Clinical Pharmacology Review

BLA Number	125,261/Supplement 150
Link to EDR	\\CDSESUB1\evsprod\BLA125261\125261.enx *(eCTD 0443)*
Submission Date	September 30, 2019
Submission Type	Efficacy/Labeling supplements
Brand Name	STELARA®
Generic Name	Ustekinumab
Related Indication	Treatment of subjects 6 years of age and older with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Applicant	Janssen Biotech, Inc.
OCP Review Team	Cindy (Liping) Pan, Ph.D. Yangbing Li, Ph.D. Jiang Liu, Ph.D. Chinmay Shukla, Ph.D.
OCP Division	DIIP
OND Division	CDER/ODEIII/DDDP

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1 EXECUTIVE SUMMARY

STELARA® (ustekinumab), a human IL-12 and IL-23 antagonist, was initially approved in 2009 for the treatment of adult subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy and was later approved in 2017 for the plaque psoriasis in adolescent subjects 12 to 17 years of age. The recommended dosage for psoriasis patients 12 years or older is weight-based dosage subcutaneously (SC) administered at Weeks 0 and 4, then every 12 weeks (Q12W) thereafter (Table 1).

Table 1   Recommended Dosage

Adult (18 years and older)			Adolescent (12 to 17 years)	
Weight Range (kg)	Dosage		Weight Range (kg)	Dosage
≤ 100	45 mg		< 60	0.75 mg/kg
> 100	90 mg		60 to 100	45 mg
			> 100	90 mg

There were a Post-Marketing Requirement (PMR#1) in the original Biologics License Application (BLA) approval letter and a PMR 2331-1 in the approval letter of the Supplemental BLA (sBLA 125,261/s138) for the treatment of psoriasis in adolescent subjects ≥12 to < 18 years of age:

PMR#1   Conduct studies to evaluate the safety and efficacy of ustekinumab in pediatric subjects with plaque psoriasis

PMR 2331-1 Complete the ongoing open-label study CNTO1275PSO3013, assessing the efficacy, safety, and pharmacokinetics of subcutaneously administered ustekinumab in pediatric subjects 6 to <12 years of age with moderate to severe chronic plaque psoriasis.

Currently, the Applicant submitted a sBLA with the results of Study CNTO1275PSSO3013 (PSO3013) to fulfill the aforementioned PMR#1 and PMR 2331-1 and is seeking the approval of ustekinumab for the treatment of psoriasis in pediatric subjects ≥6 to <12 years of age. Labeling revisions to reflect the results of Study PSO3013 have been submitted in this application.

The Applicant proposed the recommended adolescent dose regimen (Table 1) for the treatment of psoriasis in pediatric subjects aged 6 to 11 years.

Of note, the pediatric study requirement for ages under 6 years was waived by the Agency due to a low study population (*see Approval Letter in DARRTS dated 10/13/2017, Reference ID 4167129*).

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1.1 Recommendation

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) has reviewed the information contained in Supplement 150, BLA 125,261 and concluded that the Applicant has fulfilled PMR#1 and PMR 2331-1. The review team recommends approval of this sBLA from a Clinical Pharmacology's perspective.

2 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

2.1 Recommended Dosage Regimen

The clinical outcomes for efficacy and safety in Study PSO3013 support that the proposed dose regimen of ustekinumab is appropriate for pediatric subjects aged 6 to 11 years with moderate to severe chronic plaque psoriasis.

Efficacy findings:

The efficacy results of the proposed ustekinumab dosing regimen for primary efficacy endpoint Physician's Global Assessment clear (0) or minimal (1) (PGA0/1) and secondary endpoints in pediatric patients at Week 12 are shown in Table 2 and through Week 52 are presented in Figure 1.

Table 2   Efficacy Results at Week 12 in Study PSO3013

Efficacy endpoints	Efficacy results (n=44)	
	Proportion (%)	95% CI (%)
PGA 0/1	77.3	62.2; 88.5
PASI 75	84.1	69.9; 93.4
PASI 90	63.6	47.8; 77.6
CDLQI*	-6.3	-8.29; -4.28

*mean change from baseline in CDLQI score. 95%CI=95% confidence interval, CDLQI=Children's Dermatology Life Quality Index, PASI=Psoriasis Area and Severity Index
(Source of data: Reviewer's summary based on Clinical Study Report PSO3013, Tables 3, 4, 5, and 6)

Figure 1   Response Rates of PGA 0/1 or PASI 75 through Week 52
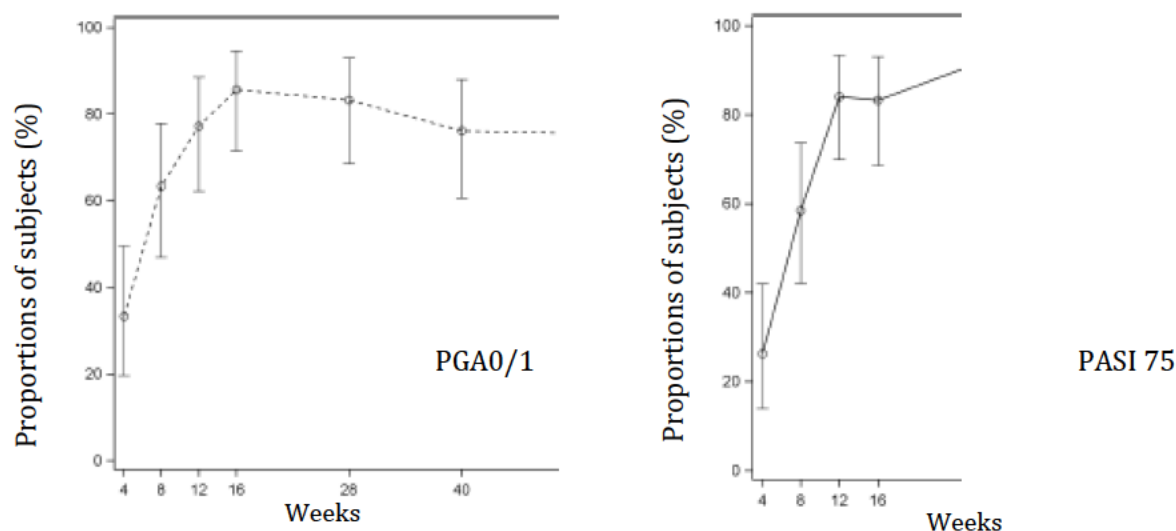
(Source of data: Clinical Study Report PSO3013, Figures 6 and 8)

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Safety findings:
No new safety issues were identified in pediatric subjects 6 to 11 years treated with ustekinumab in Study PSO3013, and the observed safety profile in these pediatric subjects was similar to the safety profile observed in ustekinumab-treated adult (≥18 years) and adolescent subjects aged 12 to 17 years with psoriasis. See Clinical review for more details.

2.2 Pharmacokinetics

Following multiple SC doses of ustekinumab in pediatric psoriasis patients aged 6 to 11 years, steady-state serum concentrations of ustekinumab were achieved by Week 28. Median trough serum ustekinumab concentrations at Weeks 28, 50, and 52 were 0.34 mcg/mL, 0.40 mcg/mL, and 0.38 mcg/mL, respectively. There was no evidence of accumulation in serum ustekinumab concentrations over time.

2.3 Immunogenicity

Approximately 9.5% (4/42) of subjects treated with ustekinumab developed anti-drug antibodies (ADA) by Week 56 in Study PSO3013. Of the ADA positive subjects, 50% (2/4) of subjects were positive for neutralizing ADA (NAb).

2.4 Summary of Labeling Recommendations

Labeling recommendations are summarized as in Table 3. The text in red is proposed by the Applicant. The ~~strikethrough in red~~ text indicates recommended deletion by the reviewer. The text in blue are recommended labeling by the reviewer.

Table 3   Reviewer's Recommendations on Labeling

Proposed labeling by the Applicant	Reviewer's labeling recommendations
12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics *Age: Pediatric Population* Following multiple recommended doses of STELARA® in pediatric subjects 6 to 17 years of age with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean ±SD steady-state trough serum ustekinumab concentrations were 0.36 ± 0.26 mcg/mL and 0.54 ± 0.43 mcg/mL, respectively, in pediatric subjects 6 to 11 years of age and adolescent subjects 12 to 17 years of age.	12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics *Age: Pediatric Population* Following multiple recommended doses of STELARA® in pediatric subjects 6 to 17 years of age with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean ±SD steady-state trough serum ustekinumab concentrations were 0.36 ± 0.26 mcg/mL and 0.54 ± 0.43 mcg/mL, respectively, in pediatric subjects 6 to 11 years of age and adolescent subjects 12 to 17 years of age.

Reviewer comments: *This reviewer finds the Applicant's submitted labeling language adequate.*

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3   COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1   Overview of the Product and Regulatory Background

STELARA® (ustekinumab) is a human immunoglobulin G1 kappa monoclonal antibody that binds to the p40 subunit of human interleukin (IL)-12 and IL-23.

Ustekinumab was initially approved in 2009 for the treatment of adult subjects with moderate to server plaque psoriasis and later approved in 2017 for the treatment of psoriasis in adolescent subjects. Additionally, ustekinumab was approved for the treatment of psoriatic arthritis and Crohn's disease in adult subjects in 2013 and 2016, respectively.

In the currently efficacy supplement, the Application proposed to extend the current psoriasis indication to include pediatric subjects aged 6 to 11 years with the Clinical Study Report PSO3013.

3.2   Overview of Clinical Study PSO3013

3.2.1   *Study PSO3013 in pediatric subjects aged 6 to 11 years with psoriasis*

Study PSO3013 was a Phase 3 open-label study that evaluate the efficacy and safety of ustekinumab in pediatric subjects 6 to 11 years of age with moderate to severe chronic plaque psoriasis. The study design is presented in Figure 2.

Figure 2   **Study Design**

Summary: eligible subjects received ustekinumab SC doses at Weeks 0, 4, 16, 28, and 40.
Efficacy and safety assessments were collected through Week 52 and 56, respectively.
(Source of data: Clinical Study Report PSO3013, Figure 1)
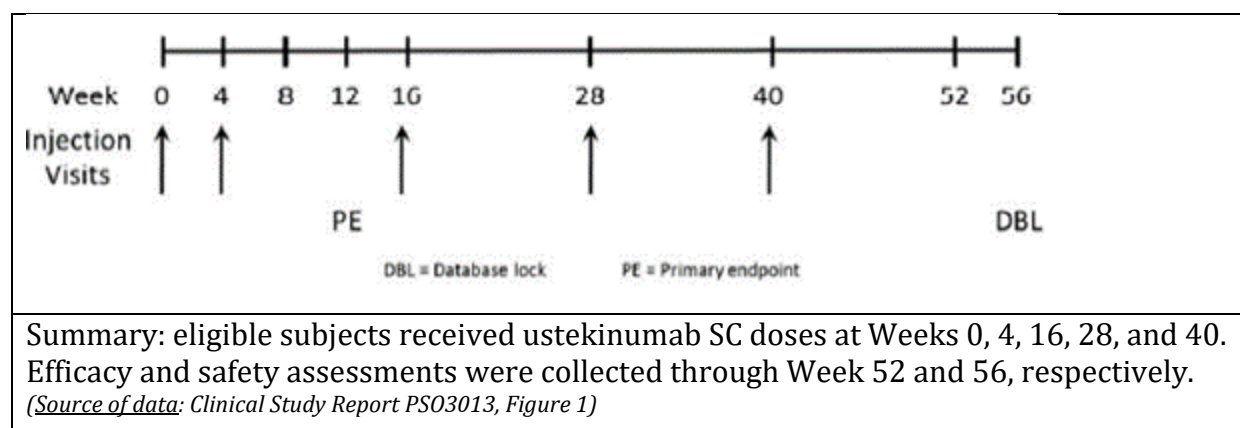
Study population:
Study PSO3013 enrolled 44 subjects with the following demographic and disease characteristics:
- Sex: females 61.4%, males 38.6%
- Most subjects were white (90.9%)
- The median body weight was 33.3 kg, with the majority of subject (91%) having a body weight of <60 kg (40/44)
- The median age was 9.5 years, with 50% of subjects <10 years of age
- The median BMI was 18 kg/m^2
- The median duration of psoriasis was 2.9 years

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- The median percent of BSA affected was 18%
- Majority of subjects (66%) had PGA scores of 3 (moderate), with 34% of subjects having a PGA score of marked or severe
- The median PASI score was 16.1

Dosing regimen:

All subjects enrolled in the study were to receive the weight-based SC ustekinumab at Weeks 0 and 4 followed by a maintenance dose every 12 weeks thereafter, with the last dose at Week 40 (Figure 2). Subjects received 1 of the following dose levels depending on their weight:

Weight Range (kg)	Dosage
< 60	0.75 mg/kg
60 to 100	45 mg
> 100	90 mg

__Reviewer's comments__: *The dose regimen used in Study PSO3013 was the same as that approved dose regimen for adolescent patients aged 12 to 17 years (Table 1).*

Primary efficacy endpoint

The primary efficacy endpoint of the study was the proportion of subjects with a PGA 0/1 at Week 12.

Pharmacokinetics

Blood samples for measurement of serum ustekinumab concentrations were collected at Weeks 0, 4, 12, 16, 28, 40, and 52. A sample was also collected at the final visit from subjects who terminated study participation early.

Immunogenicity

Blood samples for immunogenicity assessment were collected at Weeks 0, 12, 28, and 52. A sample was also collected at the final visit from subjects who terminated study participation early.

3.2.2   Supportive clinical study and associated bioanalytical methods for PK and immunogenicity assessment

The pediatric psoriasis development program of ustekinumab consists of Studies CNTO1275PSO3006 (PSO3006) and PSO3013. In this review, the data from the current submission (Study PSO3013) will be compared to the data obtained from the Phase 3 study (PSO3006) in adolescents aged 12 to 17 with moderate to severe plaque psoriasis which provided efficacy evidence of ustekinumab in the treatment of psoriasis in adolescents.

All bioanalytical methods applied in the current submission (Study PSO3013) are the same as those used in the adolescent Study PSO3006. Briefly, ustekinumab PK concentrations were determined by a validated Meso Scale Discovery electro-chemiluminescent immunoassay (MSD ECLIA) method with a below quantifiable limit of quantification (LLOQ) of 0.1688 mcg/mL. ADAs and NAbs to ustekinumab were detected by a validated drug tolerant MSD ECLIA method and a validated MSD competitive ligand binding assay, respectively. The maximum observed sensitivity of the serum ADA ECLIA was 1.97 ng/mL in human serum. The ECLIA assay had drug tolerance level of 100 mcg/mL of ustekinumab in serum for detection of 50 ng/mL ADA. The mean steady-state C_{trough} in Study PSO3013 ranged from 0.34 to 0.40 mcg/mL, which were lower than the drug tolerance level of the assay (100 mcg/mL). These findings suggest that the ADA levels could be determined lower than 50 ng/mL at the proposed clinical dosage regimen.

3.3   Question-Based Clinical Pharmacology Review

Refer to the *Clinical Pharmacology Review by Dr. Jie Wang (Reference ID 4139334; dated 08/15/2017)* for detailed information of study design, results, and labeling recommendations of the adolescent Study PSO3006 which partially fulfilled the aforementioned PMR#1 (BLA 125,261, Supplement 138).

3.3.1   What are the PK profiles of ustekinumab in pediatric subjects aged 6 to 11 years? Are the PK profiles similar to those observed in the adolescent subjects?

Following multiple SC doses to the pediatric subjects aged 6 to 11 years, steady-state serum concentrations of ustekinumab were achieved by Week 28 (Figure 3). Median trough serum ustekinumab concentrations ranged from 0.34 to 0.40 mcg/mL during Week 28 to Week 52 (Figure 3). At Weeks 28, 40, and 52, the proportions of subjects with below the LLOQ trough serum ustekinumab were 17.9%, 15.4%, and 16.2%, respectively. Similar serum ustekinumab concentrations were observed for subjects with body weight <60 kg at baseline treated with 0.75 mg/kg dose and subjects with body weight ≥60 kg to ≤100 kg at baseline treated with the 45 mg dose. It should be noted that there were limited number of subjects (n=4) that had body weight ≥60 kg to ≤100 kg at baseline (Figure 4).

A comparison of PK profile of ustekinumab observed in adolescents (12 to 17 years) and pediatrics (6 to 11 years) following the same weight-based dose regimen indicates that the PK profiles were generally comparable between two age groups (Figure 5), although the mean and median ustekinumab concentrations in the adolescent subjects were numerically higher than those observed in the pediatric subjects, the difference was not significant. The results from population PK analysis from Pooled Pediatric Model also suggest that systemic exposure to ustekinumab in pediatric patients following the proposed weight-based dosage were similar to those in adolescent patients who received the approved standard dosage of ustekinumab (Figure 6).

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Overall, the weight-based standard dosage used in the PSO3013 and PSO3003 studies provided similar ustekinumab exposure in pediatric (6 to 11 years) and adolescent subjects (12 to 17 years) with psoriasis.

Figure 3   **Ustekinumab Concentrations in Pediatric Subjects 6 to 11 Years**
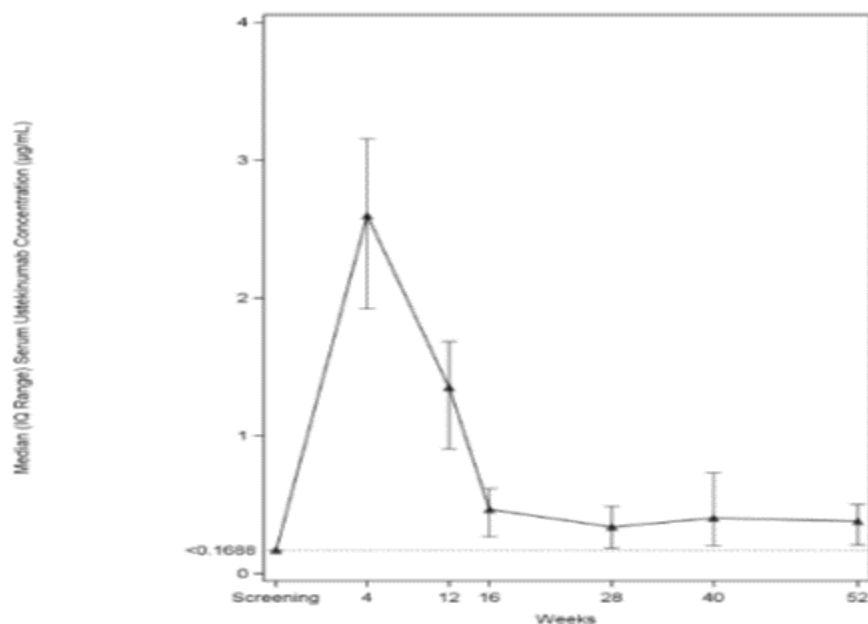
(Source of data: Clinical Study Report PSO3013, Figure 4)

Figure 4   **Ustekinumab Concentrations by Weight in Pediatrics 6 to 11 Years**
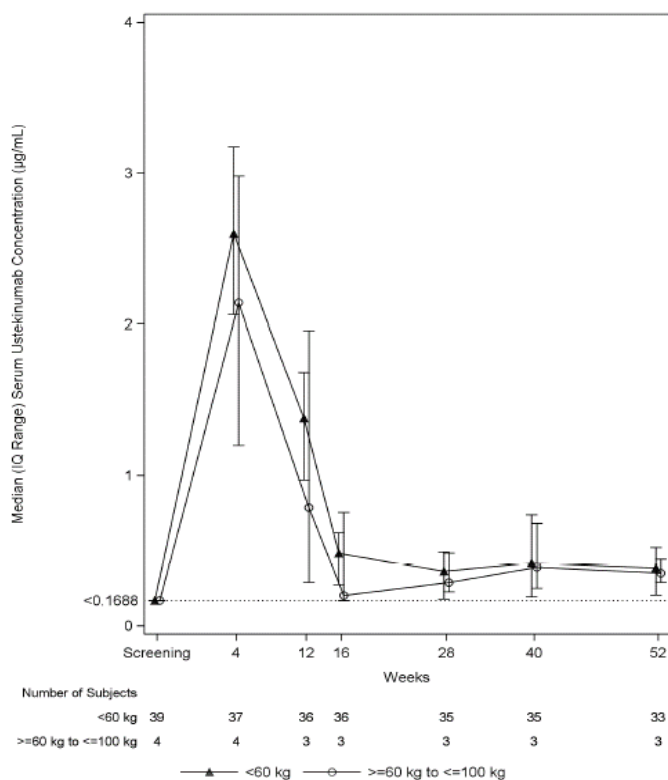
(Source of data: Clinical Study Report PSO3013, Figure 5)

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Figure 5   **Comparison of Ustekinumab Concentrations Between Adolescents (Study PSO3006) and Pediatrics 6 to 11 years old (Study PSO3013)**
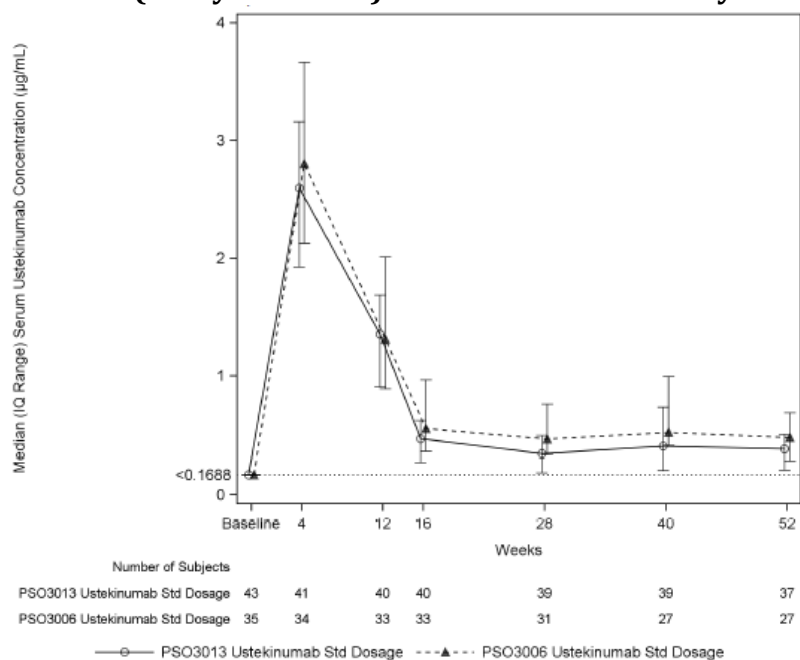
(Source of data: Summary of Clinical Pharmacology, Figure 3)

Figure 6   **Population PK Model-Simulated Ustekinumab Concentrations in Adolescents (12 to 17 years) and Pediatrics (6 to 11 years) Receiving Standard Dosage**
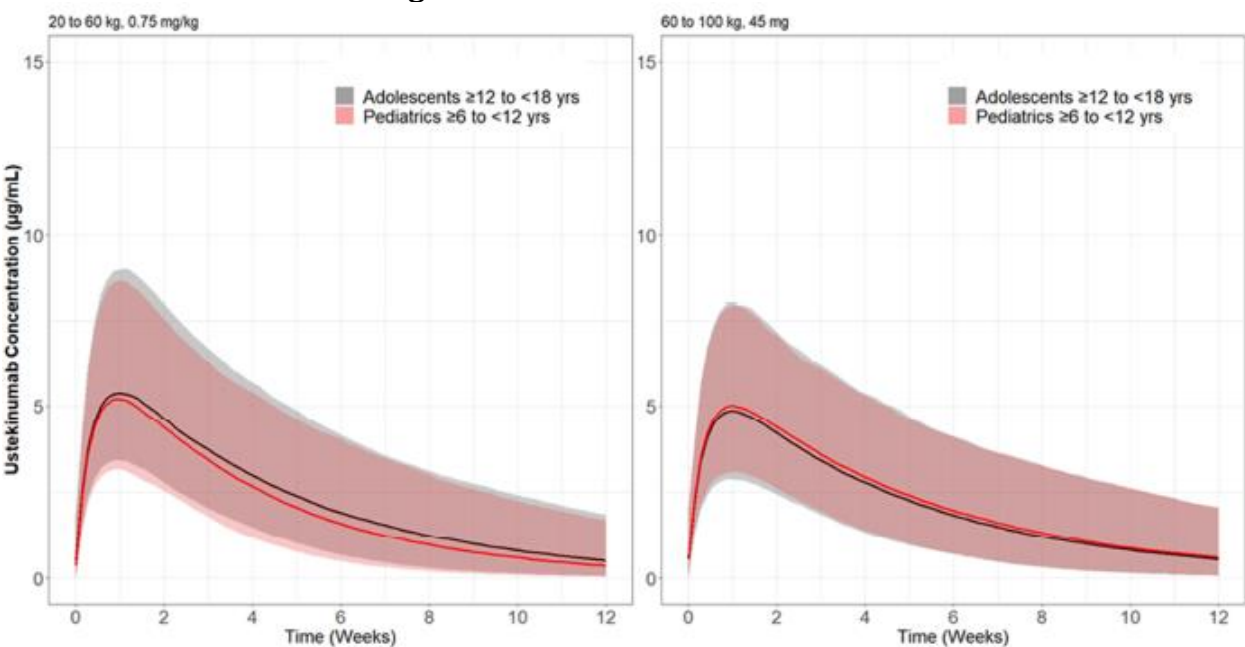
(Source of data: Summary of Clinical Pharmacology, Appendix 5)

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3.3.2 Dose the clinical pharmacology information provided support the evidence of effectiveness for the proposed dosing regimen of ustekinumab in pediatric subjects 6 to 11 years with moderate to severe psoriasis?

Yes. The clinical outcomes for efficacy support that the proposed dosage regimen of ustekinumab is appropriate for pediatric subjects aged 6 to 11 with moderate to severe psoriasis. See *Section 2.1* of this review.

An exploratory exposure-response (E-R) analysis for PGA 0/1 suggested that the PGA 0/1 response appeared to be associated with quantifiable steady-state trough ustekinumab levels. The proportion of subjects who achieved PGA 0/1 response at Week 40 was higher in subjects with quantifiable serum ustekinumab concentrations at Week 40 (100% and 75.0% for the 2 quantifiable trough categories, respectively) when compared with subjects below LLOQ of serum ustekinumab concentrations at Week 40 (33.3%) (Figure 7). Note that PGA 0/1 was the primary efficacy endpoint in Study PSO3013. Similar to the PGA 0/1 response at Week 40, the PGA 0, PASI 75 (Figure 8) or PASI 90 response at Week 40 also appeared to be associated with quantifiable steady-state trough serum ustekinumab concentration levels at Week 40. The results demonstrate E-R relationship for the four efficacy variables.

Reviewer's comments*: Among 4 ADA+ subjects, two with ustekinumab concentrations of below LLOQ (<0.1688 mcg/mL) starting at Week 12 or 16 did not achieve PGA 0/1 and PASI 75 responses by Week 40. One subject with ustekinumab concentrations of below LLOQ starting at Week 28 and a high titer (1:12800) achieved PGA 0/1 and PASI 75 by Weeks 40. One ADA+ subject with ustekinumab concentration of 0.81 mcg/mL at Week 40 achieved majority of efficacy variables during Weeks 12 to 52, except for PGA 0/1 at Week 40 (see Table 5 for details).*

Figure 7   Percent of Subjects Achieving a PGA 0/1 at Week 40 by Trough Serum Ustekinumab Concentrations at Week 40
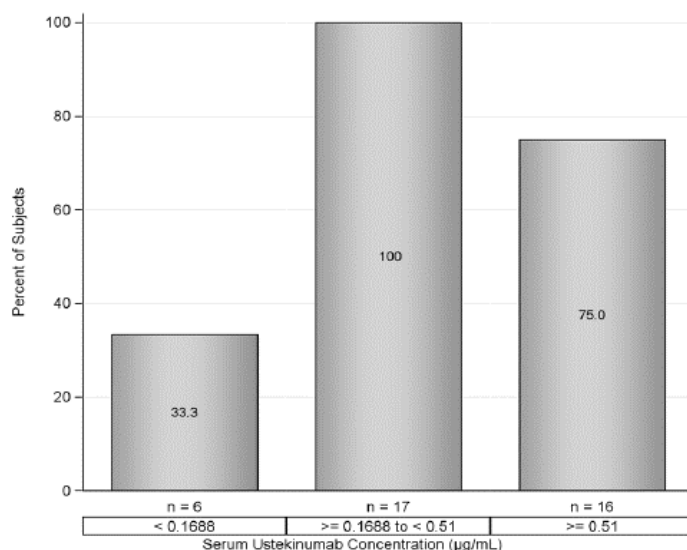
(Source of data: Clinical Study Report PSO3013, Figure 11

Figure 8   **Percent of Subjects Achieving a PASI 75 at Week 40 by Trough Serum Ustekinumab Concentrations at Week 40**
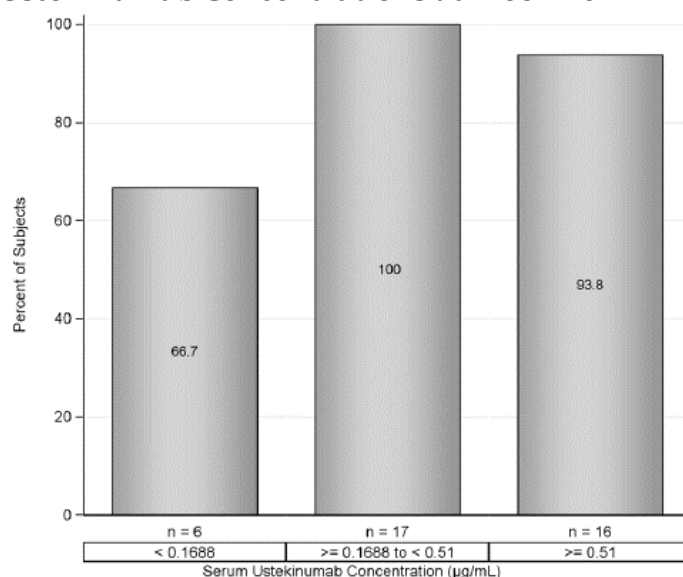
(Source of data: Clinical Study Report PSO3013, Figure 12)

E-R analysis for PGA (0/1) using observed trough concentrations of ustekinumab at Week 12 identified shallow and non-significant E-R relationship for pediatric subjects ≥6 to <12 years and pooled pediatric subjects ≥6 to <18 years (Figure 9). Concentrations below the LLOQ were excluded from the analysis. There is no significant difference in PGA (0/1) response rate in different exposure groups for pediatric subjects ≥6 to <12 years. The similar E-R relationship for PGA (0/1) response was also observed for pooled pediatric subjects ≥6 to <18 years. See section 4.2 for more information.

Figure 9   **Logistic Regression Analysis of Ustekinumab Exposure for PGA (0/1) in Pediatric and Adolescent Subjects**

(Source of data: Reviewer's independent analysis)

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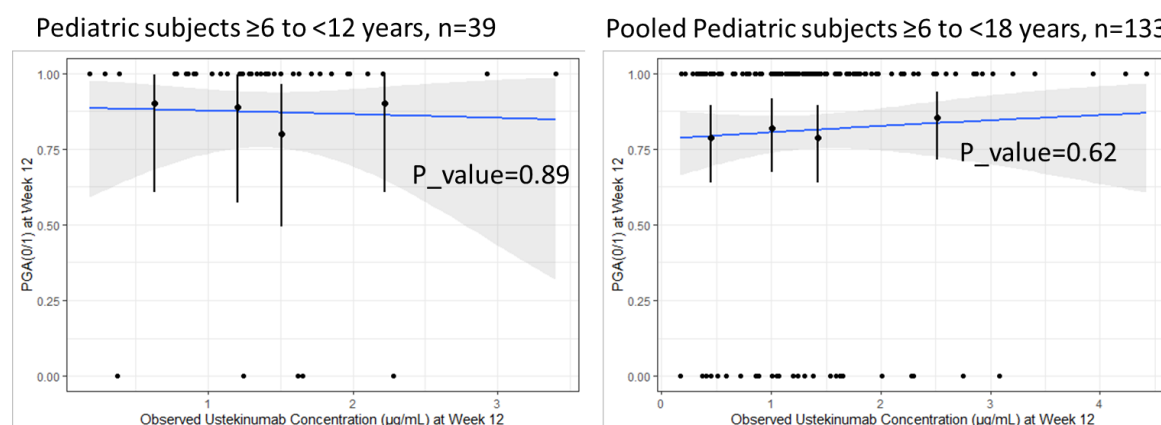
3.3.3 What is the incidence rate of anti-drug antibodies to ustekinumab in pediatrics 6 to 11 years comparing with that in adolescents? What are the impacts of anti-drug antibodies on PK and efficacy?

- Approximately 9.5% (4/42) of subjects treated with ustekinumab developed ADAs by Week 56 in Study PSO3013. The titers of ADAs ranged from 1:200 to 1:12,800. By Week 52, two of the 4 ADA positive subjects had the last sample negative for ADA to ustekinumab and one had the ADA titer level of 1:200. Of the ADA positive subjects, 50% (2/4) of subjects were positive for NAbs.

- A comparison of incidence rates of ADAs between pediatric (6 to 11 years) and adolescent (12 to 17 years) psoriasis studies is summarized in Table 4. Generally, the observed incidences of ADAs in the pediatric subjects (PSO3013) and the adolescent subjects (PSO3013) are comparable.

- Overall, the formation of ADA appears to be associated with a decrease in serum ustekinumab concentrations (Table 5). At time-points following ADA formation, majority of PK samples had serum ustekinumab concentrations of below LLOQ. The efficacy results indicate that 2 of the 4 ADA positive subjects achieved PGA 0/1 and PASI 75 responses by Week 52 (Table 5). The impact of ADA on efficacy is unclear due to the small number of subjects who were ADA positive.

Table 4   Comparison of ADA Status in Study PSO3013 and Study PSO3006

	PSO3013 Standard Dosage	PSO3006 Standard Dosage	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, $\geq$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.

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(Source of data: Summary of Clinical Pharmacology, Table 6)

Table 5   List of Subjects Positive for ADAs Trough the End of the Reporting Period

Study ID	Treatment Group	Subject ID	Age(years)/ Sex/ Race	Visit	Body Weight at Visit	Injection Given/ Dose	Injection Reaction MedDRA Preferred Term	Maximum Intensity	Serum Ustekinumab Conc.(µg/mL)	Antibody Status/ Titer[a]	NAb Status	PGA 0/1 Responder	PASI 75 Responder
CNTO1275PSO3013	Ustekinumab	(b) (6)	11/F/White	Screening		No			<0.16880	NEG		No	
				Week 0	49.0	Yes/36.90 mg						No	
				Week 4	49.0	Yes/36.90 mg			1.04705			No	No
				Week 12		No			0.18407	NEG		Yes	Yes
				Week 16	48.5	Yes/36.00 mg			<0.16880			Yes	Yes
				Week 28	48.8	Yes/36.90 mg			<0.16880	POS/400	NEG	Yes	Yes
				Week 40	49.0	Yes/36.90 mg			<0.16880			No	Yes
				Week 52	50.8	No			<0.16880	NEG		No	No
			10/F/White	Screening		No			<0.16880	POS/200	NEG	No	
				Week 0	29.0	Yes/21.60 mg						No	
				Week 4	30.5	Yes/22.50 mg			1.91393			No	No
				Week 12		No			<0.16880	POS/400	POS	No	No
				Week 16	30.5	Yes/22.50 mg			<0.16880			No	No
				Week 28	30.0	Yes/22.50 mg			<0.16880	POS/1600	POS	No	No
				Week 40	34.4	Yes/26.10 mg			<0.16880			No	No
				Week 52	34.4	No			<0.16880	POS/100	POS	No	No
			7/F/White	Screening		No			<0.16880	POS/3200	NEG	No	
				Week 0	31.0	Yes/23.40 mg						No	
				Week 4	32.0	Yes/24.30 mg			3.27902			Yes	Yes
				Week 12		No			1.71408	POS/12800	NEG	Yes	Yes
				Week 16	31.0	Yes/23.40 mg			0.52720			Yes	Yes
				Week 28	33.2	Yes/25.20 mg			<0.16880	POS/1600	POS	Yes	Yes
				Week 40	36.5	Yes/27.00 mg			<0.16880			Yes	Yes
				Week 52	37.0	No			<0.16880	POS/800	NEG	Yes	Yes
			8/F/White	Screening		No			<0.16880	NEG		No	
				Week 0	24.7	Yes/18.90 mg						No	
				Week 4	24.9	Yes/18.90 mg			3.15631			Yes	No
				Week 12		No			1.77474	NEG		Yes	Yes
				Week 16	26.2	Yes/19.80 mg			0.49000			Yes	Yes
				Week 28	27.2	Yes/20.70 mg			0.59908	POS/200	NEG	Yes	Yes
				Week 40	27.0	Yes/20.70 mg			0.81242			No	Yes
				Week 52	29.1	No			0.44219	NEG		Yes	Yes

[a] Status for anti-ustekinumab antibodies at a sample level. Samples with detectable antibodies to ustekinumab were classified as positive, while samples without detectable antibodies to ustekinumab were classified as negative.

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(*Source of data*: Summary of Clinical Pharmacology, Appendix 6)

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4 APPENDICES

4.1 Population PK

The applicant developed population PK models to describe the PK ustekinumab to support the proposed dosage regimen for pediatric subjects ≥6 to <12 years with moderate-to-severe psoriasis who are candidates for systemic therapy or phototherapy.

The studies included in the population PK analysis are shown in Table 6.

Table 6   Overview of Studies Included in the Population PK Analysis.

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(Source of data: The Applicant's population PK report, Page 15, Table 1)

C0743T08 and C0742T09 were two pivotal studies that supported the approval of the original BLA for the adult psoriasis indication. The serum concentrations of ustekinumab in these two studies were analyzed with validated electro-chemiluminescent immunoassay (ECLIA) on the BioVeris™ platform, which was discontinued by the vendor.

CNTO1275PSO3006 was a supplement efficacy study that supported the approval of the BLA for adolescent patients ≥12 to <18 years psoriasis indication. The serum concentrations of ustekinumab in this study and current pediatric psoriasis study CNTO1275PSO3013 were analyzed with a validated ECLIA on the Meso Scale Discovery (MSD®) platform. Both ECLIA methods had a similar quantification limit. However, a cross-validation comparison of the two methods showed that the results generated with using the MSD® ECLIA were higher compared with the results generated with BioVeris™ ECLIA.

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A total of 2089 subjects (1937 adults, 110 adolescent subjects ≥12 to <18 years and 42 pediatric subjects ≥6 to <12 years were included in the population PK analysis. M3 methods was implemented to evaluate the impact of BQL records for a total of 15349 records from 2089 subjects. Figure 10 shows the data stratified by study. Blood samples for measuring serum ustekinumab concentrations for PK analysis were collected at Weeks 0, 4, 12, 16, 20, 24, 28,40, 52, 60 post to the first drug administration.

Figure 10   Observed Ustekinumab Concentrations Versus Time Since First Dose for All Subjects Stratified by Study.
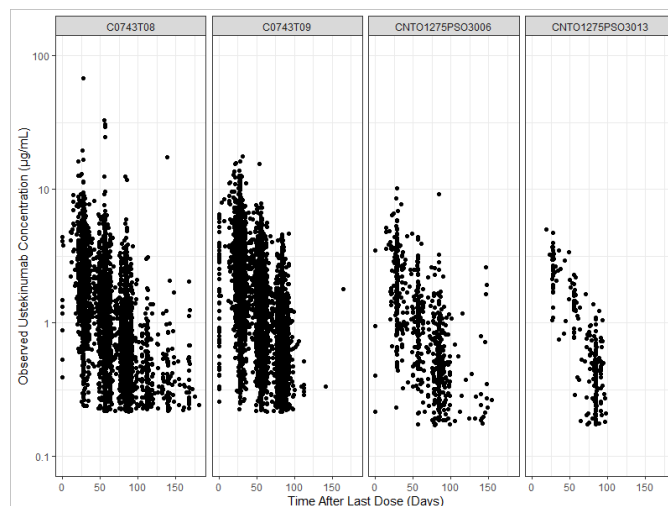
(Source of data: Reviewer's analysis)

Demographic data for subjects in each of the four studies are shown in Table 7 and Table 8. The majority of the pediatric subjects ≥6 to <12 years were Caucasian (92.9%), which were similar as adolescent subjects ≥12 to <18 years (89.1%) and adult (92.6%) subjects. The median age of pediatric subjects ≥6 to <12 years was 9 years old (range: 6-11), 38.1% were males, and median body weight was 32.4 kg (range: 18.9-98.7). The median body weight for adolescent subjects ≥12 to <18 years and adult subjects were 61.6 kg (range: 32.0-174) and 89.8 kg (range: 37.4-195), respectively. Median renal function for pediatric subjects ≥6 to <12 years, adolescent subjects ≥12 to <18 years and adult subjects were 50.2 mL/min (range: 38.8-72.8), 79.7 mL/min (range: 54.9-135) and 122.8 mL/min (range: 33.1-370.6).

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Table 7   **Demographics and Baseline Characteristics of Pooled Study Data (Continuous Variables)**

Study No	C0743T08	C0743T09	CADMUS	CADMUS JR
N	739	1198	110	42
Age (years)				
Mean (SD)	45.3 (11.7)	46.2 (12.2)	15.2 (1.65)	8.86 (1.76)
Median [Range]	45.0 [19.0, 76.0]	46.0 [18.0, 84.0]	15.5 [12.0, 17.0]	9.00 [6.00, 11.0]
Weight (kg)				
Mean (SD)	93.8 (23.5)	90.9 (21.1)	65.0 (19.2)	38.3 (15.0)
Median [Range]	91.8 [46.9, 183]	88.6 [37.4, 195]	61.6 [32.0, 174]	32.4 [18.9, 98.7]
CrCL (mL/min)				
Mean (SD)	134. (46.0)	125. (37.8)	81.4 (14.2)	51.7 (7.84)
Median [Range]	126. [39.4, 371]	121. [33.1, 308]	79.7 [54.9, 135]	50.2 [38.8, 72.8]
Serum Albumin (g/dL)				
Mean (SD)	4.36 (0.278)	4.42 (0.297)	4.27 (0.345)	4.59 (0.270)
Median [Range]	4.40 [2.60, 5.10]	4.40 [2.90, 5.40]	4.30 [3.50, 5.50]	4.60 [4.00, 5.30]
Alkaline Phosphatase (U/L)				
Mean (SD)	81.7 (23.8)	79.1 (22.5)	122. (71.0)	--
Median [Range]	79.0 [29.0, 262]	77.0 [23.0, 217]	102. [43.0, 461]	--
Psoriasis Area Severity Index				
Mean (SD)	19.6 (8.74)	19.2 (8.01)	21.1 (8.92)	18.6 (7.36)
Median [Range]	17.1 [0.400, 56.4]	17.4 [1.20, 60.3]	18.8 [12.0, 51.0]	16.8 [12.0, 53.3]

Key: N=number of subjects; SD=standard deviation;
Alkaline phosphatase values were not available for CADMUS JR

(Source of data: The Applicant's population PK report, Page 17, Table 2)

Table 8   **Demographics and Baseline Characteristics of Pooled Study Data (Categorical Variables)**

Study No	C0743T08	C0743T09	CADMUS	CADMUS JR
N	739	1198	110	42
Sex, n (%)				
Male	511 (69.1)	817 (68.2)	54 (49.1)	16 (38.1)
Female	228 (30.9)	381 (31.8)	56 (50.9)	26 (61.9)
Race, n (%)				
Caucasian	694 (93.9)	1099 (91.7)	98 (89.1)	39 (92.9)
Black	14 (1.9)	26 (2.2)	0 (0)	0 (0)
Asian	16 (2.2)	48 (4.0)	6 (5.5)	1 (2.38)
Other	15 (2.0)	25 (2.1)	6 (5.5)	2 (4.76)
Immune Response Positive[1], n (%)				
No	705 (95.4)	1170 (97.7)	101 (91.8)	38 (90.5)
Yes	34 (4.6)	28 (2.3)	9 (8.18)	4 (9.52)
History of Diabetes Mellitus, n (%)				
No	654 (88.5)	1077 (89.9)	110 (100)	42 (100)
Yes	85 (11.5)	121 (10.1)	0 (0)	0 (0)

Key: N, n=number of subjects
[1] Enzyme immunoassay (EIA) for C0743T08 and C0743T08; ECLIA assay for CADMUS and CADMUS JR

(Source of data: The Applicant's population PK report, Page 17, Table 3)

Two population PK models were developed for serum ustekinumab concentration-time data. The combined pediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years serum ustekinumab concentration-time data from pediatric studies (CNTO1275PSO3013 and CNTO1275PSO3006) were well described by a one-compartment model with first-order absorption and elimination (Pooled Pediatric Model). And the combined adult and pediatric data from pediatric and adult studies (CNTO1275PSO3013,

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CNTO1275PSO3006, C0743T08 and C0743T09,) were well described by a one compartment model with first-order absorption and elimination (Pooled Pediatric and Adult Model). Because the ECLIA assay on the MSD® platform yields markedly higher concentration results than on the BioVerisTM platform, a term for assay bias was incorporated into the base structural model via the relative bioavailability (F1) term in Pooled Pediatric and Adult Model. Given the mixture of pediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years data or adult and pediatric data, and the previous knowledge that weight is a significant covariate on the PK of ustekinumab, two alternative allometric approaches FBW (fixed allometric exponent for body weight) and EBW (estimated allometric exponent for body weight), yielding four base models, were taken with respect to the modeling of body weight effects on CL/F and V/F using the following allometric equations.

$$CL/F = \text{Typical value of CL/F} * (\text{Body weight/median of Body weight})^{\beta 1}$$

$$V/F = \text{Typical value of V/F} * (\text{Body weight/median of Body weight})^{\beta 2}$$

Where the exponents for body weight effects on CL/F and V/F were estimated for EBW and the exponent for body weight effect on CL/F and V/F was fixed to 0.75 and 1, respectively, for FBW.

Several covariates, including age, sex, race, albumin, immune response, smoke status, and diabetes comorbidity were tested for 4 base models. Race was modeled as Caucasian versus non-Caucasian. Statistically significant covariates based on stepwise covariate model building (SCM) were included in the models first, and then clinically irrelevant covariates were reduced. A clinically irrelevant covariate is defined as 10th and 90th percentile of a PK parameter estimate is less than 20% typical value. For Pooled Pediatric Model (FBW and EBW), given the potential of clinical relevance, one additional covariate (IRP, immune response positive) was retained in both models (FBW and EBW). For Pooled Pediatric and Adult Model (FBW and EBW), IRP was not retained in either model since different in immunogenicity assays were used across studies. Diabetic comorbidity (DIAB) was found to be a clinically relevant covariate on CL/F and was retained in the FBW model. DIAB was also found to be a clinically relevant covariate on CL/F in the EBW model, in addition, Sex was found to be clinically relevant on both CL/F and V/F and retained in the EBW model.

M3 method was used during the stage of evaluating of the impact of below the lowest quantifiable sample concentration of the assay records on model results. For both Pooled Pediatric Model and Pooled Pediatric and Adult Model, the M3 method provided similar parameter estimates for key PK parameters (within 15% difference) compared with the method that excluded BQL records, therefore, the M3 method was not further explored. The final FBW population PK models were selected as the primary population PK model based on the previous experience on the adolescent study (CNTO1275PSO3006). The

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parameter estimates and goodness-of-fit plots for the final FBW approaches in Pooled Pediatric Model and Pooled Pediatric and Adult Model are presented in Table 9 – Table 10 and Figure 11 – Figure 12, respectively. The VPC (visual predictive check) plots in Figure 13 – Figure 14 are stratified by dose levels and plotted versus time. Both models adequately captured the median concentration-time profile of ustekinumab as well as the associated variabilities, across the treatment groups.

Table 9   Parameter Estimates of Final FBW Pooled Pediatric 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%;

$$CL_i = CL_0 \times \left(\frac{WT}{56}\right)^{0.75} \times \left(\theta_{IRP_{CL}}\right)^{IRP} \times \exp\left(\eta_{CL,i}\right)$$
$$V_i = V_0 \times \left(\frac{WT}{56}\right)^{1} \times \exp\left(\eta_{V,i}\right)$$

(Source of data: The Applicant's population PK report, Page 25, Table 5)

Table 10   Parameter Estimates of Final FBW Pooled Pediatric 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.

$$CL_i = CL_0 \times \left(\frac{WT}{88}\right)^{0.75} \times \left(1 + \theta_{DIAB_{CL}} \times DIAB\right) \times \exp\left(\eta_{CL,i}\right)$$
$$V_i = V_0 \times \left(\frac{WT}{88}\right)^{1} \times \exp\left(\eta_{V,i}\right)$$

(Source of data: The Applicant's population PK report, Page 26, Table 6)

Figure 11   Goodness-of-fit Plots for Final FBW Pooled Pediatric 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.
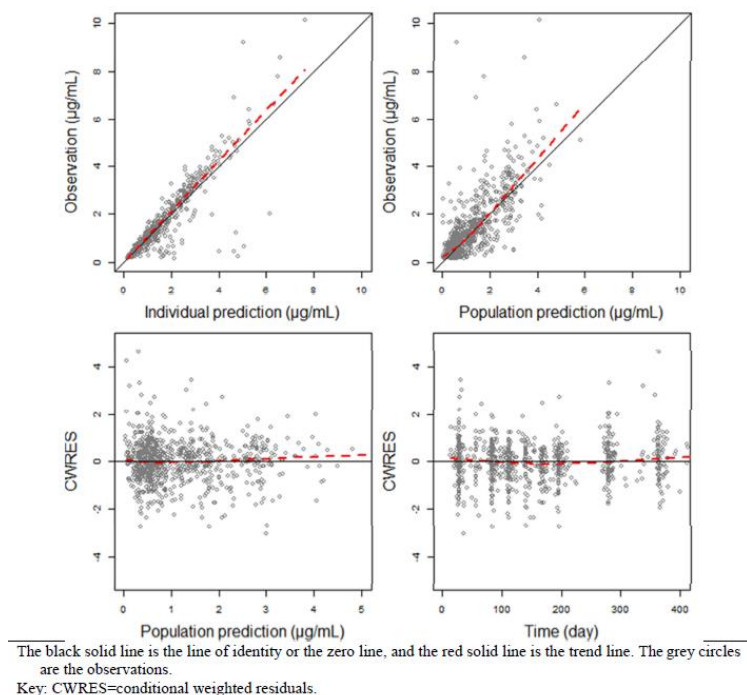
(Source of data: The Applicant's population PK report, Page 29, Figure 3)

Figure 12   Goodness-of-fit Plots for Final FBW Pooled Pediatric and Adult 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; Time = time after first dose.
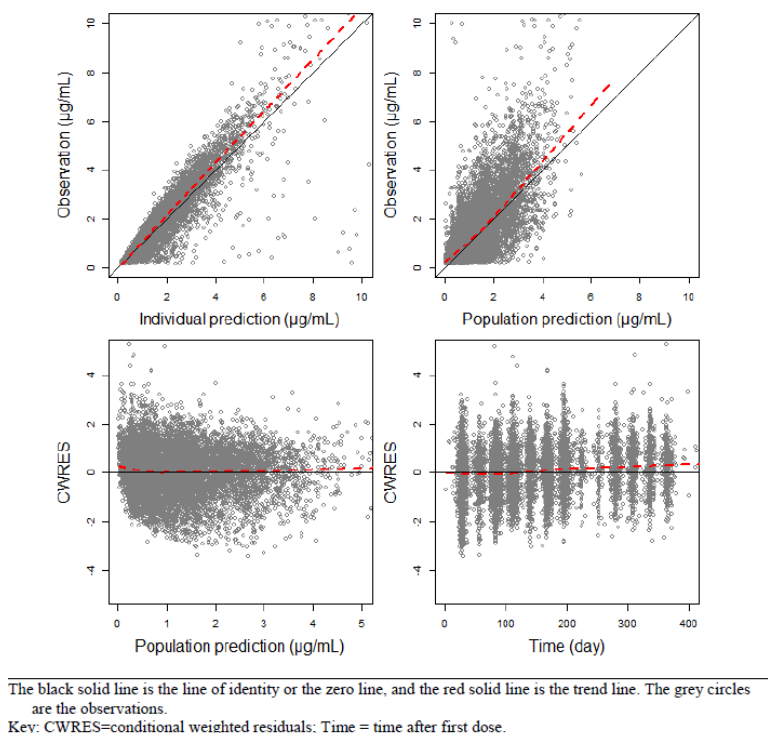
(Source of data: The Applicant's population PK report, Page 30, Figure 4)

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Figure 13   VPC Stratified by Dose Levels for Final FBW Pooled Pediatric Model.

Red solid lines represent the median of the observations. Shaded regions encompass 90% of the simulated (n = 500) values of the predicted medians, 5th, and 95th percentiles. Data points represent the observed data.
Key: Half-standard Dose = ≤60 kg, 0.375 mg/kg; >60 to ≤100 kg, 22.5mg; >100 kg, 45mg;
Standard Dose = ≤60 kg, 0.75 mg/kg; >60 to ≤100 kg, 45mg; >100 kg, 90mg;
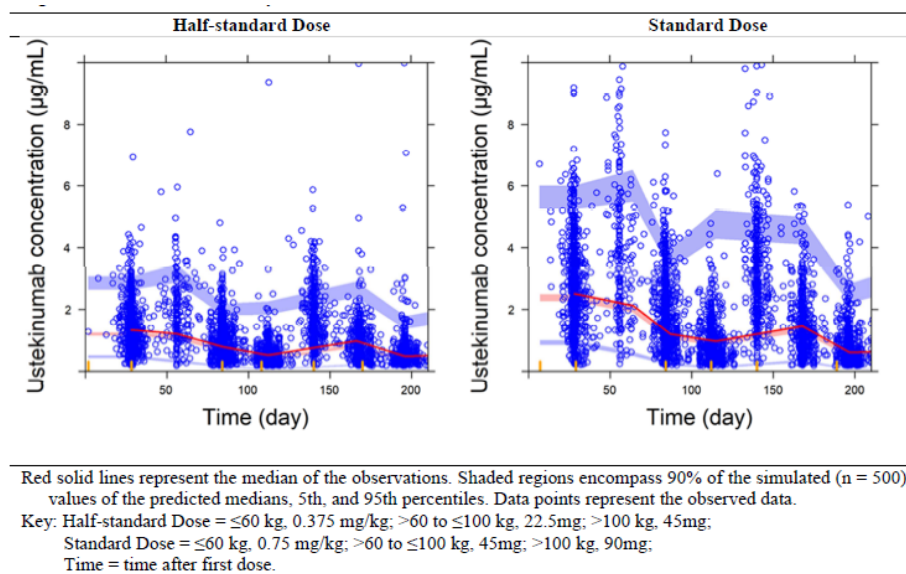Time = time after first dose.
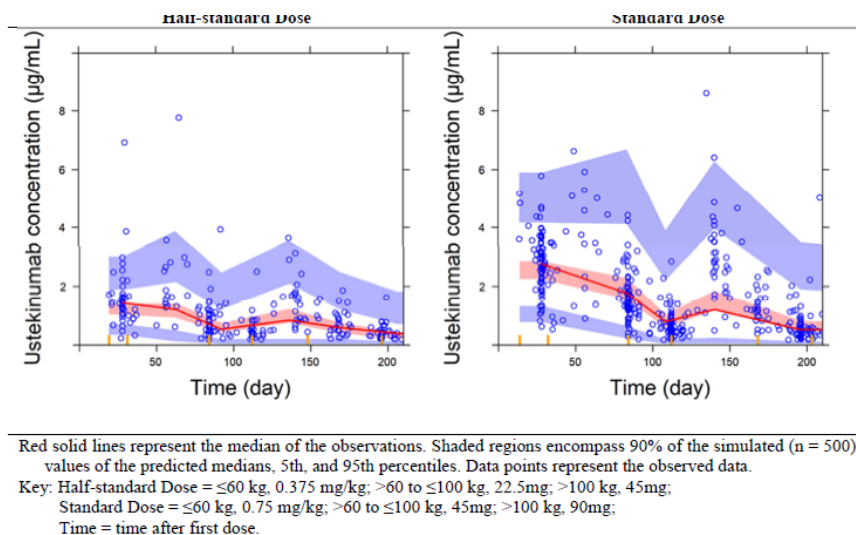
(Source of data: The Applicant's population PK report, Page 31, Figure 5)

Figure 14   VPC Stratified by Dose Levels for Final FBW Pooled Pediatric Model.

Red solid lines represent the median of the observations. Shaded regions encompass 90% of the simulated (n = 500) values of the predicted medians, 5th, and 95th percentiles. Data points represent the observed data.
Key: Half-standard Dose = ≤60 kg, 0.375 mg/kg; >60 to ≤100 kg, 22.5mg; >100 kg, 45mg;
Standard Dose = ≤60 kg, 0.75 mg/kg; >60 to ≤100 kg, 45mg; >100 kg, 90mg;
Time = time after first dose.

(Source of data: The Applicant's population PK report, Page 31, Figure 6)

Simulations were performed using final FBW Pooled Pediatric Model to confirm whether the systemic exposures in pediatric subjects ≥6 to <12 years of age with psoriasis following the proposed dosage regimens were similar to those adolescent subjects ≥12 to <18 years of age with psoriasis who received ustekinumab at the approved dosage. Figure 15 provides overlay plots for median (90% prediction interval) serum concentration-time profiles of ustekinumab in pediatric ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years in different body weight categories following the proposed/approved dosing regimens. A summary of simulated PK exposure parameters and body weight group by

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population and dosing regimen is presented in Table 11. A similar congruence between the pediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years reference populations was observed in the distributions of the model-predicted AUC, C_{max} and C_{trough} values. Following SC administration of 0.75 mg/kg q12w for the 20 to 60 kg pediatric subjects ≥6 to <12 years of age, the median C_{trough} was predicted to be 0.364 µg/mL (90% prediction interval: [0.0346, 1.68]), which is slightly lower than the median C_{trough} (0.516 µg/mL) (90% prediction interval: [0.0596, 1.86]) for the 20 to 60 kg adolescent subjects ≥12 to <18 years of age receiving 0.75 mg/kg dose q12w. All other simulated exposure parameters pediatric subjects ≥6 to <12 years of age with psoriasis following the proposed dosage regimens were comparable to those in adolescent subjects ≥12 to <18 years of age with psoriasis who received the approved standard dosage of ustekinumab for adolescent subjects ≥12 to <18 years of age.

Figure 15   Comparison of the Final FBW Pooled Pediatric Model Predicted Serum Concentration-time Profiles of Ustekinumab in Pediatric Subjects ≥6 to <12 Years of Age with Adolescent Reference Populations Receiving the Proposed/Approved Standard Dosage
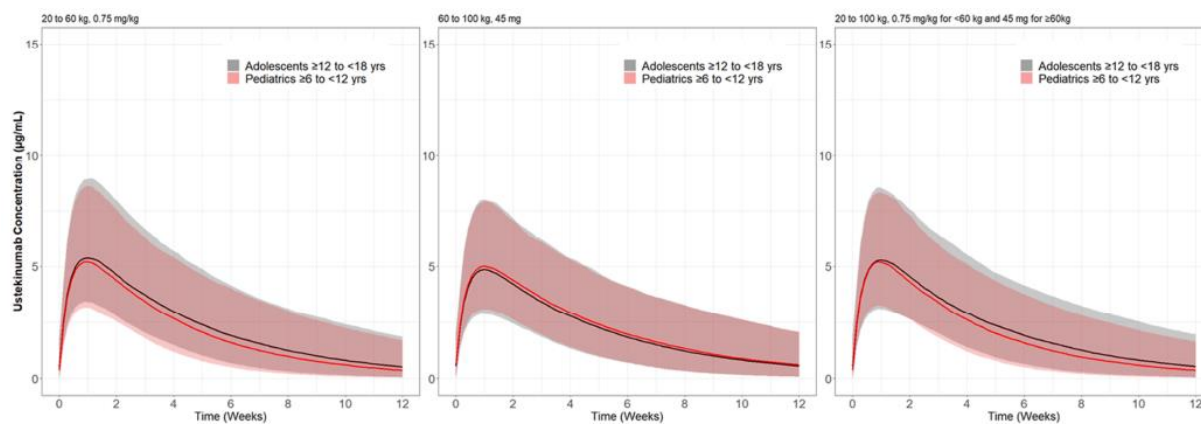
Lines represent medians of the simulated values. Shaded regions represent the $5^{th} - 95^{th}$ percentile ranges.

(Source of data: The Applicant's population PK report, Page 33, Figure 7)

Table 11   Median (90% Prediction Intervals) of Model-predicted Exposure Parameters with the Final FBW Pooled Pediatric 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

(Source of data: The Applicant's population PK report, Page 34, Table 7)

For the Pooled Pediatric and Adult Model, simulations were also performed to confirm the consistency in PK of ustekinumab between pediatric and adult subjects with psoriasis. Figure 16 provides overlay plots for median (90% prediction interval) serum concentration-time profiles of ustekinumab in pediatric and adults in different body weight categories following the proposed/approved dosing regimens. A summary of simulated PK exposure parameters and body weight group by population and dosing regimen is presented in Table 12. The results from simulations based on the final FBW Pooled Pediatric and Adult Model also confirmed that the systemic exposures of ustekinumab in each of pediatric weight groups were comparable to that in the reference adolescent subjects ≥12 to <18 years population and slightly higher than the adult population.

Figure 16   Comparison of the Final FBW Pooled Pediatric and Adult Model Predicted Serum Concentration-time Profiles of Ustekinumab in Pediatric Subjects ≥6 to <12 Years of Age with Adolescent and Adult Reference Populations Receiving the Proposed/Approved Dosage
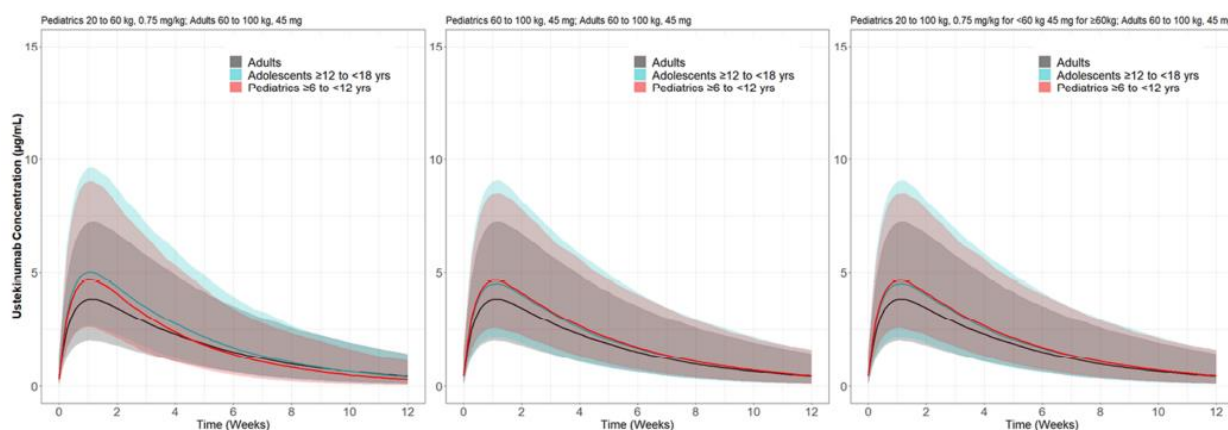
Lines represent medians of the simulated values. Shaded regions represent the 5th – 95th percentile ranges.

(Source of data: The Applicant's population PK report, Page 36, Figure 8)

Table 12   Median (90% Prediction Intervals) of Model-predicted Exposure Parameters with the Final FBW Pooled Pediatric and Adult 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	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 mg q12w	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 C_{peak}, peak serum ustekinumab concentration at steady state; C_{trough}, trough serum ustekinumab concentration at steady state

(Source of data: The Applicant's population PK report, Page 35, Table 8)

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Reviewer's comments: *The population PK models developed by the Applicant were verified by the reviewer. The models appear to be reasonable because there was a good agreement between observations and predictions.*

The Applicant incorporated a relative bioavailability term into the structural model to account for the concentration differences due to assay change across the four studies in the Pooled Pediatric and Adult Model. The concentration differences due to the different bioanalytical assays should not be assessed with population PK model as it would not be known if the differences are caused by assay methods or study populations.

Other than analytical method, the covariate analysis results were similar with previously developed population PK model based on PK data in adolescent and adults in Studies CNTO1275PSO3006, C0743T09 and C0743T08. In Pooled Pediatric and Adult Model, the diabetic comorbidity that was identified as a significant covariate on CL/F is based on the PK data in adults, as there are no pediatric subjects with a history of diabetes. The Pooled Pediatric Model PK model does not assess the impact of diabetic comorbidity in pediatric subjects with psoriasis.

The reviewer conducted an independent simulation analysis to compare the exposure for pediatric subjects ≥6 to <18 Years of Age with doses of 0.75 mg/kg, 45 mg or 90 mg in different bodyweight range. The simulation result was done with 2000 subjects from NHANES datasets (2012-2016) using the final FBW Pooled Pediatric Model developed by Applicant (Figure 17). Subjects with bodyweight lower than 20 kg had lower C_{trough} than subjects with higher bodyweight, while there was no significant difference for $C_{average}$ between subjects with bodyweight lower than 20 kg and subjects with higher body weight. Two pediatric subjects with body weight lower than 20 kg were enrolled in study CNTO1275PSO3013 and both achieved responses for PGA (0/1), PASI75 and PASI90 at week 12 and week 24. Flat E-R relationship for PGA(0/1) at week 12 with observed C_{trough} also suggests no dose adjustment is required for patients with bodyweight lower than 20 kg. (Figure 9)

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Figure 17   Comparison of C$_{trough}$ and C$_{average}$ of Ustekinumab in Pediatric Subjects ≥6 to <18 Years of Age in Different Body Weight Groups.
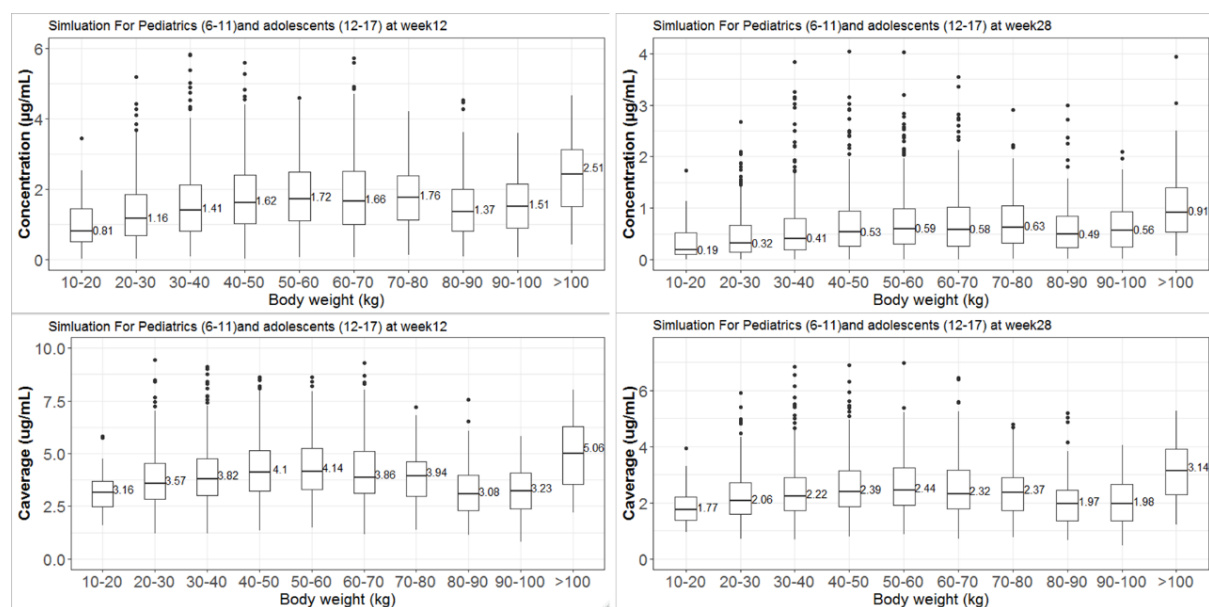
*(Source of data: Reviewer's analysis)*

4.2   Exposure-response for Efficacy

The exposure-response (E-R) relationship for efficacy of ustekinumab was evaluated in Pediatric Subjects ≥6 to <12 Years of Age with moderate to severe psoriasis. The E-R relationship was explored by graphical analyses, followed by a logistic regression modeling approach, using PGA (0/1), PASI 75 and PASI 90 as the efficacy response endpoints. The serum ustekinumab trough concentrations at Week 12 and Week 28 were predicted from population PK model (FBW model) as described above.

Two datasets (one for Week 12 and the other for Week 28) were used. In the Week 12 dataset, there were 1839 adult subjects in Studies C0743T08 and C0743T09, 105 adolescents in Study CNTO1275PSO3006 and 44 Pediatric Subjects ≥6 to <12 Years of Age in Study CNTO1275PSO3013. In the Week 28 dataset, there were 1433 adult subjects in Studies C0743T08 and C0743T09, 105 adolescent subjects ≥12 to <18 years in Study CNTO1275PSO3006 and 44 Pediatric Subjects ≥6 to <12 Years of Age in Study CNTO1275PSO3013. The data from doses of 45 mg and 90 mg in adults were combined to provide a wide ustekinumab exposure range for the analysis.

Two E-R graphical analyses were performed by comparing the binary responses of PGA (0/1), PASI 75 and PASI 90 from CNTO1275PSO3013 (pediatrics ≥6 to <12 Years of Age) and CNTO1275PSO3006 (adolescents) (Figure 18 and Figure 19) and comparing the responses from CNTO1275PSO3013 (pediatrics ≥6 to <12 Years of Age), CNTO1275PSO3006 (adolescents) and C0743T08/C0743T09 (adults) (Figure 20 and Figure 21).

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Figure 18   Exposure-response Relationships of PGA (0/1), PASI 75, PAS I90 in Pediatrics ≥6 to <12 Years of Age and Adolescents at Week 12
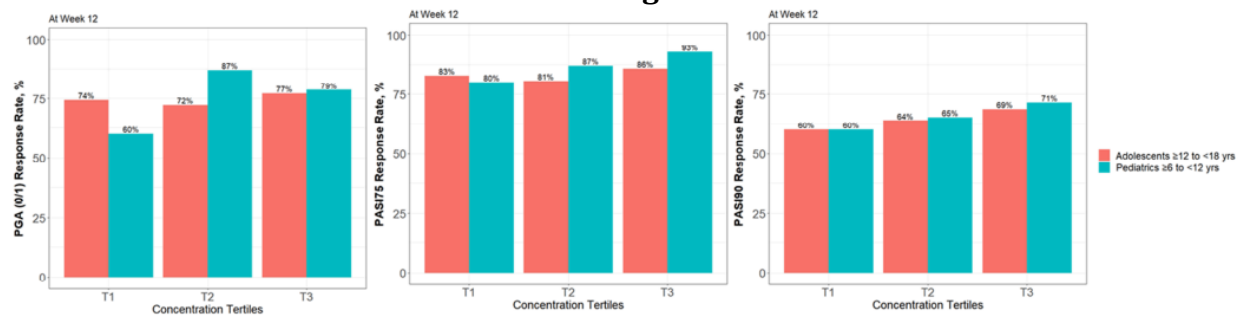
The tertile levels serum ustekinumab concentrations from CADMUS were (≥0.02 to ≤0.74), (>0.74 to ≤1.46) and (>1.46 to ≤4.73) µg/mL at Week 12; The number of pediatric subjects ≥6 to <12 years of age that fell into each tertile level was 5, 23, and 14, respectively; The number of adolescent subjects ≥12 to <18 years of age that fell into each tertile level was 35, 36, and 35, respectively.

(Source of data: The Applicant's population PK report, Page 38, Figure 9)

Figure 19   Exposure-response Relationships of PGA (0/1), PASI 75, PAS I90 in Pediatrics ≥6 to <12 Years of Age and Adolescents at Week 28
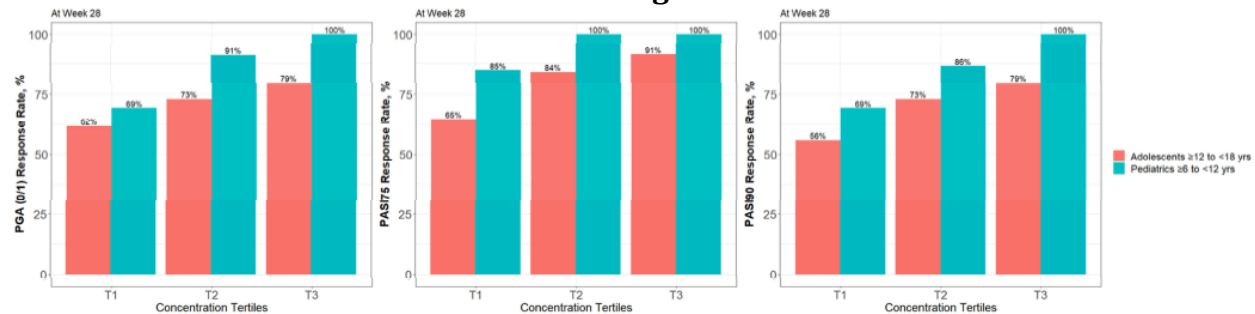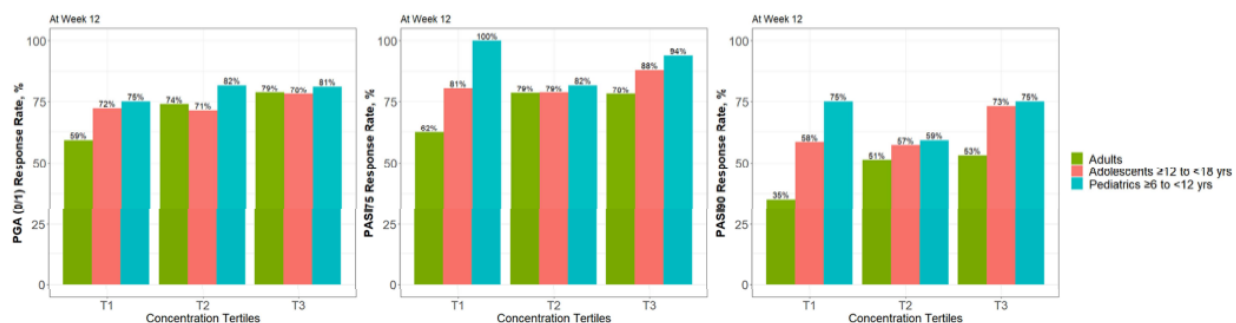

The tertile levels serum ustekinumab concentrations from CADMUS were ≥0.01 to ≤0.28, >0.28 to ≤0.46 and >0.46 to ≤ 4.63 µg/mL at Week 28. The number of pediatric subjects ≥6 to <12 years of age that fell into each tertile level was 13, 22, and 6, respectively; The number of adolescent subjects ≥12 to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

(Source of data: The Applicant's population PK report, Page 39, Figure 10)

Figure 18 and Figure 19 demonstrated that, regardless of the timepoint and clinical efficacy endpoint evaluated, the overall patterns of exposure-response relationships were similar between pediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years of age. Notably at Week 28, subjects with serum ustekinumab concentrations in the first tertile level had substantially lower response rates when compared with those who had serum ustekinumab concentrations in the 2 higher tertile levels, however this trend is not evident at Week 12.

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Figure 20   Exposure-response Relationships of PGA (0/1), PASI 75, PAS I90 in Pediatrics ≥6 to <12 Years of Age, Adolescents and Adults at Week 12

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.

(Source of data: The Applicant's population PK report, Page 40, Figure 11)

Figure 21   Exposure-response relationships of PGA (0/1), PASI 75, PAS I90 in Pediatrics ≥6 to <12 Years of Age, Adolescents and Adults at Week 28
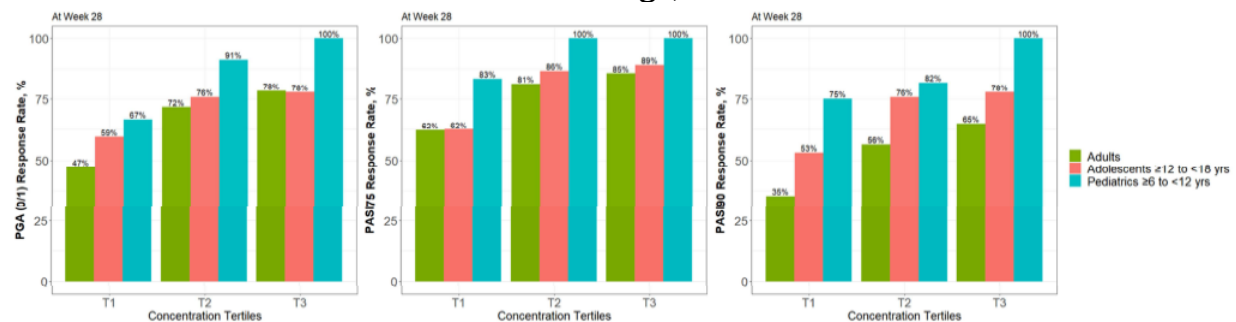
The tertile levels serum ustekinumab concentrations from CADMUS were (≥0.00 to ≤0.25), (>0.25 to ≤0.55) and (>0.55 to ≤18.0) μg/mL at Week 28. The number of pediatric subjects ≥6 to <12 years of age that fell into each tertile level was 12, 22, and 7, respectively; The number of adolescent subjects ≥12 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.

*(Source of data: The Applicant's population PK report, Page 41, Figure 12)*

The tertile levels of adult individual predicted ustekinumab concentrations from the final FBW Pooled Pediatric and Adult Model were used to evaluate the exposure-response relationship in pediatrics ≥6 to <12 Years of Age.

Figure 20 and Figure 21 suggested that, the overall patterns of exposure-response relationships were comparable between pediatric subjects ≥6 to <12 years of age, adolescent subjects ≥12 to <18 years of age and adult subjects. At week 28, the higher model-predicted serum ustekinumab concentrations were generally associated with higher clinical response rates, while due to the limit number of pediatric subjects ≥6 to <12 years of age and adolescent subjects ≥12 to <18 years of age, the results were sensitive to the cut-off for these two groups. And pediatric subjects ≥6 to <12 years of age with psoriasis had slightly higher clinical efficacy as compared with the adolescent and adult population.

Reviewer's comments: *The reviewer conducted an E-R analysis for PGA (0/1) using observed trough concentrations of ustekinumab for pediatric subjects ≥6 to <12 years of age and*

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adolescent subjects ≥12 to <18 years of age at Week 12 which identified a shallow and non-significant E-R relationship (Figure 9). The reviewer also conducted logistic regression analysis to assess the E-R relationship for PGA (0/1), PASI 75, and PASI 90 at Weeks 12 and 28 using model predicted concentrations (Figure 22). These additional analyses generally demonstrated similar shallow and non-significant relationships between exposure of ustekinumab and PGA (0/1), however with a trend especially at Week 28 that subjects with higher serum ustekinumab concentrations were associated with slightly higher response. Overall, because of the limited number of subjects and potential confounding effects (e.g. ADA, BLOQ) on both exposure and response in the E-R analysis, the apparent E-R relationships do not indicate that substantial gains in efficacy would be achieved by further increasing the dose of ustekinumab.

Figure 22 **Logistic Regression Analysis of Ustekinumab Exposure for PGA (0/1), PASI 75 and PASI 90 in Pediatric and Adolescent Subjects at Week 12 and Week 28.**
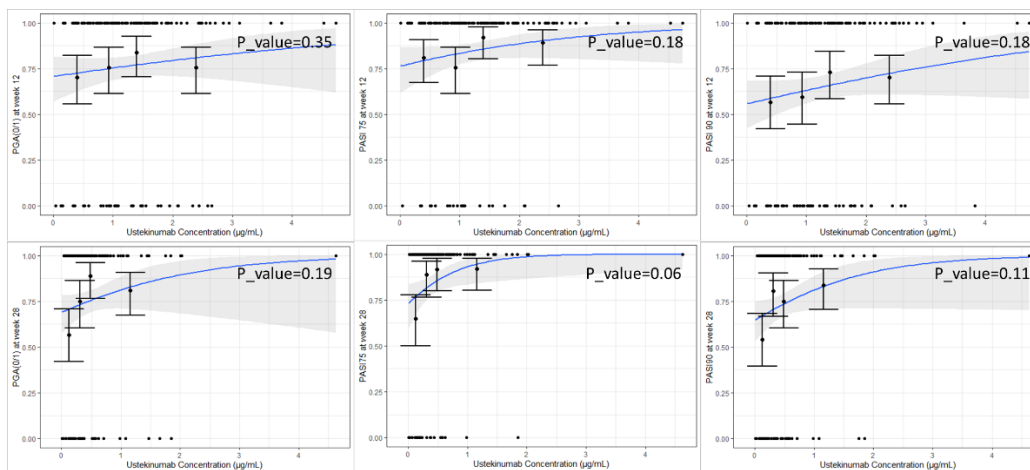
(Source of data: Reviewer's independent analysis)

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/s/

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