e.g. over time summaries), after the treatment failures, no imputation was performed for missing data (e.g. lost to follow-up, missed study visit) and the values remained as missing except for the following:

The dichotomous endpoints at Week 12:

- PGA score of cleared (0), cleared (0) or minimal (1), and mild or better (≤ 2);
- PASI 100, PASI 90, PASI 75, and PASI 50 responses;
- CDLQI of 0 or 1.

For these types of endpoints, subjects with missing PGA score, PASI score, PASI component, or CDLQI at Week 12 were considered as not achieving the respective endpoints at Week 12.

Sensitivity analyses
To assess the robustness of the primary endpoint analysis result, the following two sensitivity analyses were conducted.

Sensitivity Analysis 1
For subjects who had a missing PGA score at Week 12, the score was not imputed. That is, the analysis was performed using observed data, after treatment failure rules. Its two-sided exact 95% confidence intervals (CI) was provided.

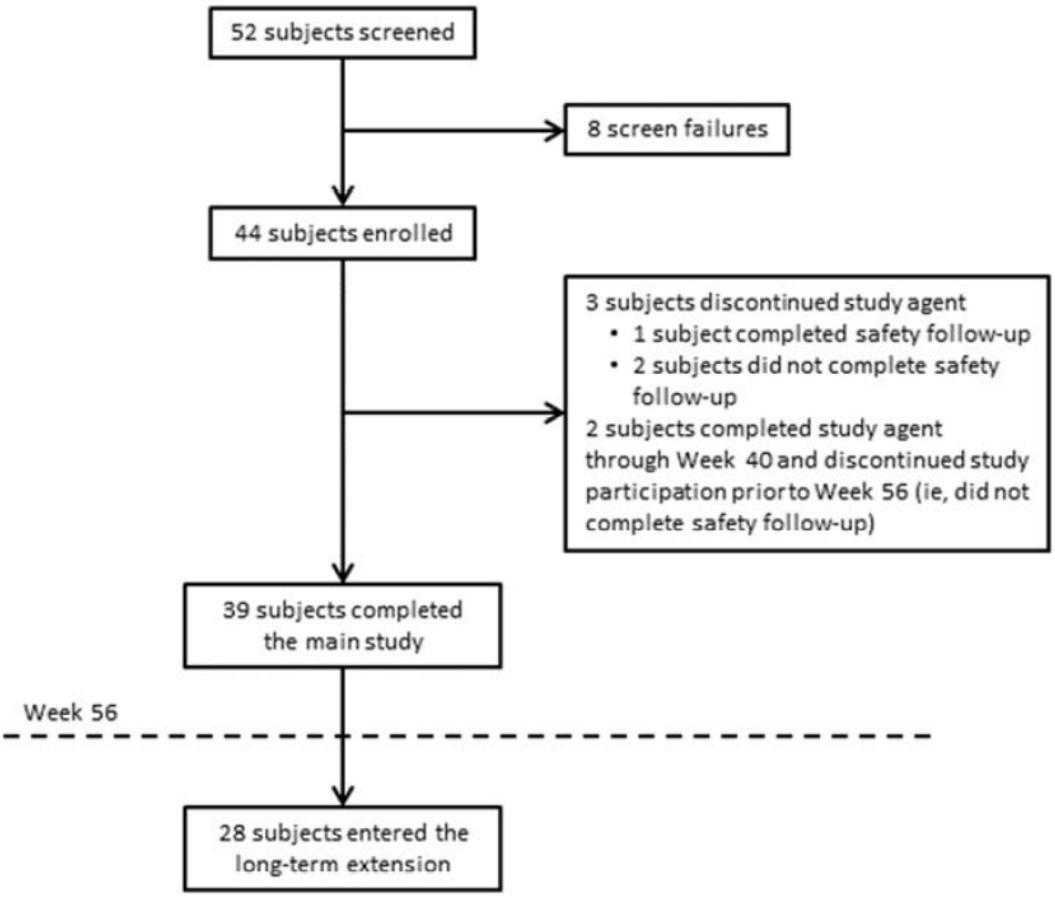
Sensitivity Analysis 2
The second sensitivity analysis was performed by using multiple imputations (MI), after applying treatment failure rules. The intermittent missing PGA score through Week 12 was imputed using the Markov Chain Monte Carlo (MCMC) algorithm with 200 imputed data sets and seed = 123 to make the missing data pattern monotone. The PGA score of cleared (0) or minimal (1) responses was then derived based on the imputed scores at or before Week 12. The remaining missing data of the PGA score of cleared (0) or minimal (1) was imputed with monotone logistic regression with baseline PGA score and PGA response status at each visit in the model with one imputed dataset and seed = 789 to fill in the remaining missing items in each of the 200 copies of datasets. Its 95% CI was also provided under the normal approximation assumption.

Results

A total of 44 subjects were enrolled and treated in this study.

Participant flow

The disposition of subjects through Week 56 is presented below:



Recruitment

The 44 enrolled subjects were from 7 countries as follows: Belgium (2 sites; 4 subjects); Canada (1 site; 2 subjects); Germany (4 sites; 7 subjects); Hungary (4 sites; 10 subjects); Netherlands (1 site; 1 subject); Poland (3 sites; 12 subjects); and United States (4 sites; 8 subjects).

Conduct of the study

Amendments to the protocol

There was one major global amendment to the protocol in May 2017. The protocol was modified to add the LTE to allow paediatric subjects who have demonstrated clinical benefit through Week 52 of the main study to continue receiving ustekinumab. Major changes included the addition of a Time and Events Schedule for the LTE, additional serum samples for safety monitoring, and additional efficacy assessments.

Protocol deviations

Major protocol deviations (MPDs) were protocol deviations that were considered to have the potential to impact subjects' safety or well-being, or the integrity and/or results of the trial. Subjects with major protocol deviations were identified prior to database lock and summarised by the following categories for the full analysis set: entered but did not satisfy study entry criteria, developed withdrawal criteria but not

withdrawn, received disallowed concomitant treatment, received a wrong treatment or an incorrect dose, and other.
Through Week 56, 3 (6.8%) subjects had 1 or more Major Protocol Deviations. All 3 subjects with major protocol deviations were under the category of "entered the study but did not meet an eligibility criterion". Two subjects had PASI scores below 12 at Week 0 prior to their first administration of study drug and were discontinued from the study after 1 dose of study agent. One subject did not have hepatitis B testing performed during the screening period, but tested negative in the subsequent visit and continued in the study.

Through Week 56, 1 subject received a protocol-prohibited concomitant treatment that met the definition of a treatment failure (methylprednisolone aceponate). This subject was considered to be a treatment failure from the time of use of the prohibited medicine onward, as pre-specified by the treatment failure rules.

The major protocol deviations identified in this study did not substantially affect subject safety or the integrity of the study. Specific deviations were addressed at an individual site level as well as through study wide communications. Finally, subjects with deviations to concomitant medicine were identified as treatment failures from the time of use onward.

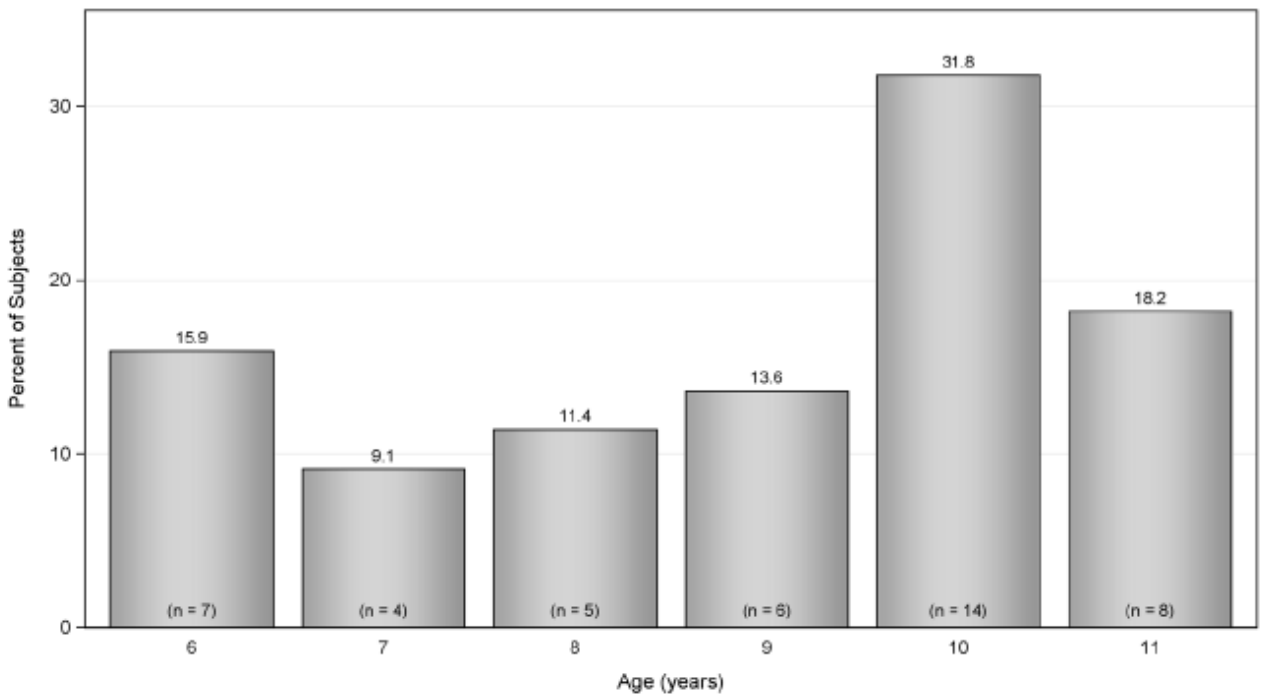
Interim analysis and data monitoring

There was no interim analysis performed and no Data Monitoring Committee for this study.

Baseline data

The study population included a majority of female subjects (61.4%) and mostly white subjects (90.9%). The median body weight was 33.3 kg, with the majority of subjects (90.9%) having a body weight of <60 kg. The median BMI was 18.0 kg/m2. The median age was 9.5 years, with 50.0% of subjects <10 years of age. All ages across the age range (≥6 to <12 year of age) were represented in the study population.

Figure 22 Distribution of Age (years) at Baseline; Full Analysis Set (Study CNTO1275PSO3013)



The median age at onset of disease was 6.0 years. The median duration of psoriasis was 2.9 years. The median percent of BSA involved was 18.0%. The majority of subjects (65.9%) had PGA scores of 3

(moderate), with 34.1% of subjects having a PGA score of marked or severe. The median PASI score was 16.1. The median CDLQI score was 7.0 (representing a moderate impact of psoriasis on quality of life). A total of 61.4% of the patients had a family history of psoriasis and 2.3% had or have Psoriatic Arthritis.

Prior psoriasis treatments were the followings:

- Topical agents: 97.7%
- Phototherapy (PUVA or UVB): 34.1%
- Non-biologic systemics (PUVA, MTX, cyclosporine, acitretin, apremilast, or tofacitinib): 18.2%
- Biologics (etanercept, infliximab, adalimumab, alefacept, efalizumab, briakinumab, secukinumab, ixekizumab, or brodalumab): 4.5%
- Non-biologic systemics or phototherapy: 43.2%

Numbers analysed

The efficacy analyses were performed on the full analysis set, which was defined as all enrolled and treated subjects who received at least 1 injection of ustekinumab (partial or complete) during the study (n=44). The full analysis set was used for all primary and secondary efficacy analyses. In addition, the primary endpoint was also analysed using the per protocol analysis set (n=42) which excluded subjects who did not meet specific inclusion or exclusion criteria, did not complete all scheduled ustekinumab administrations, or had more exposure than stipulated by the protocol.

Outcomes and estimation

A total of 44 subjects received at least 1 dose of study agent during the study. The mean number of ustekinumab administrations received at Week 40 was 4.8 administrations and the median total dose was 125.6 mg.

Primary endpoint

The primary endpoint in the pivotal paediatric study (CADMUS Jr) was the proportion of subjects who achieved a PGA 0/1 score at Week 12. At Week 12, the proportion (95% confidence interval [CI]) of subjects who achieved a PGA 0/1 score was 77.3% (62.2%; 88.5%) (Table 8).

Sensitivity analyses

Two sensitivity analyses were conducted to assess the robustness of the primary endpoint. Results in all 2 sensitivity analyses were similar to the main analysis.

Major secondary endpoints

At Week 12, the proportion (95% CI) of subjects who were PASI 75 responders was 84.1% (69.9%; 93.4%), the mean change in CDLQI was -6.3 (-8.29; -4.28), and the proportion of subjects who were PASI 90 responders was 63.6% (47.8%; 77.6%) (Table 8).

Other secondary endpoints

Among other secondary endpoints at Week 12, 38.6% of subjects achieved a PGA score of cleared (0) (PGA 0), 34.1% of subjects were PASI 100 responders, and 61.5% of subjects who had CDLQI >1 at baseline achieved CDLQI 0/1 (Table 8).

Table 8: Summary of Key Efficacy Endpoints at Week 12; Study CNTO1275PSO3013	
	Ustekinumab Standard Dosage
Analysis set: Full analysis set	44
Primary Endpoint	
Number of subjects who achieved a PGA score of cleared (0) or minimal (1)	34 (77.3%)
95% confidence interval	(62.2%; 88.5%)
Major Secondary Endpoint Analyses	
PASI 75 responders	37 (84.1%)
95% confidence interval	(69.9%; 93.4%)
Mean change from baseline in CDLQI score [a]	-6.3
95% confidence interval	(-8.29; -4.28)
PASI 90 responders	28 (63.6%)
95% confidence interval	(47.8%; 77.6%)
Other Secondary Endpoint Analysis	
Number of subjects who achieved a PGA score of cleared (0)	17 (38.6%)
95% confidence interval	(24.4%, 54.5%)
PASI 100 responders	15 (34.1%)
95% confidence interval	(20.5%, 49.9%)
Subjects with CDLQI>1 at baseline	39
Subjects with CDLQI of 0 or 1	24 (61.5%)
95% confidence interval	(44.6%; 76.6%)

Abbreviations: CDLQI=Children's Dermatology Life Quality Index; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment
[a]Sample size for CDLQI endpoint at Week 12 was 42 subjects.

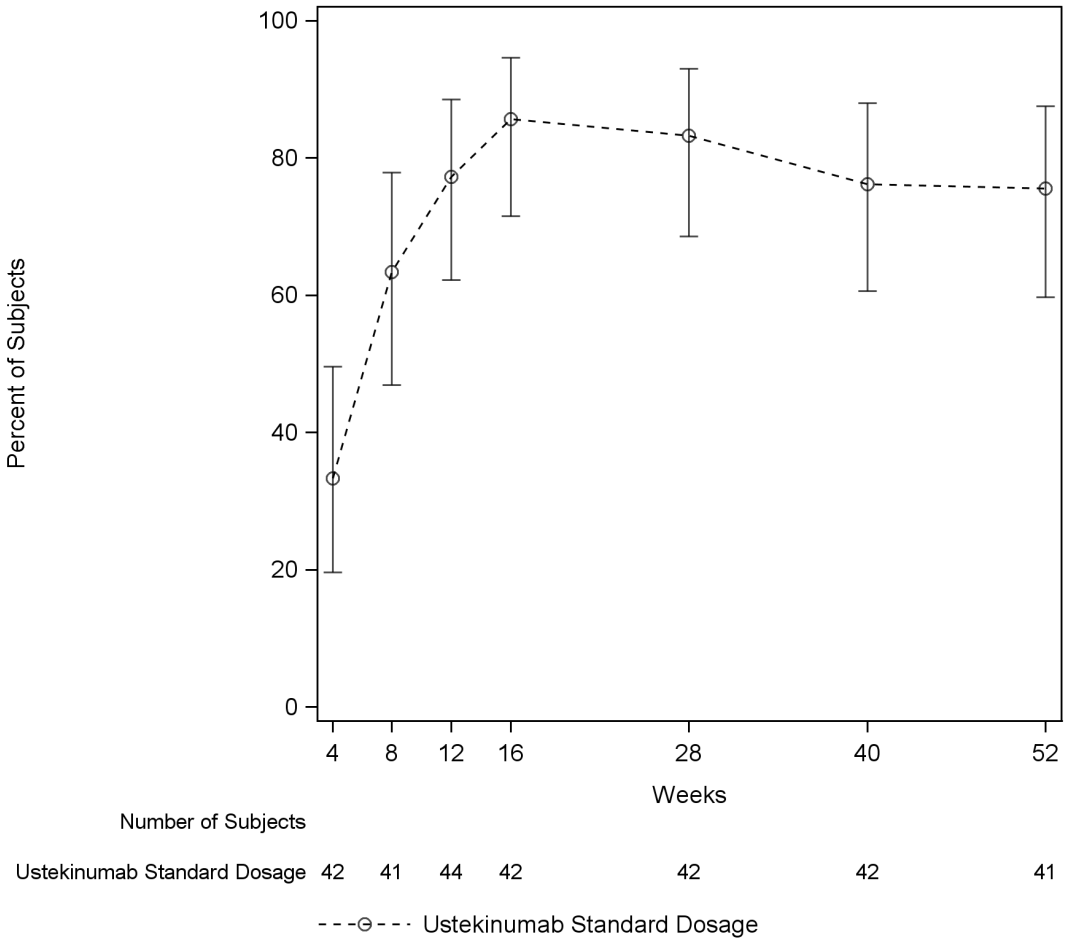
Physician's Global Assessment 0/1 and PASI 75 responses at Week 12 were generally consistent across subgroups defined by baseline demographic features, psoriasis disease characteristics, and psoriasis medication history.

Efficacy through Week 52

Maintenance of efficacy through Week 52 was shown on PGA score 0/1 (Figure 23**), PASI 75 response (Figure** 24**), PASI 90 response (**

Figure 25), PASI 100 response (Figure 26) and change from baseline in CDLQI score (Figure 27).

Figure 23: Percent of Subjects Achieving a PGA Score of Cleared (0) or Minimal (1) Through Week 52 by Visit; Full Analysis Set (Study CNTO1275PSO3013)



Note: 95% confidence intervals were based on exact method.

Figure 24: Percent of Subjects Achieving a PASI 75 Response Through Week 52 by Visit; Full Analysis Set (Study CNTO1275PSO3013)

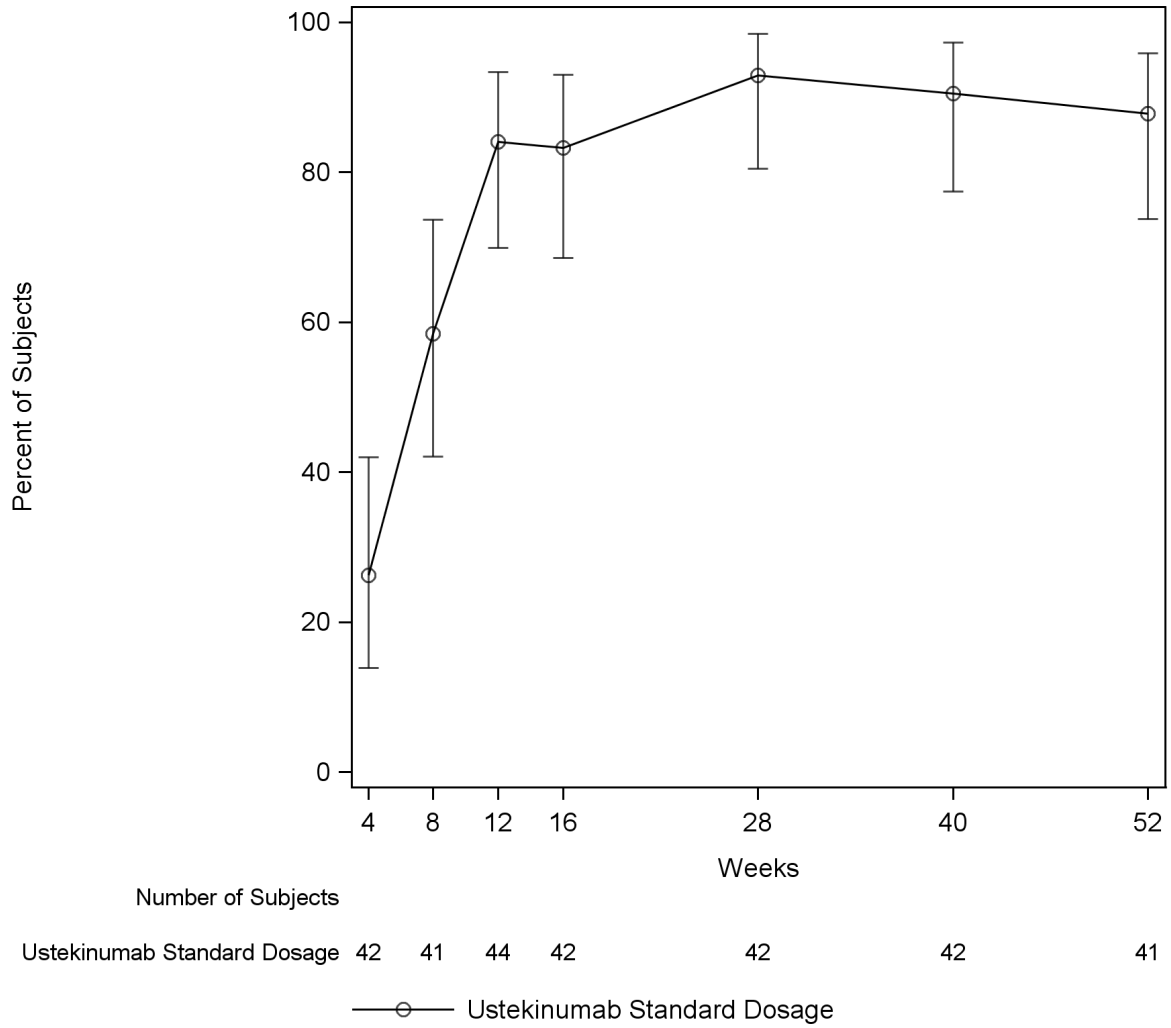


Figure 25:**Percent of Subjects Achieving a PASI 90 Response Through Week 52 by Visit; Full Analysis Set (Study CNTO1275PSO3013)**

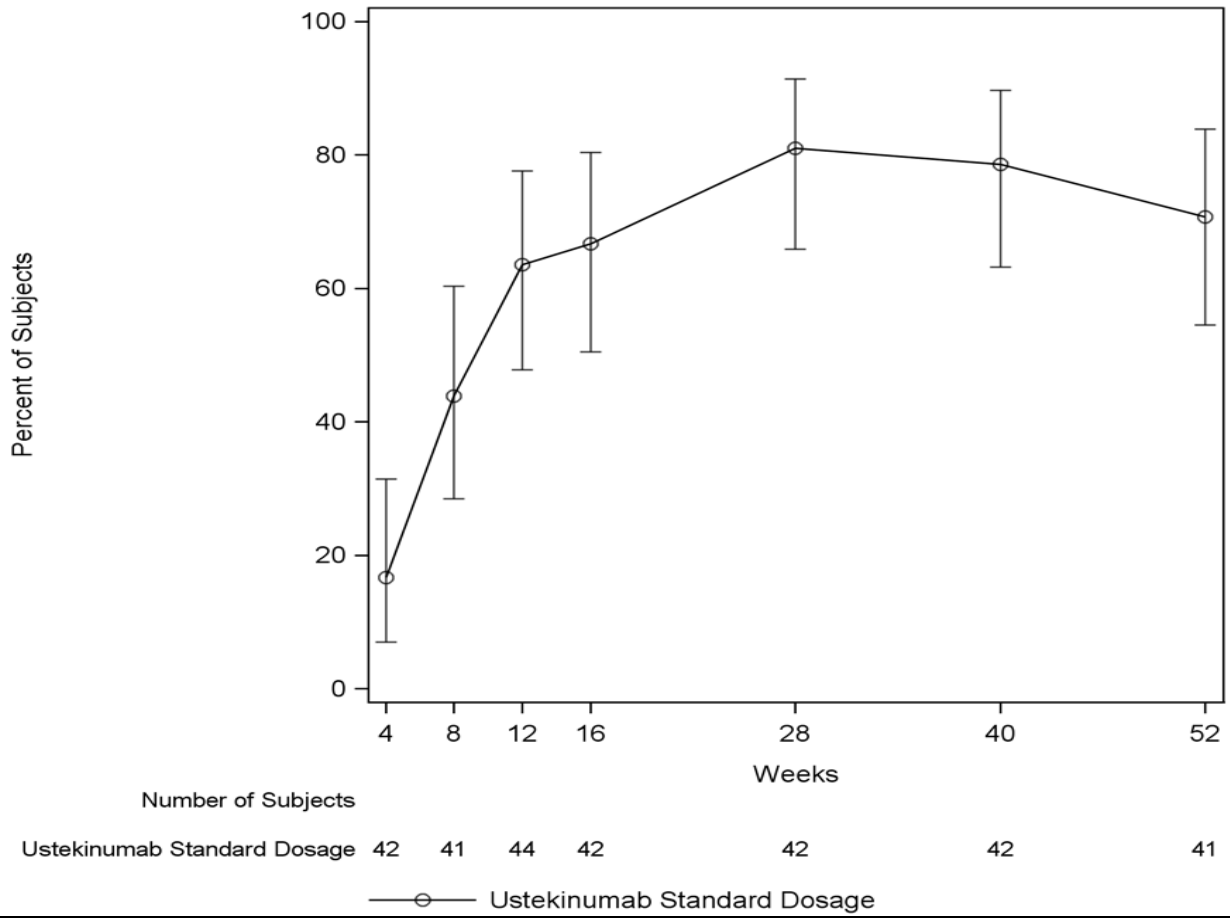
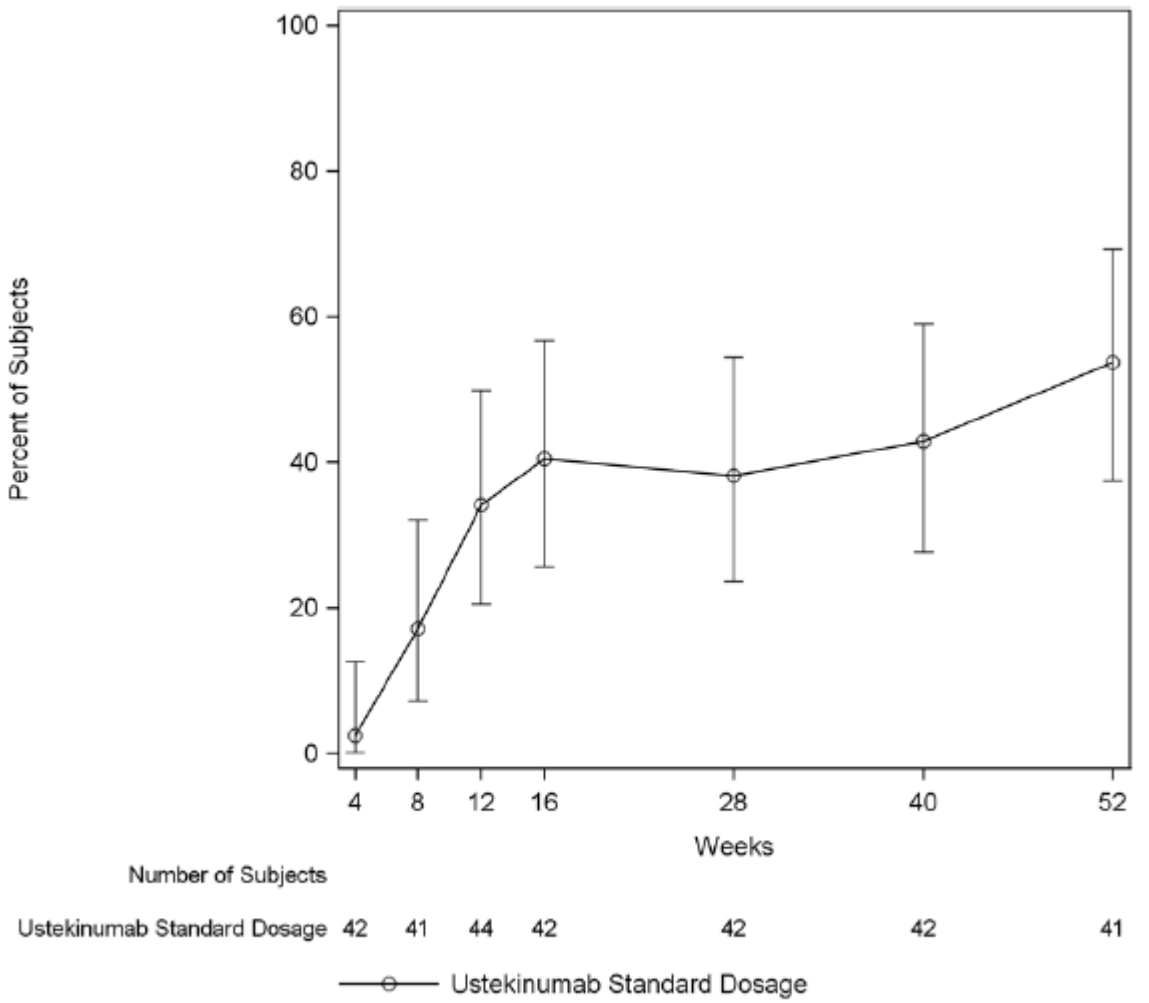


Figure 26 Percent of Subjects Achieving a PASI 100 Response Through Week 52 by Visit; Full Analysis Set (Study CNTO1275PSO3013)



Note: 95% confidence intervals were based on exact method.

Figure 27: Summary of Change From Baseline in CDLQI Score at Week 4, Week 12, Week 28 and Week 52 by Visit. Full Analysis Set. CADMUS Jr.

	Ustekinumab Standard Dosage
Analysis set: Full analysis set	44
Week 4	
N	42
Mean (SD)	-4.1 (4.88)
Median	-3.0
Range	(-16; 6)
IQ range	(-6.0; -1.0)
Week 12	
N	42
Mean (SD)	-6.3 (6.43)
Median	-6.0
Range	(-27; 7)
IQ range	(-10.0; -2.0)
Week 28	
N	42
Mean (SD)	-6.6 (5.79)
Median	-6.0
Range	(-27; 0)
IQ range	(-9.0; -2.0)
Week 52	
N	41
Mean (SD)	-6.4 (6.10)
Median	-5.0
Range	(-27; 1)
IQ range	(-10.0; -2.0)

Persistence of efficacy

The efficacy results in PSO3013 demonstrate that the weight-based standard dosage of ustekinumab resulted in efficacy that was generally maintained through 1 year in the treatment of psoriasis in paediatric subjects ≥6 to <12 years of age. However, there appeared to be a slight waning of efficacy from week 28 onwards. This apparent variability due to small sample size could have led to the fluctuations in results for certain endpoints seen up to and at week 52 (last dose was at week 40 for the primary PSO3013 study).

Duration of Response after Discontinuation of Therapy

The study design of PSO3013 did not allow for an assessment of response after discontinuation from therapy. However, the duration of response after discontinuation and retreatment after disease recurrence was extensively studied in the adult psoriasis study C0743T08.

In the C0743T08 study, the duration of response and recurrence of psoriasis were evaluated in 2 subpopulations of subjects who were PASI responders at Week 40:

- Subjects randomized at baseline to ustekinumab
- Subjects in the placebo → 45 mg and placebo → 90 mg groups

These subjects were withdrawn from therapy at Week 40. After withdrawal from therapy at Week 40, evidence of psoriasis recurrence emerged by the first visit after withdrawal of therapy, ie, by Week 44. PASI 75 response rates progressively declined over time, and the rates of loss of response were generally comparable in all groups. Subjects withdrawn from therapy were followed until loss of therapeutic effect (loss of ≥50% of their Week 40 PASI improvement).

While evidence of psoriasis recurrence began to emerge by 4 weeks after therapy withdrawal, loss of therapeutic effect occurred over a longer period of time.

Maintenance of response and response over time were superior in subjects who continued q12w maintenance therapy at Week 40 compared with subjects withdrawn from therapy.

Efficacy and antibodies to ustekinumab (ADAs)

4 of the total 44 participants developed anti-ustekinumab antibodies during CADMUS Jr. All 4 were white and female. In 2 of these participants the antibodies were found to be neutralising.

Table 9 Summary of Neutralizing Anti-Ustekinumab Antibodies Status Through Week 56; Immunogenicity Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab Standard Dosage
Analysis set: Immunogenicity analysis set	42
Subjects positive for anti-ustekinumab antibodies[a]	4
Subjects evaluable for neutralizing antibodies[b,c]	4 (100.0%)
Subjects positive for neutralizing antibodies[d]	2 (50.0%)
Subjects negative for neutralizing antibodies[d]	2 (50.0%)

[a]Subjects positive for anti-ustekinumab antibodies includes all subjects who had positive samples (treatment-boosted or treatment-induced) at any time after their first ustekinumab administration through Week 56. In the instance that a subject had a positive sample at baseline (pre-dose), the subject was considered as positive only if the peak titer of the post-treatment samples was at least a 2-fold higher (ie, ≥2-fold) than the titer of the baseline sample.
[b]An evaluable subject is a subject positive for anti-ustekinumab antibodies who also had samples available for neutralizing antibodies with no detectable interference in the neutralizing antibody assay.
[c]Denominator is subjects positive for anti-ustekinumab antibodies.
[d]Denominator is subjects evaluable for neutralizing antibodies.

Ancillary analyses

Physician's Global Assessment 0/1 and PASI 75 responses at Week 12 were generally consistent across subgroups defined by baseline demographic features, psoriasis disease characteristics, and psoriasis medication history.

Summary of main study

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

Table 1. Summary of Efficacy for trial CNTO1275PSO3013 – CADMUS Jr

Title: 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			
Study identifier	CNTO1275PSO3013 – CADMUS Jr		
Design	An open-label, single arm, multicenter study conducted at multiple sites in Europe, US, and Canada to evaluate the efficacy, safety and PK of ustekinumab in paediatric subjects ≥6 to <12 years of age.		
	Duration of main study phase: Duration of Run-in phase: Duration of Extension phase:		56 Weeks Not applicable From Week 56 up to through Week 264
Hypothesis	There was no formal hypothesis testing performed in the main study. Efficacy, safety and PK of ustekinumab in paediatric subjects were evaluated using descriptive statistics.		
Treatments groups	Weight based Ustekinumab Standard Dosage • Weight <60 kg: 0.75 mg/kg • Weight ≥60 kg to ≤100 kg: 45 mg • Weight >100 kg: 90 mg		Subcutaneous ustekinumab at Weeks 0 and 4 followed by a maintenance dose every 12 weeks (q12w) thereafter, with the last dose at Week 40 (main study phase)
Endpoints and definitions	Primary endpoint	PGA of cleared (0) or minimal (1)	The proportion of subjects with a PGA of cleared (0) or minimal (1) at Week 12
	Major Secondary endpoint	PASI 75 responders	The proportions of subjects who achieve a ≥75% improvement in PASI from baseline at Week 12
	Major Secondary endpoint	PASI 90 responders	The proportions of subjects who achieve a ≥90% improvement in PASI from baseline at Week 12
	Major Secondary endpoint	CDLQI	The change in Children's Dermatology Life Quality Index (CDLQI) from baseline at Week 12
	Major Secondary endpoint	Serum concentrations	Serum ustekinumab concentrations over time
Database lock	27 November 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	other: all enrolled and treated subjects who received at least 1 injection of ustekinumab during the study. time point: Week 12		
Descriptive statistics and estimate variability	Treatment group		Weight based Ustekinumab Standard Dosage
	Number of subjects		44
	PGA of cleared (0) or minimal (1)		34 (77.3%)
	95% CI		(62.2%; 88.5%)
Effect estimate per comparison	Primary endpoint	Comparison groups	NA
		Test statistic	NA
		Variability statistic	NA
		P-value	NA
Analysis description	**Major Secondary Analysis**		
Analysis population and time point description	other: all enrolled and treated subjects who received at least 1 injection of ustekinumab during the study. time point: Week 12		
Descriptive statistics and estimate variability	Treatment group		Weight based Ustekinumab Standard Dose
	Number of subjects		44
	PASI 75 responders		37 (84.1%)
	95% CI		(69.9%; 93.4%)
Effect estimate per comparison	Major Secondary endpoint	Comparison groups	NA
		Test statistic	NA
		Variability statistic	NA
		P-value	NA
Analysis description	**Major Secondary Analysis**		
Analysis population and time point description	other: all enrolled and treated subjects who received at least 1 injection of ustekinumab during the study. time point: Week 12		
Descriptive statistics and estimate variability	Treatment group		Weight based Ustekinumab Standard Dose
	Number of subjects		44
	PASI 90 responders		28 (63.6%)
	95% CI		(47.8%; 77.6%)

Effect estimate per comparison	Major Secondary endpoint	Comparison groups	NA
		Test statistic	NA
		Variability statistic	NA
		P-value	NA
Analysis description	**Major Secondary Analysis**		
Analysis population and time point description	other: all enrolled and treated subjects who received at least 1 injection of ustekinumab during the study. time point: Week 12		
Descriptive statistics and estimate variability	Treatment group		Weight based ustekinumab Standard Dose
	Number of subjects		44
	Subjects evaluable for CDLQI Mean (SD) 95% confidence interval Median Range IQ range		42 -6.3 (6.43) (-8.29; -4.28) -6.0 (-27; 7) (-10.0; -2.0)
Effect estimate per comparison	Major Secondary endpoint	Comparison groups	NA
		Test statistic	NA
		Variability statistic	NA
		P-value	NA
Analysis description	**Major Secondary Analysis**		
Analysis population and time point description	other: subjects who received at least one injection of ustekinumab and have at least one valid blood sample drawn time point: Weeks 28, 40, 52		
Descriptive statistics and estimate variability	Treatment group		Weight based ustekinumab Standard Dose
	Number of subjects		44
	Serum concentrations		Median trough serum ustekinumab concentrations at Weeks 28, 40, and 52 were 0.34 µg/mL, 0.40 µg/mL, and 0.38 µg/mL, respectively.
	Adjusted treatment difference (95% CI)		NA
Effect estimate per comparison	Major Secondary endpoint	Comparison groups	NA
		Test statistic	NA
		Variability statistic	NA
		P-value	NA

Notes	Mean or median trough serum ustekinumab concentrations were maintained at a steady state from Week 28 through Week 52. There was no evidence of accumulation in serum ustekinumab concentrations over time.

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

The approval for the treatment of moderate to severe plaque-type psoriasis in adolescent patients ≥12 to <18 years of age was based upon results from CNTO1275PSO3006 (CADMUS; PSO3006), a Phase 3, randomized, double-blind, placebo-controlled, multicentre study in 110 subjects. The study was adequately powered to provide an assessment of the efficacy of ustekinumab in the treatment of psoriasis in paediatric subjects ≥12 to <18 years of age.

Inclusion criteria were consistent between Study PSO3013 (≥6 to <12 years of age) and Study PSO3006 (≥12 to <18 years of age), each enrolling a population of subjects with moderate to severe plaque-type psoriasis (defined by PASI ≥12, PGA ≥3, and BSA involvement ≥10%) for at least 6 months prior to the first administration of study agent.

Other than expected differences (e.g., age, weight, height, age of onset, duration of disease), demographics and baseline clinical disease characteristics were similar between the paediatric (≥6 to <12 years of age) and adolescent (≥12 to <18 years of age) populations and were consistent with the general clinical presentation of moderate to severe plaque-type psoriasis.

When comparing prior use of psoriasis therapies, the proportions of subjects who had ever used biologics was low in both populations, while prior use of conventional systemic agents (e.g., psoralen plus ultraviolet A light, methotrexate, cyclosporine, acitretin, apremilast, tofacitinib) was lower in paediatric subjects (≥6 to <12 years of age) than in adolescent subjects (≥12 to <18 years of age).

Table 10: Summary of Baseline Clinical Disease Characteristics; Full Analysis Set

	PSO3013	PSO3006
	Standard Dosage	Standard Dosage
Analysis set: Full analysis set	44	36
Psoriasis disease duration (years)		
N	44	36
Mean (SD)	3.5 (2.49)	5.5 (3.78)
Median	2.9	5.5
Range	(0; 9)	(1; 14)
IQ range	(1.5; 5.0)	(2.0; 8.5)
Age at diagnosis (years)		
N	44	36
Mean (SD)	5.6 (2.40)	9.3 (4.34)
Median	6.0	9.0
Range	(1; 10)	(0; 16)
IQ range	(4.0; 7.5)	(6.0; 13.5)
Psoriatic arthritis		
N	44	36
Yes	1 (2.3%)	2 (5.6%)
No	43 (97.7%)	34 (94.4%)
BSA (%)		
N	44	36
Mean (SD)	23.3 (13.71)	31.9 (23.15)
Median	18.0	21.5
Range	(11; 73)	(10; 100)
IQ range	(13.5; 29.5)	(15.5; 41.5)
BSA		
N	44	36
≥ 20%	19 (43.2%)	20 (55.6%)
< 20%	25 (56.8%)	16 (44.4%)

Table 10: Summary of Baseline Clinical Disease Characteristics; Full Analysis Set

	PSO3013	PSO3006
	Standard Dosage	Standard Dosage
PASI score (0-72)		
N	44	36
Mean (SD)	17.9 (7.73)	21.7 (10.40)
Median	16.1	16.8
Range	(4; 53)	(12; 51)
IQ range	(13.7; 19.8)	(14.4; 25.9)
PASI score		
N	44	36
≥ 20	10 (22.7%)	14 (38.9%)
< 20	34 (77.3%)	22 (61.1%)
PGA score		
N	44	36
Cleared (0)	0	0
Minimal (1)	0	0
Mild (2)	0	0
Moderate (3)	29 (65.9%)	24 (66.7%)
Marked (4)	14 (31.8%)	10 (27.8%)
Severe (5)	1 (2.3%)	2 (5.6%)
PGA score		
N	44	36
Marked or severe (≥4)	15 (34.1%)	12 (33.3%)
CDLQI (0-30)		
N	44	32
Mean (SD)	8.1 (5.69)	10.3 (6.63)
Median	7.0	9.0
Range	(0; 27)	(1; 26)
IQ range	(3.5; 11.5)	(4.0; 15.5)

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Analyses in the adolescent submission showed that the approved weight-based dosage provided serum ustekinumab concentrations in subjects ≥12 to <18 years of age which were generally comparable to those in the adult psoriasis population treated with the approved ustekinumab dosage for adult psoriasis. In addition, other analyses in the adolescent submission showed that the efficacy, safety, and exposure-response profiles of the weight-based standard dosage of ustekinumab in adolescents were comparable to those seen in adults with psoriasis. The bridge between adolescent and adult psoriasis populations was therefore established for ustekinumab prior to the current paediatric variation submission.

Efficacy assessment at Week 12: Full Analysis Set

The same efficacy endpoints (PGA, PASI, and CDLQI) and timepoints (through Week 52) were utilized in studies PSO3013 and PSO3006, that supports the comparison of results in paediatric subjects (≥6 to <12 years of age) with those seen in adolescent subjects (≥12 to <18 years of age) (Table 11).

Table 11: Summary of Key Efficacy Endpoints at Week 12; Full Analysis Set

	PSO3013	PSO3006
	Standard Dosage	Standard Dosage
Analysis set: Full analysis set	44	36
PGA of cleared (0) or minimal (1)	34 (77.3%)	25 (69.4%)
95% confidence interval	(62.2%, 88.5%)	(51.9%, 83.7%)
PGA of cleared (0)	17 (38.6%)	17 (47.2%)
95% confidence interval	(24.4%, 54.5%)	(30.4%, 64.5%)
PASI 75 responders	37 (84.1%)	29 (80.6%)
95% confidence interval	(69.9%, 93.4%)	(64.0%, 91.8%)

Table 11: Summary of Key Efficacy Endpoints at Week 12; Full Analysis Set

	PSO3013	PSO3006
	Standard Dosage	Standard Dosage
PASI 90 responders	28 (63.6%)	22 (61.1%)
95% confidence interval	(47.8%, 77.6%)	(43.5%, 76.9%)
PASI 100 responders	15 (34.1%)	14 (38.9%)
95% confidence interval	(20.5%, 49.9%)	(23.1%, 56.5%)
Subjects evaluable for CDLQI		
N	42	32
Mean change from baseline (SD)	-6.3 (6.43)	-6.7 (5.63)
95% confidence interval	(-8.29; -4.28)	(-8.69; -4.63)
Median	-6.0	-5.5
Range	(-27; 7)	(-19; 6)
IQ range	(-10.0; -2.0)	(-11.0; -3.0)
Subjects with CDLQI >1 at baseline	39	30
Subjects with CDLQI of 0 or 1	24 (61.5%)	17 (56.7%)
95% confidence interval	(44.6%, 76.6%)	(37.4%, 74.5%)

Abbreviations: CDLQI=Children's Dermatology Life Quality Index; IQ=interquartile; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment.

Note 1: 95% confidence interval was an exact confidence interval based on the binomial distribution.
Note 2: Evaluable subjects for CDLQI are subsets with evaluable outcome measurements at both Week 0 and Week 12
Note 3: 95% confidence interval for change from baseline in CDLQI score was based on normal approximation.

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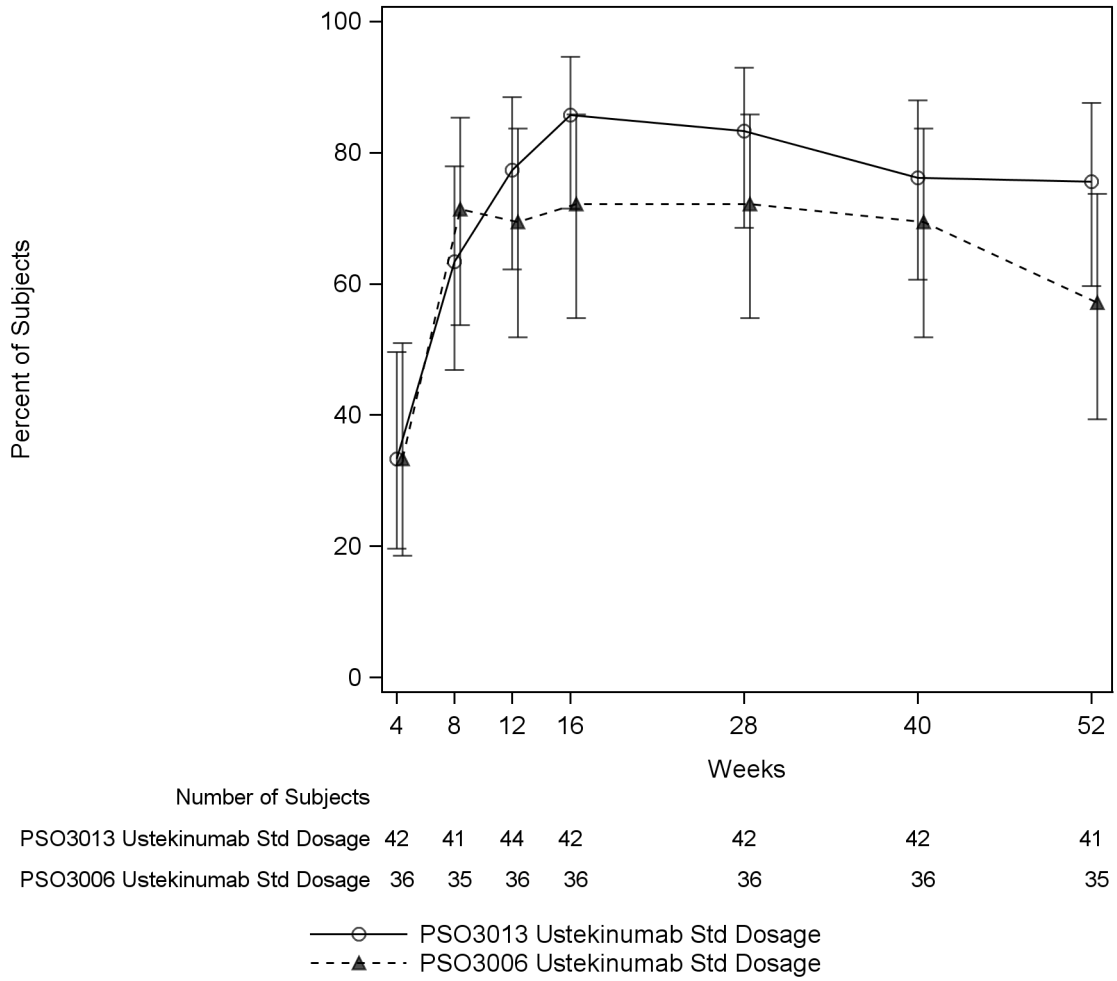
[TEFMS02.RTF] [CNTO1275\Z_SCS\DBR_2018_11\RE_2018_11\PROD\TEFMS02.SAS] 10JAN2019, 14:36

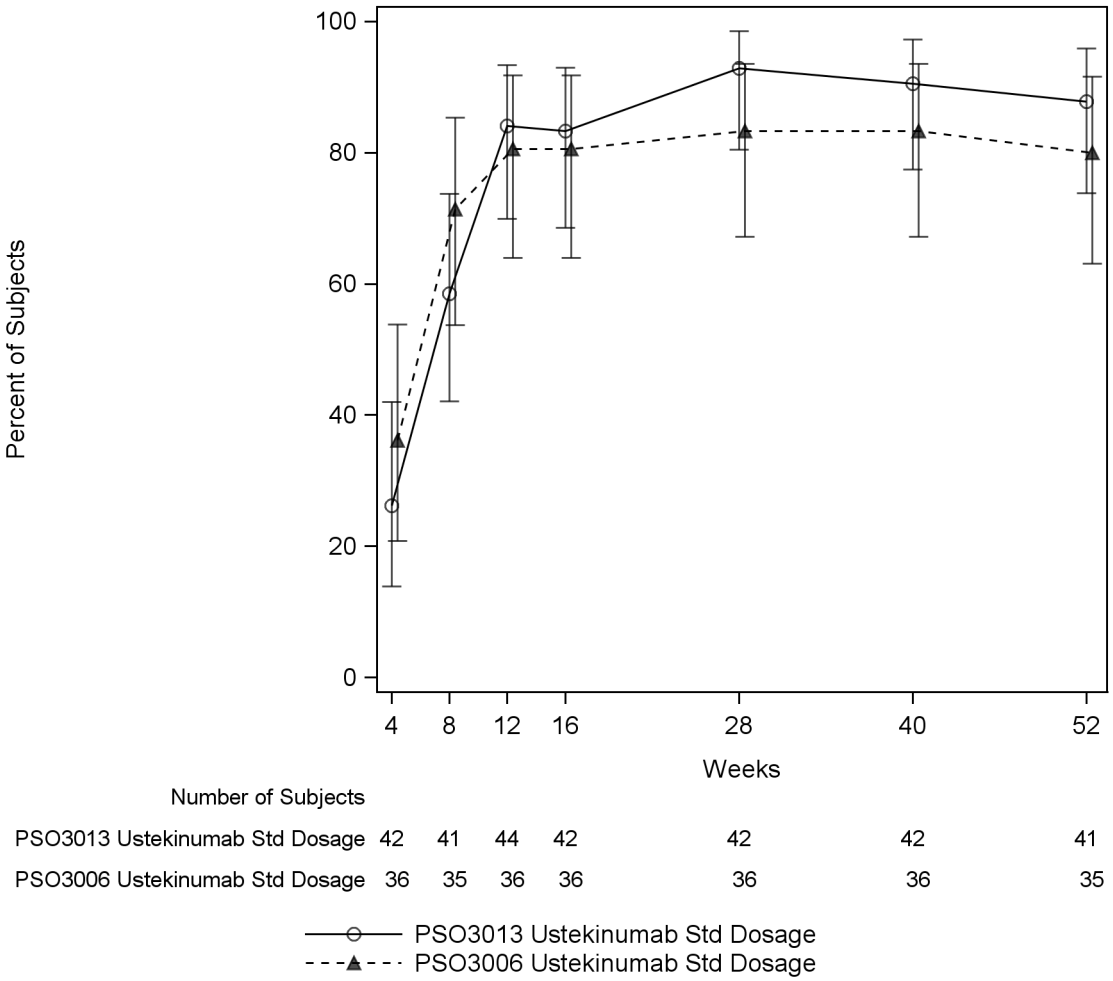
After Week 12, a numerical difference, but with overlapping CIs, between the two study populations was observed for the PGA 0/1 response rate, with a somewhat higher proportion of subjects achieving PGA 0/1 in PSO3013 compared with PSO3006 (Figure 28). Similar response curves and separation between PSO3013 and PSO3006 were also observed for PASI 75 response (Figure 29).

Figure 28: Percent of Subjects Achieving a PGA Score of Cleared (0) or Minimal (1) Through Week 52 by Visit; Full Analysis Set



Note 1: 95% CI based on exact method.

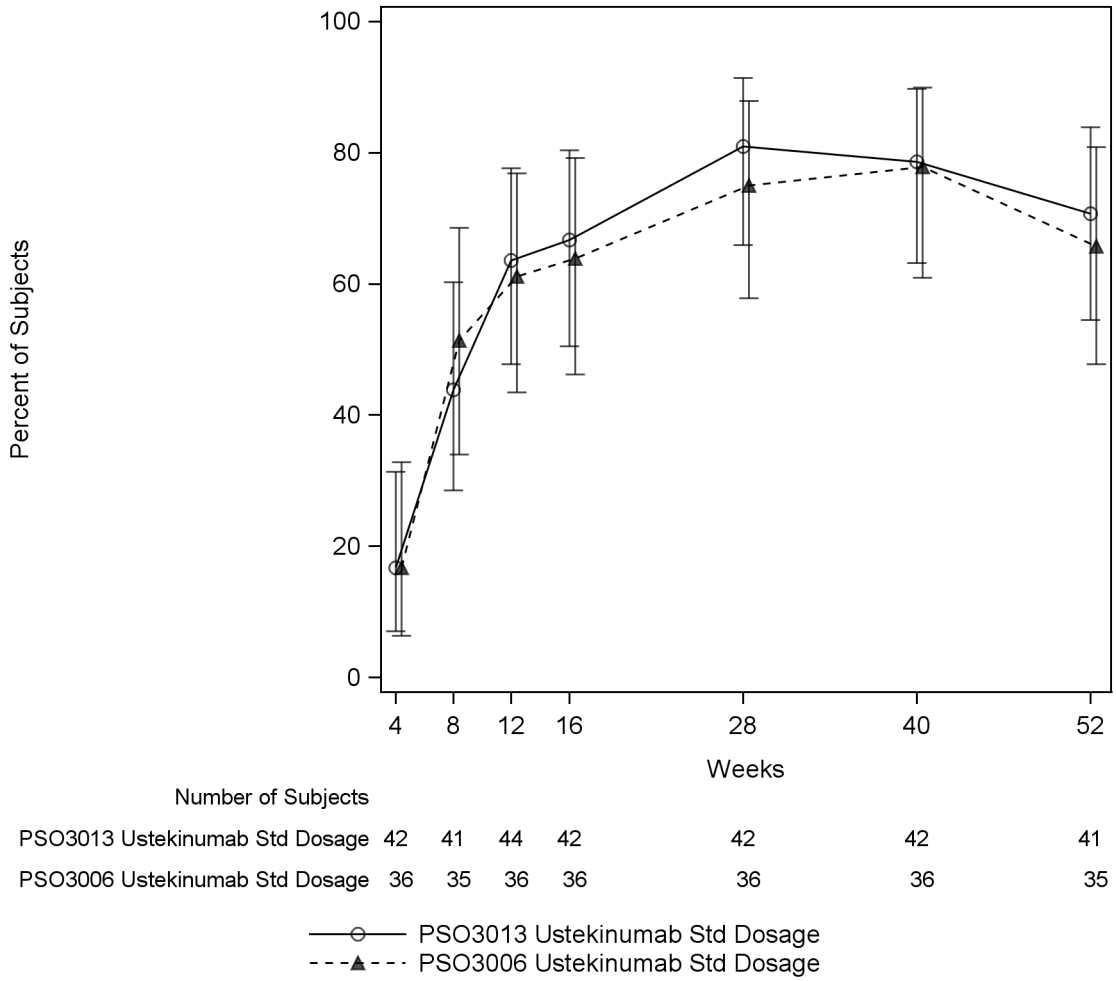
Figure 29: Percent of Subjects Achieving a PASI 75 Response Through Week 52 by Visit; Full Analysis Set



Note 1: 95% CI based on exact method.

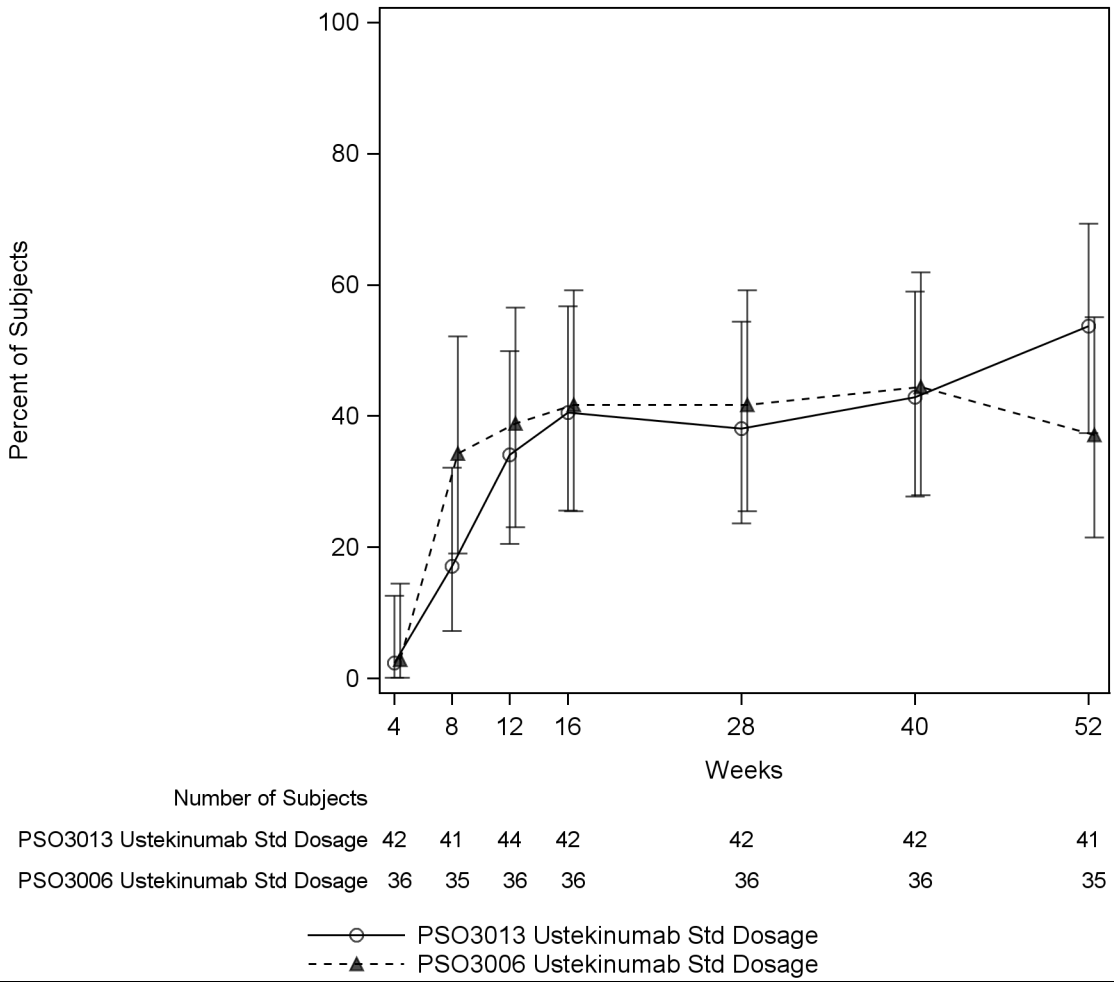
However, response rates for PASI 90, PASI 100 and PGA 0, through Week 52 were generally comparable between PSO3013 and PSO3006. Additionally, the patient-reported outcome of CDLQI 0/1 (for subjects with CDLQI >1 at baseline) showed comparable response rates at Week 28 and Week 52.

Figure 30: Percent of Subjects Achieving a PASI 90 Through Week 52 by Visit; Full Analysis Set



Note 1: 95% CI based on exact method.

Figure 31 Percent of Subjects Achieving a PASI 100 Through Week 52 by Visit; Full Analysis Set



Note 1: 95% CI based on exact method.

Figure 32 Number of Subjects with CDLQI Score of 0 or 1 through Week 52; Full Analysis Set

	PSO3013	PSO3006
	Standard Dosage	Standard Dosage
Analysis set: Full analysis set	44	36
Subjects with CDLQI >1 at baseline		
Week 28		
N[a]	37	30
Subjects with CDLQI of 0 or 1	23 (62.2%)	20 (66.7%)
Week 52		
N[a]	36	29
Subjects with CDLQI of 0 or 1	21 (58.3%)	17 (58.6%)

Figure 32 Number of Subjects with CDLQI Score of 0 or 1 through Week 52; Full Analysis Set

	PSO3013	PSO3006
	Standard Dosage	Standard Dosage

Abbreviation: CDLQI=Children's Dermatology Life Quality Index

Note 1: Evaluable subjects for CDLQI are subsets with evaluable outcome measurements at both Week 0 and Week 12
Note 2: 95% confidence interval for change from baseline in CDLQI score was based on normal approximation.
Note 3: 95% confidence interval for CDLQI of 0 or 1 was an exact confidence interval based on the binomial distribution.

Response rates for efficacy endpoints at Week 12 in PSO3013 and PSO3006 were similar to those seen in the 2 global, pivotal Phase 3 studies in adults (C0743T08 and C0743T09) (Table 12).

Table 12: Subjects with PGA Scores of Cleared (0) or Minimal (1), PASI 75, PASI 90 and PASI 100 at Week 12; All Randomized Subjects in the Phase 3 Paediatric and Adult Global Psoriasis Studies

	Paediatric Psoriasis			Adult Psoriasis					
	CNTO1275PSO3013	CNTO1275PSO3006		C0743T08			C0743T09		
	Ustekinumab		Ustekinumab		Ustekinumab			Ustekinumab	
	Standard Dosage	Placebo	Standard Dosage	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Randomized Subjects	44	37	36	255	255	256	410	409	411
PGA of cleared (0) or minimal (1)	77.3%	5.4%	69.4%	3.9%	59.2%	60.9%	4.9%	68.0%	73.5%
(95% CI) or p-value	(62.2%; 88.5%)		<0.001		<0.001	<0.001		<0.001	<0.001
PASI 75 responders	84.1%	10.8%	80.6%	3.1%	67.1%	66.4%	3.7%	66.7%	75.7%
(95% CI) or p-value	(69.9%; 93.4%)		<0.001		<0.001	<0.001		<0.001	<0.001
PASI 90 responders	63.6%	5.4%	61.1%	2.0%	41.6%	36.7%	0.7%	42.3%	50.9%
(95% CI) or p-value	(47.8%; 77.6%)		<0.001		<0.001	<0.001		<0.001	<0.001
PASI 100 responders	34.1%	2.7%	38.9%	0.0%	12.5%	10.9%	0.0%	18.1%	18.2%
(95% CI) or p-value	(20.5%, 49.9%)		<0.001		<0.001	<0.001		<0.001	<0.001

Abbreviations: CI=confidence interval; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The paediatric study supporting this extension of indication to the treatment of paediatric patients aged 12 years and above with moderate to severe plaque psoriasis is an open-label study in in paediatric subjects ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis.

The study design was agreed with PDCO and the study was conducted in accordance with PIP procedure (EMEA-C-000311-PIP01-08-M04).

The baseline characteristics in the CADMUS Jr study population are considered to be representative of the target population for the intended indication. The median age of onset of "childhood onset" psoriasis has been reported to be between 7 and 10 years (Eichenfield et al. 2018) with a mean onset of 8 years. According to a systematic review, psoriasis was rare in children younger than 9 years, varying between 0% in Norway to 0.55% in the UK (Parisi et al 2013). While non-white participants were under-represented in this study, there is a low incidence of plaque psoriasis in people of West African or Japanese ethnicity.
The primary efficacy criteria used in adults, PASI, is not validated for use in children and young people. The primary and secondary efficacy endpoints were the same as they were for the corresponding adolescent study (CADMUS) and are considered acceptable by the CHMP. The CDLQI endpoint used is a validated assessment tool for children with any type of psoriasis.
The approach used towards missing data is acceptable and the highlighted protocol deviations were addressed satisfactorily.

The eligibility criteria also mirrored the adolescent study, PSO3006 (CADMUS) enabling comparison across both paediatric Stelara studies. The same doses and similar dosing periodicity were used in the corresponding adolescent trial (CADMUS). In the adolescent study a ustekinumab/placebo injection was administered at Week 12 which did not occur in the paediatric (CADMUS Jr) trial.
With the exception of expected differences (e.g. weight, disease duration, biologics use), the baseline characteristics were broadly similar to that in the adolescent CADMUS study. The CADMUS Jr study had a greater proportion of females and a greater proportion of participants had a family history of psoriasis. The median PASI score was slightly higher in the adolescent group (18.8) and a slightly higher percentage had developed psoriatic arthritis (5.5%). However, there was not such an imbalance between the participants in both studies that comparisons between both studies could not be made.
The majority (93.2%) of subjects received all planned ustekinumab doses through to week 40 (end of efficacy period).

Efficacy data and additional analyses

Pivotal study

The majority (77.3%; 95% CI 62.2-88.5%) of study participants satisfied the primary endpoint at week 12. 84.1% of participants achieved a 75% reduction in PASI score by week 12. 63.6% of participants achieved a 90% reduction in PASI score by week 12. More than one third (38.6%) of participants achieved fully clear skin by week 12. Therefore, the week 12 endpoints for this study have been met. The sensitivity analyses confirmed the results. There was a median reduction of 6 points in the quality of life scoring system CDLQI. Maintenance of effect has not been investigated in the $\geqslant$6 to <12 years of age paediatric group.

Anti-drug antibodies

Presence of ADAs did not preclude a clinical response. There are however indications of lower efficacy in ADA positive subjects. The CHMP agreed that no SmPC update is needed, as this is already reflected in the SmPC.

Ancillary analyses

For the ancillary analyses, the numbers of participants in each subgroup were very small which impaired to draw any conclusions based on such subgroup analyses.

Comparison across the studies

Broadly similar results were seen at week 12 for all key efficacy endpoints in the paediatric versus the adolescent study. The primary endpoint of PGA cleared (0) or minimal (1) for both studies was assessed at week 12.

Benefits were generally sustained out to 52 weeks in the paediatric CADMUS Jr study. Apparent differences suggestive of better efficacy in children than in adolescents and of better efficacy in both adolescents and children than in adults were not considered relevant by the CHMP in view of the study that was not designed to evaluate such effect and of the limited sample size.

Overall, a weight-based standard dosage administered up until week 40 providing comparable exposure to adolescents resulted in clinically relevant improvements from week 4 to 52.

Efficacy of Stelara in plaque psoriasis in adults and adolescents (who are candidates for such a systemic therapy) has already been established and a marketing authorisation has been granted in this target group. Subject numbers treated in the adult studies were greater than in the paediatric studies. The primary endpoint in the adult studies was also different to the paediatric studies. All 3 adult studies assessed the proportion of subjects achieving a PASI 75 response at Week 12. This was the secondary endpoint in CADMUS and CADMUS Jr. However, results for the primary endpoint in the 3 adult studies (Phoenix 1, Phoenix 2 and ACCEPT) were generally consistent across the two doses studied (45 mg and 90 mg). The adult data support therefore the justification for the 90 mg dose in patients weighing more than 100 kg.

Maintenance treatment and duration of response have not been investigated in paediatric subjects ⩾6 to <12 years of age in study PSO3013 where the final ustekinumab injection was administered at week 40. In adults, the benefit of maintenance treatment has been demonstrated in up to 5 years, and duration of response after discontinuation and retreatment after recurrence has been investigated supporting continuous q12w treatment to maintain response. The Applicant proposed to extrapolate maintenance treatment from adults and adolescents to paediatric subjects ≥6 to <12 years of age. The proposal was agreed by CHMP. However, even though psoriasis is a chronic condition, fluctuations in symptoms and severity is seen over time, the CHMP enquired on how long-term maintenance of effect in paediatric patients ⩾6 to <12 years would be monitored. The Applicant confirmed that long term maintenance of effect in paediatric patients ⩾6 to <12 years of age will be monitored in the post-authorisation safety study in this age group as defined in the RMP.

2.5.3. Conclusions on the clinical efficacy

Patients with childhood-onset psoriasis are more likely to have significant disease and flares compared with those with adult-onset psoriasis (Burden-Teh et al 2016) and so adequate systemic treatment options are required in this age-group. The pivotal study PSO3013 in subjects who have moderate to severe plaque psoriasis and are aged 6 to 12 years met its primary endpoint. The results for the

secondary endpoints were also positive and were similar to those seen in the adolescent study which led to authorisation in that age-group. As in adults and adolescents, the presence of ADAs did not preclude a clinical response but a trend for a lower efficacy as captured in the Stelara SmPC.
Long term maintenance of effect of ustekinumab will be monitored in the post-authorisation safety study in paediatric patients with psoriasis as defined in the RMP.

2.6. Clinical safety

Introduction

Across the clinical development programme, the most common adverse reactions (> 5%) in controlled periods of the adult clinical studies with ustekinumab were nasopharyngitis and headache. The safety profile appears to be similar for adult patients across the clinical development programme and no new safety issues specific to adolescents were identified for the adolescent psoriasis indication (patients aged ≥12 to <18 years).

Hypersensitivity reactions (including rash and urticaria), serious hypersensitivity reactions (including anaphylaxis and angioedema), lower respiratory tract infection, allergic alveolitis, eosinophilic pneumonia, erythrodermic psoriasis, and pustular psoriasis, have been identified as ADRs from post-marketing experience.

Serious infections (including mycobacterial and salmonella infections) and malignancies represent important potential risks due to the mechanism of action. Post-marketing registries for patients with moderate to severe psoriasis, adolescent psoriasis, Crohn's disease and ulcerative colitis aim to further characterise long term safety for these indications.

Study data groupings:

The safety data for paediatric psoriasis for PSO3013 were presented through 1-year (week 56) for all subjects who received at least 1 (partial or complete) dose of ustekinumab.

Supportive safety analyses from the pivotal phase 3 psoriasis studies were also presented including the following table which outlines the safety profile of paediatric and adolescent patients in studies PSO3013 and PSO3006 through 1 year compared to the safety profile observed in the two pivotal adult psoriasis studies C0743T08 and C0743T09:

Table 13 Summary of Safety Findings Through One Year; Subjects Treated With Ustekinumab in Pediatric Study CNTO1275PSO3013, Adolescent Study CNTO1275PSO3006, and in Pooled Psoriasis Phase 3 Adult Studies C0743T08 and C0743T09

	CNTO1275PSO3013	CNTO1275PSO3006	C0743T08 and C0743T09
Treated subjects	44	73	1965
Avg duration of follow-up (weeks)	53.15	56.61	46.49
Subjects who discontinued study agent because of 1 or more adverse events	0	2 (2.7%)	57 (2.9%)
Subjects with one or more:			
Adverse events	34 (77.3%)	62 (84.9%)	1618 (82.3%)
Serious adverse events	3 (6.8%)	6 (8.2%)	94 (4.8%)

Table 13 Summary of Safety Findings Through One Year; Subjects Treated With Ustekinumab in Pediatric Study CNTO1275PSO3013, Adolescent Study CNTO1275PSO3006, and in Pooled Psoriasis Phase 3 Adult Studies C0743T08 and C0743T09

	CNTO1275PSO3013	CNTO1275PSO3006	C0743T08 and C0743T09
Any infections	29 (65.9%)	50 (68.5%)	1206 (61.4%)
Serious infections	1 (2.3%)	2 (2.7%)	17 (0.9%)
Infections requiring treatment	12 (27.3%)	20 (27.4%)	445 (22.6%)

Patient exposure

In PSO3013, 44 subjects were treated, and all subjects received the ustekinumab standard dosage.

In PSO3006, 110 subjects were treated: 37 subjects in the placebo group, 37 subjects in the ustekinumab half-standard dosage group, and 36 subjects in the ustekinumab standard dosage group). All subjects received their assigned treatment. Results presented for study PSO3006 included only subjects who were randomized to the ustekinumab half-standard and standard dosage groups. Placebo crossover subjects were excluded due to the shorter duration of ustekinumab exposure and follow-up.

The total number of ustekinumab administrations were similar across the 2 studies, but the total dose of ustekinumab received by subjects in study PSO3013 was lower than subjects receiving the standard dose in study PSO3006 due to the lower body weight range for paediatric subjects in the ≥6 to <12 years of age population enrolled in PSO3013 (Table 14). The average duration of follow-up was slightly lower in study PSO3013 than in study PSO3006 (53.15 weeks vs 56.61 weeks, respectively) due to the different study durations (56 weeks vs 60 weeks, respectively). The duration of follow-up in the pivotal adult psoriasis studies was slightly lower at 46.49 weeks.

Table 14 Summary of Exposure to Ustekinumab Through the End of the Reporting Period; Safety Analysis Set

	PSO3013	PSO3006		
	Standard Dosage	Standard Dosage	Half-Standard Dosage	Combined
Analysis set: Safety analysis set	44	36	37	73
Avg number of ustekinumab injections	4.8	5.0	4.8	4.9
Total dose (mg)				
N	44	36	37	73
Mean (SD)	142.7 (63.09)	207.4 (54.29)	106.7 (30.07)	156.4 (66.72)
Median	125.6	223.2	109.8	143.1
Range	(27; 405)	(80; 450)	(57; 225)	(57; 450)
IQ range	(106.7; 179.6)	(183.6; 225.0)	(90.0; 112.5)	(109.8; 225.0)

Adverse events

Through Week 56, 34 (77.3%) subjects reported 1 or more AEs. The SOC with the highest incidence of AEs was Infections and infestations (29 [65.9%] subjects), followed by General disorders and administration site conditions (9 [20.5%] subjects). When reported by MedDRA preferred term, nasopharyngitis was the most frequently reported AE through Week 56 (11 [25.0%] subjects), followed by pharyngitis, upper respiratory tract infection (URTI), and injection site erythema (6 [13.6%] subjects each).

Table 15 Number of Subjects With Treatment-Emergent Adverse Events With Frequency of at Least 5% Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1275PSO3013)

	Ustekinumab Standard Dosage
Analysis set: Safety analysis set	44
Avg duration of follow-up (weeks)	53.15
Avg exposure (number of administrations)	4.77
Subjects with 1 or more AEs	34 (77.3%)
System organ class Preferred term	
Infections and infestations	29 (65.9%)
Nasopharyngitis	11 (25.0%)
Pharyngitis	6 (13.6%)
Upper respiratory tract infection	6 (13.6%)
Tonsillitis	4 (9.1%)
Gastroenteritis	3 (6.8%)
Otitis media	3 (6.8%)
General disorders and administration site conditions	9 (20.5%)
Injection site erythema	6 (13.6%)
Gastrointestinal disorders	6 (13.6%)
Abdominal pain	3 (6.8%)
Skin and subcutaneous tissue disorders	5 (11.4%)
Psoriasis	3 (6.8%)

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 21.0.

No AEs of severe intensity were reported through Week 56.

Related adverse events

Through Week 56, 19 (43.2%) subjects reported 1 or more related AEs. 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). When reported by MedDRA preferred term, 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).

Serious adverse event/deaths/other significant events

Deaths

There were no deaths reported through week 56.

Serious Adverse Events

Treatment emergent Serious Adverse Events occurred in three patients (6.8%), an eyelid injury, infectious mononucleosis, and attention deficit/hyperactivity disorder. All events resolved, and subjects continued study treatment. These events were considered by the investigator to be not related to study agent.

Adverse Events That Resulted in Study Agent Discontinuation

Through Week 40, no subjects discontinued study agent due to 1 or more AEs.

Other significant events

Infections

Any infections

Through Week 56, 29 (65.9%) subjects reported 1 or more AEs that were considered infections by the investigator. The most common AEs that were considered to be infections were nasopharyngitis (11 [25.0%] subjects), pharyngitis (6 [13.6%] subjects), and URTI (6 [13.6%] subjects).

Infections Requiring Antimicrobial Treatment

Through Week 56, 12 (27.3%) subjects reported 1 or more infections which required oral or parenteral antimicrobial treatment. The most common infections which required oral or parenteral antimicrobial treatment were otitis media and URTI (3 [6.8%] subjects each).

Serious Infections, TB or opportunistic infections

One serious infection (infectious mononucleosis) was reported through Week 56. This case occurred in a 6-year-old female patient who was reported to have experienced moderate pharyngitis and tonsillitis on study day 121 and was subsequently diagnosed with infectious mononucleosis on study day 127 following hospitalisation with persistent fever, sore throat, one episode of vomiting, and abdominal pain. The patient received intravenous ampicillin and was discharged after 4 days. She was reported as having recovered from the event of infectious mononucleosis on study day 134.

There were no reports of TB infection through Week 56.

Injection-Site Reactions

Through Week 40, 16 (7.6%) injections were associated with injection-site reactions in 6 (13.6%) subjects, with some subjects reporting multiple injection-site reactions. All 16 injection-site reactions were mild in intensity and resolved in less than 1 day. The most common injection-site reactions were injection site erythema (6 [13.6%] subjects). Of note, 5 of the 6 subjects with injection-site reactions reported were from a single study site and all injection-site reactions in these subjects were injection site erythema.

Table 16 Summary of Injection-Site Reactions Through Week 40 by MedDRA System-Organ Class and Preferred Term; Safety Analysis Set

	PSO3013	PSO3006		
	Standard Dosage	Standard Dosage	Half-Standard Dosage	Combined
Treated subjects by active study agent injection received	44	36	37	73
Average number of ustekinumab injections	4.8	5.0	4.8	4.9
Total number of ustekinumab injections	210	181	178	359
Injections with injection-site reactions	16 (7.6%)	1 (0.6%)	0	1 (0.3%)

Table 16 Summary of Injection-Site Reactions Through Week 40 by MedDRA System-Organ Class and Preferred Term; Safety Analysis Set

	PSO3013	PSO3006		
	Standard Dosage	Standard Dosage	Half-Standard Dosage	Combined
Subjects with 1 or more injection-site reactions	6 (13.6%)	1 (2.8%)	0	1 (1.4%)
System-organ class/preferred term				
General disorders and administration site conditions	6 (13.6%)	1 (2.8%)	0	1 (1.4%)
Injection site haemorrhage	0	1 (2.8%)	0	1 (1.4%)
Injection site erythema	6 (13.6%)	0	0	0
Injection site pruritus	1 (2.3%)	0	0	0
Injection site swelling	1 (2.3%)	0	0	0
Injection site warmth	1 (2.3%)	0	0	0

There was no apparent association between the development of antibodies to ustekinumab and the development of injection-site reactions. None of the 4 subjects who were positive for antibodies to ustekinumab reported any injection-site reactions after the development of antibodies to ustekinumab through Week 56.

Adverse Events of Psoriasis

Through Week 56, 3 subjects reported 4 AEs of psoriasis. Two subjects reported single AEs of psoriasis (exacerbation of psoriasis and psoriasis aggravated, respectively) which occurred after the Week 40 dose of study agent and beyond the recommended 12-week dosing interval. One subject reported 2 events of psoriasis (both events of exacerbation of psoriasis) around the Week 40 dose, of which 1 event represented a greater than 12-week dosing interval and the other event occurred 16 days after the Week 40 dose.

Adverse Events of Clinical Interest

There were no malignancies, major adverse cardiovascular events (MACE), reports of TB, possible anaphylactic reactions, or possible serum sickness-like reactions through Week 56.

Pregnancy

Through Week 56, no pregnancies were reported.

Physical findings

Summaries of physical findings (weight, height, and BMI) were provided from week 0 to week 52 in terms of mean, median and range. These findings were outlined to have increased slightly over time through Week 52, consistent with the age of the subjects and expected growth over 52 weeks.

Laboratory findings

No treatment effects were noted in terms of ALT, AST, albumin, total protein, BUN/Urea, creatinine, total bilirubin, indirect bilirubin, non-fasting glucose, haemoglobin, haematocrit, red blood cell count, platelets, white cell count, eosinophils, lymphocytes, basophils or monocytes.

Withdrawal and rebound

Withdrawal and rebound were not studied in the paediatric psoriasis programme but were studied in the adult psoriasis programme. Psoriasis rebound is defined as a PASI of 125% of baseline, of new generalized pustular, erythrodermic or more inflammatory psoriasis occurring within 3 months of stopping therapy. In the C0743T08 study, which had a randomized withdrawal period (ie, ustekinumab was discontinued and subjects were followed). No pattern was observed to suggest the occurrence of psoriasis rebound.

Comparison Between Paediatric Study PSO3013 and adolescent study PSO3006

Nasopharyngitis, pharyngitis, and URTI were among the most commonly reported AEs in both studies. The AEs of tonsillitis, gastroenteritis, and otitis media occurred more frequently in PSO3013, however, these events are known to be more commonly reported in younger paediatric subjects, and do not represent newly identified safety concerns in this younger population.

Through 1 year in studies PSO3013 and PSO3006, the proportions of subjects who discontinued study agent due to an AE, had an SAE, infection, serious infection, or treated infection were comparable between the 2 populations. The proportions of subjects who had SAEs or serious infections were low across both datasets.

Table 17 Summary of Safety Findings Through One Year in Paediatric Study CNTO1275PSO3013 and Adolescent Study CNTO1275PSO3006; Safety Analysis Set

	PSO3013 Standard Dosage	PSO3006 Standard Dosage	Half-Standard Dosage	Combined
Treated subjects by active study agent injection received	44	36	37	73
Average duration of follow-up (weeks)	53.15	58.03	55.23	56.61
Average number of ustekinumab injections	4.8	5.0	4.8	4.9
Subjects who discontinued study agent because of 1 or more adverse events	0	0	2 (5.4%)	2 (2.7%)
Subjects with 1 or more:				
Adverse events[a]	34 (77.3%)	29 (80.6%)	33 (89.2%)	62 (84.9%)
Nasopharyngitis	11 (25.0%)	11 (30.6%)	12 (32.4%)	23 (31.5%)
Injection-site erythema	6 (13.6%)	0	0	0
Pharyngitis	6 (13.6%)	3 (8.3%)	4 (10.8%)	7 (9.6%)
Upper respiratory tract infection	6 (13.6%)	5 (13.9%)	4 (10.8%)	9 (12.3%)
Tonsillitis	4 (9.1%)	1 (2.8%)	1 (2.7%)	2 (2.7%)
Abdominal pain	3 (6.8%)	2 (5.6%)	3 (8.1%)	5 (6.8%)
Gastroenteritis	3 (6.8%)	1 (2.8%)	1 (2.7%)	2 (2.7%)
Otitis media	3 (6.8%)	0	0	0
Psoriasis	3 (6.8%)	1 (2.8%)	4 (10.8%)	5 (6.8%)
Serious adverse events	3 (6.8%)	1 (2.8%)	5 (13.5%)	6 (8.2%)
Any infections	29 (65.9%)	24 (66.7%)	26 (70.3%)	50 (68.5%)
Infections requiring treatment	12 (27.3%)	11 (30.6%)	9 (24.3%)	20 (27.4%)
Serious infections	1 (2.3%)	1 (2.8%)	1 (2.7%)	2 (2.7%)
Injection-site reaction	6 (13.6%)	1 (2.8%)	0	1 (1.4%)
Total number of injections	210	181	178	359
Injections with injection-site reactions	16 (7.6%)	1 (0.6%)	0	1 (0.3%)

[a] *Adverse events reported for ≥5% of subjects in the CNTO1275PSO3013 population*

Post marketing experience

Safety Surveillance

As of 31 December 2018, an estimated 11,349 subjects have been exposed to ustekinumab in the clinical development programme in a wide variety of study populations including healthy adults and individuals with psoriasis, PsA, Crohn's disease, sarcoidosis, primary biliary cirrhosis, multiple sclerosis, rheumatoid arthritis, atopic dermatitis, axial spondyloarthritis, systemic lupus erythematosus, and ulcerative colitis.

Since the first approval of ustekinumab on 12 December 2008, substantial information has been accruing that contributes to the understanding of the overall safety profile of ustekinumab and its overall benefit-risk profile. The estimated cumulative worldwide exposure to ustekinumab from launch to 31 December 2018 is 1,375,007 person-years. The evaluation of postmarketing data is part of the applicant's comprehensive safety surveillance program, which also includes review of data from ongoing clinical studies and registries. Ustekinumab continues to have a favourable benefit-risk profile for the treatment of patients with moderate to severe plaque psoriasis, PsA and Crohn's disease.

Study CNTO1275PSO4056

PSO4056 is an observational post-authorisation safety study of ustekinumab in the treatment of paediatric patients aged ≥12 years of age with moderate to severe plaque psoriasis conducted in Europe. This study was initiated on 25 October 2017 and the first interim report was completed on 26 March 2019. For this interim report, the AE profile of ustekinumab in 18 paediatric patients aged ≥12 years to <18 years treated with ustekinumab for moderate to severe plaque psoriasis was reviewed through 18 months after the start of data collection. The most frequently reported SOC was general disorders and administration site conditions (5 patients [27.8%]). Fatigue was the most frequently reported AE (5 patients [27.8%]), followed by headache and oropharyngeal pain both reported by 2 patients (11.1%) each. No other AE was reported by more than 1 patient. One patient reported an AE of alopecia; however, this event was linked to psoriasis of the scalp. No serious AEs were reported.

Postmarketing Registry: PSOLAR

Ustekinumab is also being evaluated in PSOLAR, a multicentre, prospective, observational study that tracks the long-term safety experience and clinical status of patients with psoriasis who are eligible to receive (or are actively receiving) systemic therapies for psoriasis. PSOLAR has enrolled more than 4,807 patients who were exposed to ustekinumab at some time during their treatment for psoriasis, of whom 4,600 received ustekinumab during observation in PSOLAR, corresponding to a total of 15,526 patient-years of follow-up. No unfavourable imbalances in cumulative, unadjusted incidence rates of AEs, SAEs, or targeted all-cause mortality, MACE, malignancy, and serious infection were noted for the ustekinumab cohort compared with that for other cohorts.

Protocol-specified statistical analyses indicated that ustekinumab exposure was not a significant predictor of serious infection. Protocol-specified AEs of special interest (ie, serious depression/suicidality and systemic hypersensitivity, preselected neurologic events), did not reveal any new safety signals, although numbers of events were low for some AEs of special interest.

Overall, the data analysis conducted for the PSOLAR registry has not identified any new safety signals for ustekinumab.

2.6.1. Discussion on clinical safety

The safety dataset for PSO3013 includes 44 patients treated as part of an open-label, multicentre trial 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.

Through week 56, 34 (77.3%) subjects reported 1 or more AEs. The System Organ Class (SOC) with the highest incidence of AEs was Infections and infestations (29 [65.9%] subjects), followed by General disorders and Administration site conditions (9 [20.5%] subjects). When reported by MedDRA preferred term, nasopharyngitis was the most frequently reported AE through Week 56 (11 [25.0%] subjects), followed by pharyngitis, upper respiratory tract infection (URTI), and injection site erythema (6 [13.6%] subjects each).

A greater proportion of patients included in PSO3013 compared to patients included in PSO3006 experienced injection site reactions (6 patients, 13.6% with at least one, versus 1 patient, 2.8% with two; 16 injections with injection site reactions, 7.6%, versus 1 injection with an injection site reaction, 0.6%). The CHMP did not consider that this represents a new safety concern in this population as all injection site reactions were mild and resolved in less than one day, with the most commonly reported PT injection site erythema. Furthermore, it is also noted that 5 of the 6 subjects with infection site reactions were from a single site and that all reactions in these 5 subjects were injection site erythema.

There were no deaths reported and treatment emergent serious AEs occurred in three patients (6.8%), an eyelid injury, infectious mononucleosis, and attention deficit/hyperactivity.

The safety profile in PSO3013 appears generally comparable with that seen in the adolescent psoriasis study and the 2 pivotal adult psoriasis studies.

Important identified risks for ustekinumab include serious systemic hypersensitivity reactions, facial palsy, pustular psoriasis and erythrodermic psoriasis. There were no reported events related to these risks in study PSO3013.

Important potential risks included serious infections, malignancy, cardiovascular events, serious depression including suicidality, reversible posterior leukoencephalopathy syndrome, venous thromboembolism and exposure during pregnancy. Aside from a single serious infection which resolved without a change to ustekinumab dose, there were no related events reported for these risks.

The safety dataset, which is based on an open-label study design, did not allow for evaluation of differences between ustekinumab-treated subjects and a control group. There are limitations in terms of identifying any differences in safety profile in this population, especially in light of the small sample size and of the study duration. There is however supportive safety data available in adult and adolescent patients ≥12 years from clinical trials and post-marketing data including post-marketing registry studies. The MAH proposed that ustekinumab be used as a continuous maintenance treatment in paediatric patients aged 6 years and above, in-line with the current approved indication in adolescents and adults and in-keeping with the chronic nature of psoriasis. The bridging of the longer-term adult safety data to the paediatric population 6 years and above and the data from adults regarding the safety of withdrawal is acceptable to the CHMP. However, the long-term safety in this younger paediatric population requires further study together with exploration of whether long-term usage results in any potential effects on growth or development. Longer-term safety data will be available from the ongoing long-term extension study PSO3013. In addition, long-term safety data in patients ≥6 to <12 years of age will be collected in the post-authorisation safety study for adolescent psoriasis patients that will be expanded to include paediatric psoriasis patients ≥6 to <12 years of age as defined in the RMP.

2.6.2. Conclusions on clinical safety

The safety profile in patients ≥6 to <12 year of age with moderate to severe chronic plaque psoriasis was generally comparable with that seen in psoriasis patients aged ≥12 years, as well as in the adult psoriasis studies. No new adverse events or safety issues were identified in PSO3013. Despite the limitations in terms of sample size and duration of the paediatric study, it is acknowledged that significant safety data is available in adults and also in adolescents age ≥12 years, both from clinical trials and from the post-marketing setting. Comparable safety profiles observed in adolescent and paediatric subjects support the extrapolation approach.

As long-term use of ustekinumab has not been evaluated in this population, but data are expected to be available from the ongoing long-term extension study PSO3013. In addition, expected long-term safety profile of ustekinumab use in this population and any potential effect on growth and development will be explored through expansion to patients ≥6 to <12 years of age of the post-authorisation study for adolescent psoriasis patients as defined in the RMP.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 16.1 is acceptable, provided that the MAH submits a further amended protocol for the Adolescent Psoriasis Registry as a post-authorisation measure within 6 months of the European Commission Decision. This should incorporate a fulsome discussion and justification for the proposed sample size. The MAH should consider whether additional sites (particularly in both currently participating and non-participating EU/EEA countries) could be recruited, in order to provide a larger sample size than that currently proposed. Given that results from sites outside Europe may not be generalizable to the EU/EEA, the MAH is requested to also provide a stratification of the results by jurisdiction.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 16.1 with the following content:

Safety concerns

Important identified risks	Serious systemic hypersensitivity reactions
	Facial palsy
	Pustular psoriasis
	Erythrodermic psoriasis
Important potential risks	Serious infections (including mycobacterial and salmonella infections)
	Malignancy
	Cardiovascular events
	Serious depression including suicidality
	Reversible posterior leukoencephalopathy syndrome
	Venous thromboembolism
	Exposure during pregnancy
Missing information	Use in patients with a history of latent TB or TB
	Use in patients with concurrent malignancy or a history of malignancy
	Use in patients with recent or concomitant use of immunosuppressive therapy other than MTX, 6-MP, AZA, 5-ASA, and corticosteroids
	Long-term safety in pediatric psoriasis patients 6 years and older
	Long-term impact on growth and development in pediatric psoriasis patients 6 years and older

Long-term safety in adult patients with moderately to severely active Crohn's disease

Long-term safety in adult patients with moderately to severely active UC

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
C0168Z03 PSOLAR (plaque psoriasis [overlapping forms of psoriasis may be included]): A multicenter, prospective, observational registry of patients with psoriasis who are candidates for systemic therapy including biologics Ongoing	To evaluate the safety of STELARA in patients with moderate to severe plaque psoriasis (plaque psoriasis [overlapping forms of psoriasis may be included]).	• Serious systemic hypersensitivity reactions • Facial palsy • Pustular psoriasis • Erythrodermic psoriasis • Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Reversible posterior leukoencephalopathy syndrome • Use in patients with a history of latent TB or TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with recent or concomitant use of immunosuppressive therapy other than MTX, 6-MP, AZA, 5-ASA, and corticosteroids	Protocol submission	25 June 2009

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Registry start	20 June 2007: The trial was expanded to include STELARA patients on 19 March 2009 and the first STELARA patient was enrolled in PSOLAR on 24 March 2009.
			Registry finish	31 December 2020
			Final report	31 August 2021
CNTO1275PSO4005 (Nordic Database Initiative): A review and analysis of AEs from the Swedish and Danish national registry systems Ongoing	Collection and analysis of AEs/SAEs of interest in psoriasis patients (any form of psoriasis) exposed to STELARA, relative to the background risk in non-biologic-exposed controls	• Serious systemic hypersensitivity reactions • Facial palsy • Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Reversible posterior leukoencephalopathy syndrome • Use in patients with a history of latent TB or TB • Use in patients with concurrent malignancy or a history of malignancy	Protocol submission	25 June 2009
			Registry start	20 July 2009
			Registry finish	15 December 2019
			Final report	01 September 2020
CNTO1275PSO4007 (Pregnancy Research	Collection and analysis of	• Exposure during pregnancy	Protocol submission	25 June 2009

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Initiative): Exposure to ustekinumab during pregnancy: A review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers Ongoing	information pertaining to pregnancy outcomes of women exposed to STELARA during pregnancy and health status in the first year of life of infants born to women following prenatal exposure to STELARA compared with controls		Registry start	20 July 2009
			Registry finish	15 December 2020
			Final report	01 May 2021
CNTO1275PSO4056 (Pediatric Psoriasis Registry): An observational postauthorization safety study of ustekinumab in the treatment of pediatric patients aged 6 years and older with moderate to severe plaque psoriasis Ongoing	To confirm the long-term safety profile of STELARA use in pediatric patients 6 years and older and to explore any potential effect on growth and development in pediatric patients 6 years and older in-line with the consideration in the STELARA PIP	• Long-term safety in pediatric psoriasis patients 6 years and older • Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	Protocol submission	21 December 2015
			Trial start	25 October 2017
			Trial finish	31 August 2032
			Final report	31 March 2033
Long-term extension of CNTO1275CRD3003 (A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate the safety and efficacy of ustekinumab maintenance therapy in adult patients with moderately to severely active Crohn's disease) Ongoing	To evaluate the long-term safety of STELARA in adult patients with moderately to severely active Crohn's disease from Week 44 through Week 272.	• Venous thromboembolism • Long-term safety in adult patients with moderately to severely active Crohn's disease	Protocol submission	31 March 2011
			Trial start	30 September 2011
			Trial finish	31 October 2019
			Final report	30 April 2020
RRA-20745: An observational postauthorization safety study to describe the safety of ustekinumab and other Crohn's disease	To monitor the long-term safety profile of STELARA use in adult patients with moderately to severely active Crohn's disease.	• Venous thromboembolism • Long-term safety in adult patients with moderately to severely active Crohn's disease	Protocol submission	27 September 2017
			Trial start	To be determined
			Trial finish	To be determined

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
treatments in a cohort of patients with Crohn's disease Planned			Final report	To be determined
Long-term extension of CNTO1275UCO3001 (A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis) Ongoing	To evaluate the long-term safety of STELARA in adult patients with moderately to severely active UC from maintenance Week 44 through Week 220.	• Long-term safety in adult patients with moderately to severely active UC	Protocol submission	January 2019
			Trial start	19 August 2015 (start of induction phase of trial)
			Trial finish	2021
			Final report	2022
An observational postauthorization safety study to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using SWIBREG Planned	To evaluate the long-term safety of ustekinumab in adult patients with moderately to severely active UC.	• Venous thromboembolism • Malignancy • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active UC	Protocol submission	30 April 2020
			Trial start	Not applicable (secondary use of data)
			Trial finish	31 August 2026
			Final report	31 May 2027
An observational postauthorization safety study to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using SNDS Planned	To evaluate the long-term safety of ustekinumab in adult patients with moderately to severely active UC.	• Venous thromboembolism • Malignancy • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active UC	Protocol submission	30 April 2020
			Trial start	Not applicable (secondary use of data)
			Trial finish	31 August 2026
			Final report	31 May 2027

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.6 of the SmPC for Stelara solution for injection have been updated. Section 4.8 of the SmPC for Stelara concentrate for solution for infusion is also updated to include some paediatric data. In addition, minor editorial change is made to section 4.5 of the SmPC for all Stelara formulations.

The Package Leaflet has been updated accordingly. The list of local representatives in the PL has been revised.

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet was performed, which is acceptable as it was carried out at the time of the adolescent psoriasis variation procedure and no major changes in addition to the new population are brought with the extension to patients ≥6 to <12 years of age.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Psoriasis is a chronic skin disease characterized by hyperproliferation of epidermal keratinocytes and inflammation of the epidermis and dermis. While the pathogenesis of psoriasis is not completely understood, the disease is thought to be a complex interaction involving immunologic and environmental factors in a genetically predisposed individual.

Studies addressing the age of onset of psoriasis have suggested that 2 subgroups exist: early onset disease (before 30 years of age, including paediatric onset) and late onset disease (after age 30). Generally, the clinical manifestations of psoriasis in patients with paediatric onset and those with adult or late onset disease are similar, and not clinically distinguishable. The consensus is that psoriasis is a life-long chronic disease with a variable age of onset, and that paediatric psoriasis is probably most accurately characterized as early onset disease, with the same underlying immunopathogenesis and biology, rather than as an entity distinct from adult psoriasis. Furthermore, there appears to be no distinction between psoriasis occurring in younger children compared with adolescents in terms of the underlying immunologic mechanism and clinical manifestations.

3.1.2. Available therapies and unmet medical need

The treatment paradigm for psoriasis is a stepwise approach starting with topical agents, followed by phototherapy, conventional systemic agents, and then biologics. The optimal treatment approach for paediatric patients with moderate to severe psoriasis is less clear than for adults and with fewer approved treatment options. Phototherapy can be impractical for school-age children with multiple daytime treatments and conventional systemic immunomodulating agents (e.g. methotrexate, cyclosporine, and acitretin) are mostly not approved for use in the paediatric population. Two TNFα inhibitors (etanercept and adalimumab) are approved for the treatment of paediatric patients below the age of 12 requiring frequent administrations (injections given weekly or every other week) and are associated with the

potential safety concerns known with use of TNFα inhibitors. Therefore, another treatment option would be useful to provide an additional option for the treatment of paediatric psoriasis in children less than 12 years of age.

3.1.3. Main clinical studies

The clinical development of ustekinumab in paediatric psoriasis includes PSO3006 (CADMUS) and PSO3013 (CADMUS Jr).

CADMUS supported approval of ustekinumab in 2015 for the treatment of psoriasis in patients aged from 12 to less than 18 years and was a randomized, double-blind, placebo-controlled, multicentre trial to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of ustekinumab in children aged from ≥12 to <18 years with moderate to severe chronic plaque psoriasis. The study is completed.

CADMUS Jr is a Phase 3 study supporting the extension of indication in children aged from ≥6 to <12 years and is an open-label, single-arm, multicentre trial 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. This study was compliant with the Paediatric Investigation Plan for ustekinumab. The main study through to Week 56 is complete, the long-term extension is ongoing.

The eligibility criteria and endpoints in the adolescent and children studies were the same. The weight-based doses used were the same and dosing interval was very similar across both studies. The primary endpoint used in the paediatric studies (proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at week 12) was different to that used in the adult ustekinumab studies.

Overall, 154 paediatric subjects with psoriasis (≥6≤18 years of age) have been treated in ustekinumab clinical trials, 44 of these were aged ≥6 to <12 years (ITT population). These subjects were mostly female (27 female vs 17 male) and mostly Caucasian (40/44 subjects). The average duration of follow-up was 53.15 weeks.

3.2. Favourable effects

Comparable clinical manifestation and similar underlying immuno-pathogenesis and biology of psoriasis in adults, adolescents and paediatric subjects support the extrapolation approach used in this submission.

PK analyses using observed and model-predicted data showed that weight-based standard dosage of ustekinumab used in PSO3013 resulted in comparable PK and exposure in paediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years of age and adults.

In study PSO3013, 77.3% (95% C.I. 62.2 - 88.5%) of the subjects met the primary endpoint of clear or almost clear skin by week 12. The median PASI score at baseline was 16.1 and a significant majority 84.1% (95% C.I. 69.9%; 93.4%) of participants achieved a 75% improvement in this PASI score. The other key secondary endpoints were also met with 63.6% (95% C.I. 47.8%; 77.6%) of subjects achieved a 90% improvement from their baseline PASI score at week 12, 34.1% (95% C.I. 20.5%; 49.9%) of subjects achieved a 100% improvement from their baseline PASI score at week 12. The median change from baseline in CDLQI score at week 12 was -6.0 (Range -27 to +7).

At Week 12, efficacy was comparable for the primary endpoint of PGA 0/1 and for the major secondary endpoints in paediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years of age and adults. Responses were maintained from Week 12 through Week 52 and were generally comparable over time between the paediatric age groups and similar than responses in adults. The numbers of subjects included in any subgroup analyses were too small to draw any meaningful conclusions from such analyses.

The sensitivity analyses performed confirm the positive results of the primary analyses.

Ustekinumab provides an alternative mode of action to the currently approved biologics for the treatment of paediatric psoriasis in children ≥6 to <12 years of age. In addition, ustekinumab also offers improved convenience of administration (q12w administrations of ustekinumab versus injections given weekly or every other week with etanercept and adalimumab, respectively).

3.3. Uncertainties and limitations about favourable effects

The application to extend the indication is based on a single open label study with small numbers of subjects (n=44). However, the magnitude of effect seen in the objective outcome measurements in the pivotal study PSO3013 is considered of clinical importance.

Study PSO3013 included five ustekinumab injections from week 0 to week 40 and included efficacy assessments until week 52. Long-term efficacy i.e. maintenance treatment has not been investigated in paediatric subjects ≥6 to <12 years of age or adolescents and will be evaluated in the post-authorisation safety study in this age group as defined the RMP.

3.4. Unfavourable effects

In the open label study PSO3013, 34 (77.3%) of patients experienced 1 or more adverse event through week 56. Serious adverse events were experienced by 3 [6.8%] subjects. The most common adverse reactions reported by preferred term include nasopharyngitis (11 [25.0%] subjects), followed by pharyngitis, upper respiratory tract infection (URTI), and injection site erythema (6 [13.6%] subjects each).

No new safety issues were identified in the paediatric subjects ≥6 to <12 years of age. Overall, the safety results were comparable across the age groups.

The incidence of antibodies through week 56 was 9.5% and does not appear to be higher than in adolescent or adults. None of the 4 paediatric subjects who were positive for antibodies to ustekinumab reported injection-site reactions after development of antibodies to ustekinumab.

3.5. Uncertainties and limitations about unfavourable effects

Safety data are limited in paediatric subjects ≥6 to <12 years of age with only 44 subjects included in study PSO3013. Furthermore, the open label single arm design is a limitation to rule out the potential for differences in safety profile.

Long-term safety data are not available neither with ustekinumab nor with other agents which act on both IL-12 and IL-23 in this population. The study conducted was not powered to detect safety concerns with longer latencies (e.g. malignancies, some infections).

One serious infection occurred PSO3013 (infectious mononucleosis which resolved following hospitalisation and without a change in ustekinumab treatment). There were no reports of malignancies through Week 56.

Long-term safety data will be collected from the extension study PSO3013. In addition, registry PSO4056 designed to characterise the long-term safety and long-term impact on growth and development in paediatric psoriasis patients 12 years and older will be amended to include also paediatric patients as of 6 years of age as defined in the RMP.

3.6. Effects Table

Table 18 Effects Table for ustekinumab plaque psoriasis indication to children aged 6-12 years (Week 12 data, CADMUS Jr)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PGA	Proportion of subjects achieving PGA of 0 or 1	%	77.3% (62.2%; 88.5%)	N/A	Open label study design, n=44	
PASI 75	Proportion of subjects achieving a 75% improvement in their PASI score	%	84.1% (69.9%; 93.4%)	N/A	Open label study design, n=44	
PASI 90	Proportion of subjects achieving a 90% improvement in their PASI score	%	63.6% (47.8%; 77.6%)	N/A	Open label study design, n=44	
PASI 100	Proportion of subjects achieving a 100% improvement in their PASI score	%	34.1% (20.5%; 49.9%)	N/A	Open label study design, n=44	
CDLQI	Median change from baseline	#	-6.0 (Range -27; +7)	N/A	Open label study design, n=44	
Unfavourable Effects						
Adverse Events	Subjects with 1 or more AEs through week 56	%	77.3% subjects	N/A	No safety data beyond 1 year /Open label study design, n=44	
Serious AE	Subjects with 1 or more AEs through week 56	%	6.8% subjects	N/A	No safety data beyond 1 year /Open label study design, n=44	
Serious infections	Subjects with 1 or more AEs through week 56	%	2.3% subjects	N/A	No safety data beyond 1 year /Open label study design, n=44	

Abbreviations: PGA=Physician's Global Assessment. PASI=Psoriasis Area and Severity Index. CDLQI=Children's Dermatology Life Quality Index, max score is 30.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The magnitude of effect seen in the objective outcome measurements in the pivotal study PSO3013 is of clinical importance in this unsightly chronic condition with 77.3% (95% C.I. 62.2 - 88.5%) of the patients who met the primary endpoint of clear or almost clear skin by week 12. Ustekinumab injections were

administered at weeks 0, 4 and 12 weekly thereafter (week 16, 28, 40). The median PASI score at baseline was 16.1 and a significant majority (84.1%) of participants achieved a 75% improvement in this PASI score. By week 12, more than one third of subjects had achieved completely clear skin (PGA 0). Given that the eligibility criteria meant those with moderate to severe plaque psoriasis, this represents a positive and clinically meaningful outcome for participants. A median reduction of 6 points was reached in the quality of life scoring system CDLQI, which can be considered significant given that the baseline CDLQI was 7. Efficacy was generally maintained beyond week 12.

With the median % BSA affected at baseline being 18.0%, the improvements in measured parameters represent a clinically meaningful result for subjects.

The beneficial effects seen in the CADMUS Jr study are in line with previous efficacy demonstrated in adolescents and adults.

While subcutaneous administration is not the most suitable in such young patients, the treatment burden is considered limited as injections are administered 12-weekly.

The safety profile appears to be consistent with the known safety profile for ustekinumab. No new safety concern was identified. Further long-term safety data on ustekinumab in paediatric patients will be generated the long-term safety extension of the maintenance study PSO3013 and from a category 3 Study as defined in the RMP.

3.7.2. Balance of benefits and risks

The improvement seen in objective and subjective efficacy measurements at week 12 and beyond are considered to be clinically relevant in a patient population aged 6-12 years who have moderate to severe plaque psoriasis. Considering all favourable and unfavourable effects, the benefit-risk balance is considered positive in this target group. Whilst routine risk minimisation remains sufficient to minimise the risks of the product, long term maintenance and effect on safety in patients aged 6-12 years with moderate to severe plaque psoriasis is included in the RMP as an area of missing information and will be addressed by the Registry PSO4056 as described in the RMP. Further long-term safety data will be generated from the maintenance study PSO3013.

3.7.3. Additional considerations on the benefit-risk balance

An extrapolation approach has been used to support the submission. Comparable clinical manifestation and similar underlying immuno-pathogenesis and biology of psoriasis in adults, adolescents and paediatric subjects has been adequately justified. Comparable exposure in children ≥6 to <12 years of age resulting in comparable efficacy in addition to no new identified safety concerns support the extrapolation approach.

3.8. Conclusions

The overall B/R of Stelara is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and

therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include the treatment of children aged 6 to 12 years with moderate to severe psoriasis for Stelara solution for injection; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Section 4.8 for Stelara concentrate for solution for infusion is updated accordingly. Minor editorial changes are made to Section 4.5 for both formulations.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 16.1 has also been submitted.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0003/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

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

Scope

Extension of indication to include the treatment of children aged ≥6 to <12 years with moderate to severe psoriasis for Stelara solution for injection; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Section 4.8 for Stelara concentrate for solution for infusion is updated accordingly. Minor editorial changes are made to Section 4.5 for both formulations.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 16.1 has also been submitted.

Summary

Please refer to the Scientific Discussion Stelara-H-C-958-II-73.