Clinical Pharmacology Review

BLA Number	125,261 (Supplement 138)
Link to EDR	*\\cdsesub1\evsprod\bla125261\125261.enx* *(SDN 1460, eCTD 0367)*
Submission Date	December 15, 2016
Submission Type	Efficacy supplement
Brand Name	STELARA®
Generic Name	Ustekinumab
Proposed Indication	Treatment of adolescent patients (12 to <18 years of age) with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. *[STELARA was initially approved in 2009 for the treatment of the same indication in adult patients (18 years or older).]*
Proposed dosing regimen	Weight-based dosing administered initially and 4 weeks later, then every 12 weeks thereafter:

Weight Range (kg)	Dosage
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
greater than 100 kg	90 mg

Route of Administration	Subcutaneous injection
Applicant	Janssen Biotech, Inc.
Related IND	009,590
OCP review team	Jie Wang, Ph.D. Luning (Ada) Zhuang, Ph.D. Jeffry Florian, Ph.D. Yow-Ming Wang, Ph.D.
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1. EXECUTIVE SUMMARY

STELARA® (ustekinumab) is a human interleukin (IL)-12 and IL-23 antagonist. Ustekinumab was initially approved in 2009 for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The recommended dosage is 45 mg for patients weighing ≤100 kg and 90 mg for patients weighing >100 kg, administered subcutaneously at Weeks 0 and 4 and every 12 weeks (Q12W) thereafter.

The Applicant is seeking the approval of STELARA for the treatment of adolescent patients (12 to <18 years of age) with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. To support this supplemental BLA, the Applicant conducted Study CNTO1275PSO3006 to assess the efficacy and safety of "Standard" and "Half-Standard" dosages of ustekinumab in adolescent subjects aged 12 to 17 years with moderate to severe psoriasis (Table 1). The Applicant proposed Standard dosage for the treatment of adolescent psoriasis patients.

Table 1 Standard and Half-Standard ustekinumab dosages tested in adolescent subjects aged 12 to 17 years with moderate to severe psoriasis in Study CNTO1275PSO3006.
Ustekinumab was administered subcutaneously at Weeks 0 and 4 and every 12 weeks thereafter.

Subjects Body Weight (kg)	Standard Dosage	Half-Standard Dosage
≤60 kg	*0.75 mg/kg*	*0.325 mg/kg*
>60 kg to ≤100 kg	*45 mg*	*22.5 mg*
>100 kg	*90 mg*	*45 mg*

1.1 Recommendation

The Divisions of Clinical Pharmacology 3 and Pharmacometrics have reviewed the information contained in Supplement 138, BLA 125,261. The review team recommends approval of this supplemental BLA from a Clinical Pharmacology's perspective.

2. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

2.1 Recommended dosage regimen

Overall, the dose-response relationships for efficacy and safety in CNTO1275PSO3006 support that the proposed Standard ustekinumab dosage is appropriate for adolescent subjects aged 12 to 17 years with moderate to severe psoriasis.

Initial treatment period: efficacy results at Week 12

- Both Standard dosage and Half-Standard dosage demonstrated statistically significantly higher response rate than placebo for primary efficacy endpoint PGA (0/1) and key secondary efficacy endpoint PASI 75. The Standard dosage group showed approximately 2% higher response rates than Half-Standard dosage group for PGA (0/1) and PASI 75 (Table 2).

- Both ustekinumab Standard dosage and Half-Standard dosages demonstrated significantly higher response rates than placebo for more stringent efficacy measures including PGA 0, PASI 90, and PASI 100. The Standard dosage showed 7-17% higher response rate than Half-Standard dosage across these efficacy endpoints (Table 2).

Table 2 Efficacy results at Week 12 in Study CNTO1275PSO3006.
[a]p<0.001 compared with placebo; [b]p<0.05, compared with placebo. Half-Std, Half-Standard dosage; Std, Standard dosage. (*Source of Data: Table 3, CSR Study CNTO1275PSO3006; Table 4, Summary of Clinical Efficacy*).

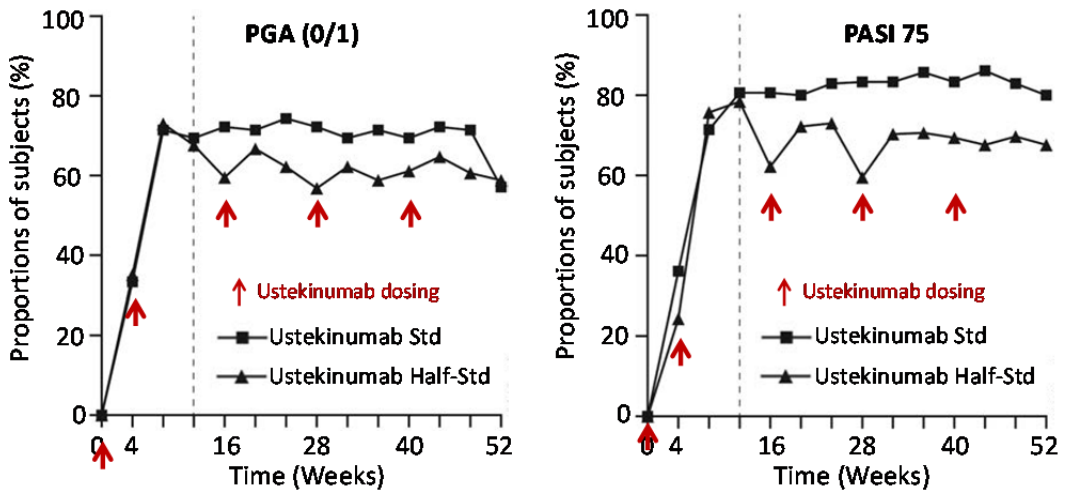
Efficacy endpoints	Placebo (N=37)	Ustekinumab dosage	
		Half-Standard (N=37)	Standard (N=36)
PGA (0/1)	5.4% (2)	67.6% (25)[a]	69.4% (25)[a]
PGA (0)	2.7% (1)	32.4% (12)[a]	47.2% (17)[a]
PASI 75	10.8% (4)	78.4% (29)[a]	80.6% (29)[a]
PSAI 90	5.4% (2)	54.1% (20)[a]	61.1% (22)[a]
PASI 100	2.7% (1)	21.6% (8)[b]	38.9% (14)[a]

Maintenance treatment: Efficacy results through Week 52

- The response rates for PGA (0/1) and PASI 75 were generally higher and better sustained in Standard dosage group relative to Half-Standard dosage group during the maintenance phase of Study CNTO1275PSO3006 (Figure 1).

- Loss of efficacy was more frequently observed toward the end of the 12-week dosing interval in the Half-Standard dosage group indicating inadequate exposure during maintenance phase of the Half-Standard dosage (Figure 1).

Figure 1 PGA (0/1) or PASI 75 response rates through Week 52 in Study CNTO1275PSO3006.



(*Source of data: Figure 5, Summary of Clinical Efficacy*)

Safety findings

- According to the summary of clinical safety, there were no new safety findings identified in Study CNTO1275PSO3006 relative to the safety profile observed in adult subjects with psoriasis.

- Through Week 60, there was no evidence of a dose-response relationship in the occurrence of AEs (e.g., infections) between Half-Standard and Standard dosages of ustekinumab. See section 3.3.2 for more information.

2.2 Pharmacokinetics

Following multiple subcutaneous doses of ustekinumab in adolescent subjects aged 12 to 17 years with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean ±SD steady-state trough concentrations at Week 28 were 0.54 ±0.43 mcg/mL in subjects who received Standard dosage and 0.25 ±0.26 mcg/mL in subjects who received Half-Standard dosage.

The observed ustekinumab concentrations in adolescent subjects treated with Standard dosage were generally comparable to those in adult subjects receiving the approved dosage regimens (Table 3).

Table 3 Trough serum ustekinumab concentrations in adolescent and adult subjects with psoriasis.
Adolescent subjects with psoriasis received Standard dosage in Study CNTO1275PSO3006. Adult subjects with psoriasis received approved dosages in Study CNTO1275PSO3009.

	Dose and body weight groups	**Mean ±SD trough serum ustekinumab concentrations (mcg/mL)**		
		Week 4	**Week 16**	**Week 28**
Adolescents (Standard dosage)	0.75 mg/kg (≤60 kg)	2.97±1.19 (n=15)	0.85±0.56 (n=15)	0.65±0.313 (n=13)
	45 mg (>60 to ≤100 kg)	2.84±1.26 (n=18)	0.56±0.37 (n=17)	0.50±0.49 (n=17)
	90 mg (> 100 kg)	0.52 (n=1)	0 (n=1)	0 (n=1)
	Pooled all body weight groups	2.83±1.26 (n=34)	0.67±0.49 (n=33)	0.54±0.43 (n=31)
Adults (Approved dosage)	45 mg (≤100 kg)	2.50±1.13 (n=302)	0.79±0.82 (n=294)	0.69±0.69 (n=284)
	90 mg (>100 kg)	3.26±1.75 (n=168)	0.86±0.95 (n=157)	0.74±0.78 (n=153)

2.3 Immunogenicity

Approximately 8% (9/110) of subjects treated with ustekinumab developed anti-drug antibodies (ADA) by Week 60 in Study CNTO1275PSO3006. Of the ADA positive subjects, 33.3% (3/9) were positive for neutralizing ADA (NAb). The formation of ADA appears to have negative impacts on both serum ustekinumab concentrations and efficacy.

2.4 Summary of Labeling Recommendations

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

Proposed labeling by the Applicant	Reviewer's labeling recommendations
12.3 Pharmacokinetics Specific Populations Age: Pediatric Population (b) (4) [redacted]	12.3 Pharmacokinetics Specific Populations *Subjects with development of antibodies to ustekinumab* Development of antibodies to ustekinumab was associated with lower serum ustekinumab concentrations. *Age: Pediatric Population* Following multiple doses of STELARA in adolescent subjects 12 to 17 years of age with moderate to severe psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean ±SD steady-state trough serum ustekinumab concentration was 0.54 ± 0.43 mcg/mL.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

STELARA® (ustekinumab) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds to the p40 subunit of the IL-12 and IL23 cytokines.

Ustekinumab was initially approved in 2009 for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Ustekinumab was subsequently approved for the treatment of adult patients with active psoriatic arthritis (PsA) in 2013 and for the treatment of adult patients with Crohn's disease (CD) in 2016 (under BLA 761,044). The recommended ustekinumab dosage regimens for the treatment of psoriasis in adult patients are 45 mg for patients ≤100 kg and 90 mg for patients >100 kg subcutaneously administered at Weeks 0 and 4 and every 12 weeks (Q12W) thereafter.

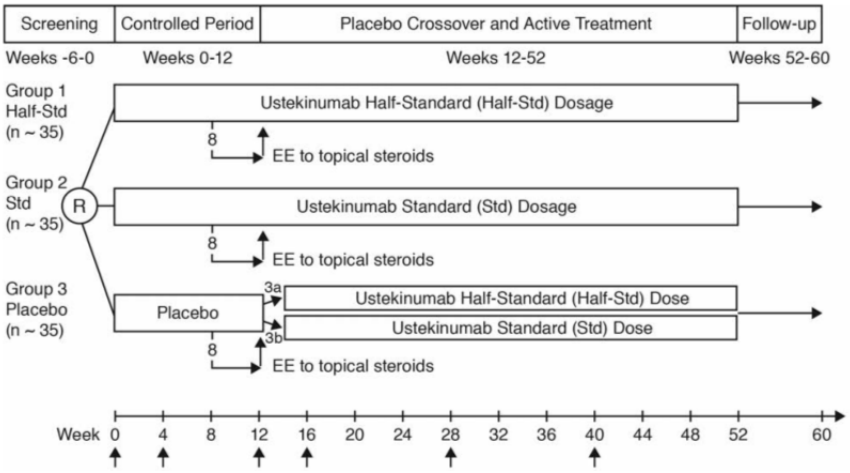
In the current efficacy supplement, the Applicant proposed to add a pediatric indication for STELARA for the treatment of adolescent patients (12 to <18 years of age) with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The proposed new indication in this pediatric supplement is primarily supported by the efficacy, safety, and PK data from a Phase 3 study CNTO1275PSO3006 in adolescent subjects (ages 12 to <18 years) with moderate to severe plaque psoriasis. Note that the results from Study CNTO1275PSO3006 have supported the approval of STELARA for use in adolescents with moderate to severe plaque psoriasis in EU and a few other countries.

3.2 Overview of Clinical Studies

3.2.1 Study CNTO1275PSO3006 in Adolescent Subjects with Psoriasis

Study CNTO1275PSO3006 is a Phase 3 randomized, double-blind, placebo-controlled study that evaluated the efficacy, safety, PK, and immunogenicity of ustekinumab in subjects ≥12 to <18 years of age with moderate to severe psoriasis. The study design is presented in Figure 2.

Figure 2 Study design (Study CNTO1275PSO3006).



At Week 0, a total of 110 subjects were randomized to receive subcutaneous injections of the ustekinumab Half-Standard dosage (n=37), the ustekinumab Standard dosage (n=36), or placebo (n=37). Randomization was stratified by baseline weight (≤60 kg or >60 kg). At Week 12, subjects in the placebo group crossed over to receive either Half-Standard dosage (n=19) or Standard dosage (n=18) of ustekinumab. Subjects were followed for efficacy through Week 52 and for safety through Week 60.
↑ represents an injection for ustekinumab/placebo. EE, early escape; Half-Std, Half-Standard dosage; Std, Standard dosage. (*Source of Data: Figure 1, CSR Study CNTO1275PSO3006*)

Study population

Study CNTO1275PSO3006 enrolled 110 subjects with the following demographic and disease characteristics:

- Sex: Male 49% (54/110); Female 51% (56/110)
- Age (median): 15.5 years
- Body weight: 65±19 kg (mean±SD); 61.6 kg (median)
- Median psoriasis disease duration: 5.3 years
- Psoriasis disease condition for inclusion: BSA involvement ≥10%; PASI ≥12, PGA ≥3

Dosage regimens

Study CNTO1275PSO3006 evaluated two weight-based ustekinumab dosages: the Standard dosage and the Half-Standard dosage (Table 1).

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects who achieve a Physician's Global Assessment (PGA) score of cleared (1) or minimal (0) at Week 12.

Pharmacokinetics

Blood samples for measurement of serum ustekinumab concentrations were collected at Weeks 0, 4, 12, 16, 20, 24, 28, 40, 52, and 60.

Immunogenicity

Blood samples for immunogenicity assessment were collected at Weeks 0, 12, 52, and 60.

3.2.2 Supportive Clinical Studies and Associated Bioanalytical Methods for Measurement of Serum Ustekinumab Concentrations

Ustekinumab PK data from five Phase 3 studies in adult subjects with psoriasis are provided for the purpose of comparing ustekinumab exposure between pediatrics and adults. The study population, study doses, and the bioanalytical methods used for measurement of serum ustekinumab concentrations are summarized in Table 4. Among the adult studies, we consider PK data from Study CNTO1275PSO3009 appropriate for comparison with those in the pediatric study CNTO1275PSO3006.

The Applicant have used an electrochemiluminescent immunoassay (ECLIA) method with two different assay platforms, the Meso Scale Discovery® (MSD) platform and the BioVeris™ assay platform, for measurement of serum ustekinumab concentrations in these psoriasis clinical trials. The BioVeris assay platform which was initially used in the pivotal Phase 3 studies (C0743T08 and C0743T09) has been discontinued and is no longer in use. The MSD platform was used in later psoriasis trials including Studies CNTO1275PSO3006, CNTO1275PSO3009, C0743T23, and C0743T25. A cross-validation comparison of the two methods have shown that the results generated using the MSD platform were generally higher compared to the results generated using the BioVeris platform. See BLA 125,261 Clinical Pharmacology reviews dated October 26, 2012 and March 10, 2017 for more information of the PK assays.

Table 4 Ustekinumab Phase 3 studies in subjects with psoriasis.
Ustekinumab was administered at Week 0, 4 and every 12 weeks (Q12W) thereafter in all the Phase 3 studies. Study CNTO1275PSO3009 used the approved body weight-tired dose regimens and evaluated additional dosing regimens including Q16W, Q20W, and Q24W during the maintenance phase of the study. In Studies C0743T08 and C0743T09, the 45 mg or 90 mg dose was not body weight-based. Studies C0743T23 and C0743T25 tested the 45 mg dose in all patients regardless of the body weight. Studies C0743T23 and C0743T25 were small regional studies conducted in China, Taiwan, and South Korea. MSD, Meso Scale Discovery. (*Source of data: Table 1, Summary of Clinical Pharmacology and Individual CSRs*)

Study	Study description	Psoriasis population	Study doses	PK assay platform
C0743T08	Pivotal Phase 3 (original BLA)	Adults	45 mg 90 mg	BioVeris™
C0743T09	Pivotal Phase 3 (original BLA)	Adults	45 mg 90 mg	BioVeris™
C0743T23	Phase 3	Adults (China)	45 mg	MSD
C0743T25	Phase 3	Adults (South Korea, Taiwan)	45 mg	MSD
CNTO1275PSO3009	Phase 3b PMC	Adults	45 mg for subjects ≤100 kg; 90 mg for subjects >100 kg	MSD
CNTO1275PSO3006	Pediatric Phase 3 (current sBLA)	Adolescents (≥12 to <18 years of age)	Standard Half-standard	MSD

3.3 Question-Based Clinical Pharmacology Review

3.3.1 Does the dose-response relationship for efficacy support the proposed dosage regimen of ustekinumab in adolescent subjects with moderate to severe psoriasis?

Overall, the dose-response relationship for efficacy supports that the proposed Standard dosage of ustekinumab is appropriate for adolescent subjects aged 12 to 17 years with moderate to severe psoriasis. See section 2.1.

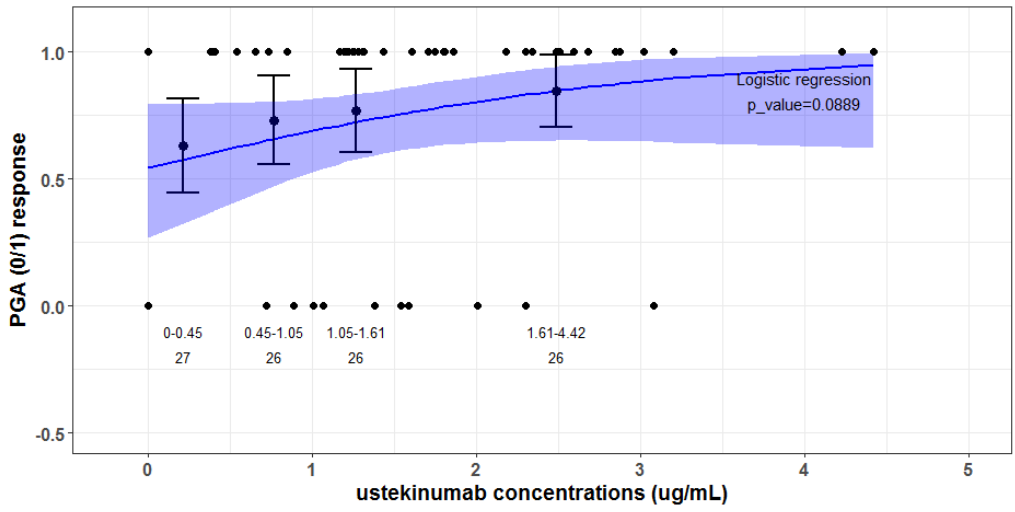
Initial treatment period: Week 12 efficacy results

- Both ustekinumab Standard and Half-Standard dosages demonstrated a significantly higher response rate than placebo for the primary efficacy measure of PGA (0/1) and for the major secondary efficacy measure of PASI 75 (Table 2). The ustekinumab Standard dosage showed approximately 2% higher response rates than Half-Standard dosage for PGA (0/1) and PASI 75.

- Both ustekinumab Standard dosage and Half-Standard dosages demonstrated significantly higher response rate than placebo for more stringent efficacy measures including PGA 0, PASI 90, and PASI 100. The ustekinumab Standard dosage showed 7-17% higher response rate than the Half-Standard dosage across these endpoints (Table 2).

- *Exploratory exposure-response (E-R) analysis results for PGA (0/1)*: An exploratory E-R analysis for PGA (0/1) using observed trough concentrations of ustekinumab at Week 12 identified a shallow and non-significant E-R relationship (Figure 3). Subjects with higher serum ustekinumab concentrations were associated with higher PGA (0/1) response rates. Because of the limited number of subjects in the E-R analysis and potential confounding factors (e.g., disease) on both exposure and response, the observed apparent E-R relationship does not indicate that substantial gains in efficacy would be achieved by further increasing the dose. See section 4.2 for more information.

Figure 3 Observation-based exposure-response for PGA (0/1) at Week 12.



The shaded area is the 95% CI of the predicted response. (*Source of data: Reviewer's analysis. See section 4.2 for more information*)

Maintenance treatment period: results through Week 52

The time-course of PGA (0/1) and PASI 75 response rates through Week 52 in Study CNTO1275PSO 3006 are shown in Figure 1.

- The response rates for PGA (0/1) and PASI 75 were generally higher and better sustained in Standard dosage group relative to Half-Standard dosage group during the maintenance phase of Study CNTO1275PSO3006.

- Loss of efficacy was more frequently observed toward the end of the 12-week dosing interval in the Half-Standard dosage group indicating inadequate exposure during maintenance phase of the Half-Standard dosage.

3.3.2 Is there a dose-response relationship for safety?

No, there was no evidence of a dose-response relationship in the occurrence of AEs (e.g., infections) between Half-Standard and Standard dosages of ustekinumab based on safety findings through Week 12 (Table 5) and Week 60 (Table 6) in Study CNTO1275PSO3006. According to the Summary of Clinical Safety, there were no new safety findings identified in Study CNTO1275PSO3006 relative to the safety profile observed in previous clinical trials with adult subjects with psoriasis.

Table 5 Summary of safety findings through Week 12 in Study CNTO1275PSO3006.
(*Source of data: Table 6, Clinical Overview*)

	CNTO1275PSO3006			
		Ustekinumab		
	Placebo	Half-Standard Dosage	Standard Dosage	Combined
Treated subjects	37	37	36	73
Average duration of follow-up (weeks)	12.17	12.17	12.40	12.28
Subjects who discontinued study agent because of 1 or more adverse events	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with 1 or more:				
Adverse events	21 (56.8%)	19 (51.4%)	16 (44.4%)	35 (47.9%)
Serious adverse events	0 (0.0%)	1 (2.7%)	0 (0.0%)	1 (1.4%)
Any infections	14 (37.8%)	12 (32.4%)	8 (22.2%)	20 (27.4%)
Serious infections	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections requiring treatment	4 (10.8%)	1 (2.7%)	2 (5.6%)	3 (4.1%)

Table 6 Summary of safety findings through Week 60 in Study CNTO1275PSO3006.
(*Source of data: Table7, Clinical Overview*)

	CNTO1275PSO3006				
	Ustekinumab				
	Placebo → Half-Standard Dosage	Placebo → Standard Dosage	Half-Standard Dosage	Standard Dosage	Combined
Subjects treated	19	18	37	36	110
Average duration of follow-up (weeks)	45.87	46.87	55.23	58.03	53.16
Subjects who discontinued study agent because of 1 or more adverse events	2 (10.5%)	0	2 (5.4%)	0	4 (3.6%)
Subjects with 1 or more:					
Adverse events	15 (78.9%)	13 (72.2%)	33 (89.2%)	29 (80.6%)	90 (81.8%)
Serious adverse event	0	0	5 (13.5%)	1 (2.8%)	6 (5.5%)
Any infection	13 (68.4%)	11 (61.1%)	26 (70.3%)	24 (66.7%)	74 (67.3%)
Serious infection	0	0	1 (2.7%)	1 (2.8%)	2 (1.8%)
Infection requiring treatment	4 (21.1%)	4 (22.2%)	9 (24.3%)	11 (30.6%)	28 (25.5%)

3.3.3 What are the pharmacokinetic characteristics of ustekinumab in pediatric subjects with psoriasis? Are serum ustekinumab concentrations in adolescent psoriasis patients similar to these observed in adult psoriasis patients?

Steady state concentrations were achieved by Week 28. At Week 28, the mean±SD trough serum ustekinumab concentrations were 0.25±0.26 mcg/mL for Half-Standard dosage and 0.54±0.43 mcg/mL for Standard dosage. Observed serum ustekinumab concentrations by treatment groups in Study CNTO1275PSO3006 are summarized in Table 7.

The PK of ustekinumab in adolescent subjects treated with Standard dosage was generally comparable to that in adult subjects receiving the approved dosage regimen, supported by direct comparisons of the observed concentrations.

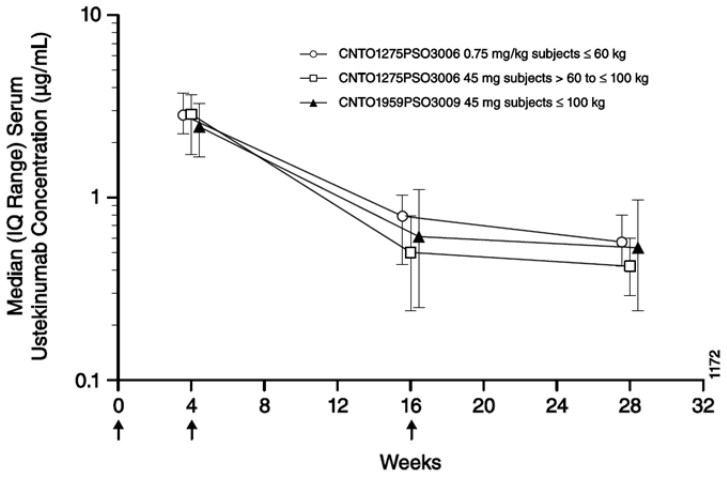
- Comparison of the observed serum ustekinumab concentrations in Studies CNTO1275PSO3006 and CNTO1275PSO309 showed that adolescent subjects who received Standard Dosage had similar ustekinumab concentrations to adult subjects who received the approved dosage (Table 3 and
- Figure 4).

- Among adolescents receiving Standard dosage, subjects with body weight ≤60 kg and subjects with body weight >60 kg to ≤100 kg had similar serum ustekinumab concentrations (
- Figure 4).

Table 7 Serum ustekinumab concentrations by treatment groups.
Half-Std, Half-Standard dosage; Std, Standard dosage. *Data at Weeks 4, 16, 28, 40 and 52 represent pre-dose trough concentrations. (*Source of Data: Attachment TPKCONC01A, Attachment TPKCONC02, CSR Study CNTO1275PSO3006*)

Dose		Serum ustekinumab concentrations, mcg/mL (mean±SD)						
		*Week 4	Week 12	*Week 16	Week 24	*Week 28	*Week 40	*Week 52
Half-Std	N (total)	36	36	32	31	29	23	24
	n (<BQL)	3	6	10	4	11	5	13
	Median (Range)	1.41 (0-3.9)	0.77 (0-2.8)	0.33 (0-1.2)	0.59 (0-1.9)	0.21 (0-0.8)	0.23 (0-0.7)	0 (0-3.3)
	Mean±SD	1.35±0.80	0.82±0.67	0.33±0.30	0.64±0.46	0.25±0.26	0.29±0.23	0.37±0.72
Std	N (total)	34	33	33	31	31	27	27
	n (<BQL)	0	3	4	1	5	4	4
	Median (Range)	2.80 (0.5-5.8)	1.31 (0-4.2)	0.55 (0-2.3)	1.19 (0-4.7)	0.46 (0-2.0)	0.52 (0-9.2)	0.47 (0-1.6)
	Mean±SD	2.83±1.26	1.52±1.00	0.67±0.49	1.35±0.87	0.54±0.43	0.93±1.71	0.53±0.40

Figure 4 Trough serum ustekinumab concentrations by baseline body weight and ustekinumab dosage in Studies CNTO1275PSO3006 and CNTO1275PSO3009.



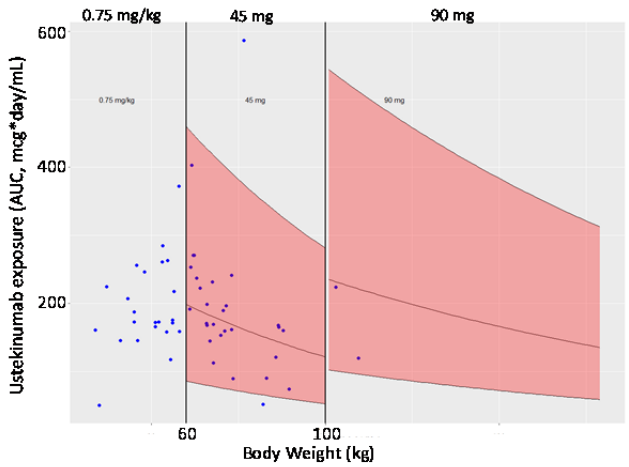
In Study CNTO1275PSO3006, pediatric subjects (>60 kg to ≤100 kg) received the 45 mg dose and pediatric subjects ≤ 60 kg received 0.75 mg/kg dose. In Study CNTO1275PSO3009, adult subjects ≤100 kg received the approved 45 mg dose. Note that concentrations in pediatric subjects with body weight >100 kg is not presented for comparison purposes due to the small number of subjects in this treatment group. There was only 1 subject with body weight >100 kg receiving Standard dosage. This individual subject had 0.52 mcg/mL serum ustekinumab concentration at Week 4 and <BQL concentrations at Weeks 16 and 28. (*Source of data: Summary of Clinical Pharmacology*)

Exploratory population PK analysis results

The Applicant developed a population PK model using PK data from Studies C0743T08, C0743T09, and CNTO1275PSO3006. The Applicant's intention was to use the population PK modeling approach to compare model-predicted serum concentrations between pediatric subjects in Study CNTO1275PSO3006 and adult subjects in pivotal Phase 3 Studies C0743T08 and C0743T09. In the population PK model, the Applicant incorporated a relative bioavailability term into the structural model to account for the concentration differences due to assay change. Although the population PK analysis indicated that the exposure of ustekinumab in adolescent subjects treated with the Standard dosage would be in general similar to that in adult subjects receiving the approved dosage regimen (Figure 5), the population PK analysis was considered exploratory only and the modeling results could not be used as an evidence for supporting PK comparability between pediatric and adult subjects because the use of the assay adjustment factor has not been justified. See section 4.1 for more information.

Because the BioVeris PK assay platform used in pivotal Phase 3 Studies C0743T08 and C0743T09 is not comparable to the MSD PK assay platform used in Study CNTO1275PSO3006, direct comparison of serum ustekinumab concentrations between adult and pediatric subjects in these three clinical trials is not feasible. This also affects the utility of the Applicant's model-based analyses. See section 3.2.2 for more information.

Figure 5 Population PK model-simulated ustekinumab exposure in adolescent and adult subjects.



The shaded area in pink represents the 95% CI for predicted ustekinumab exposure in adults receiving the approved 45 mg or 90 mg dosages. The result was based on 100 simulations using the population PK model (estimated allometric exponent for body weight) developed by Applicant. Blue dots are patient estimated ustekinumab AUC based on the population PK model. (*Source of data: Reviewer's analysis. See section 4.1 for more information*)

3.3.4 What is the incidence of the formation of anti-drug antibodies (ADA) to ustekinumab? What are the impacts of ADA on PK and efficacy?

Approximately 8% (9/110) of subjects treated with ustekinumab developed ADA by Week 60 in Study CNTO1275PSO3006. Of the ADA positive subjects, 33.3% (3/9) were positive for neutralizing ADA (NAb). The ADA incidences by ustekinumab treatment groups are summarized in Table 8.

Overall, the formation of ADA appears to be associated with a decrease in serum ustekinumab concentrations. At time-points following ADA formation, majority of PK samples showed <BQL serum ustekinumab concentrations in ADA+ subjects who received Standard or Half-Standard dosage of ustekinumab (Table 9).

The formation of ADA also appears to have a negative impact on efficacy. The efficacy outcomes for the 5 ADA positive subjects receiving Half-Standard or Standard dosages are summarized below.

- Subject#1 (Half-Standard dosage): This subject was a PGA (0/1) responder and was tested positive for ADA at Week 12. The PGA score ranged from 2 to 4 between Week 16 and Week 32 indicating a loss of efficacy.
- Subject#2 (Half-Standard dosage): This subject was tested positive for ADA at Week 12. This subjects did not achieve a PGA (0/1) response from Week 12 to Week 20.
- Subject#3 (Half-Standard dosage): This subject was tested positive for ADA at Week 12. This subject did not achieve a PGA (0/1) response from Week 12 to Week 52.

- Subject#4 (Half-Standard dosage): This subject was tested positive for ADA at Week 52 and was a PGA (0/1) responder from Week 4 through Week 52 (with PGA score assessed at Weeks 4, 12, 16, 20, 24, 28, 40 and 52). Whether ADA formation had an impact on efficacy is unknown because the efficacy result after Week 52 is not available.

- Subject#5 (Standard dosage): This subject was tested positive for ADA at Week 12 and was a PGA (0/1) responder at Week 12. Loss of efficacy was observed at Week 40 and Week 52.

Table 8 Summary of ADA incidences through Week 60 by treatment group in Study CNTO1275PSO3006.
ADA, anti-drug antibodies; Half-Std, Half-Standard dosage; Std, standard dosage. (*Source of data: Table 2, Attachment TPKNAB01B, CSR Study CNTO1275PSO3006*).

	Ustekinumab treatment groups				
	Placebo → Half-Std	***Placebo → Std***	***Half-Std***	***Std***	***Combined***
N	*19*	*18*	*37*	*36*	*110*
ADA incidence % (n1)	*10.5% (2)*	*11.1% (2)*	*10.8% (4)*	*2.8% (1)*	*8.2% (9)*
NAb (n2)	*0*	*0*	*2*	*1*	*3*

Table 9 Individual serum ustekinumab concentrations in ADA+ subjects who received Standard or Half-Standard dosage of ustekinumab in Study CNTO1275PSO3006.
ADA, anti-drug antibodies; Half-Std, Half-Standard dosage; Std, Standard dosage. *Data at Weeks 4, 16, 28, 40 and 52 represent pre-dose trough concentrations. [a] Indicates time of ADA measurement. [b] Indicates time of first ADA+ observation. (*Source of data: Attachment TPKCONC01A, Attachment TPKCONC02, CSR Study CNTO1275PSO3006*)

ADA+ Subject ID		**Serum ustekinumab concentrations, mcg/mL**						
		***Week 4**	**Week 12[a]**	***Week 16**	**Week 24**	***Week 28**	***Week 40**	***Week 52[a]**
Half-Std	1	1.717	***0*[b]**	0	0	0	n/a	n/a
	2	0	*0*[b]	0	n/a	n/a	n/a	n/a
	3	0.464	***0.174*[b]**	0	0	0	0	0
	4	1.450	0.735	0.252	0.295	0.237	0.173	***0*[b]**
Std	5	3.97	***0.381*[b]**	0	0	0	0	***0***

Reviewer's comments: *The observed negative impact of ADA formation on ustekinumab PK is consistent with previous findings in clinical studies in subjects with psoriasis and in subjects with Crohn's disease. See Clinical Pharmacology review for Study CNTO1275PSO3009 dated March 10, 2017 and Clinical Pharmacology Review for BLA 761044 dated September 7, 2017 for more information. We recommend including information regarding the negative impact of immunogenicity in Stelara product labeling.*

4. APPENDICES:

4.1 Population PK

The Applicant developed a population PK model to describe the PK of ustekinumab to support the proposed dosage regimen for adolescent subjects with moderate to severe psoriasis.

The studies included in the population PK analysis are shown in Table 10.

Table 10 Overview of Studies Included in the Population PK Analysis

	C0743T08	C0743T09	CNTO1275PSO3006 (CADMUS)
Study Phase	Phase 3	Phase 3	Phase 3
Indication	moderate to severe plaque psoriasis	moderate to severe plaque psoriasis	moderate to severe plaque psoriasis
Subject population	Adults	Adults	Adolescents
No. of subjects with PK data available	739	1198	110
Dosage	45 or 90 mg at Weeks 0 and 4, then q12w	45 or 90 mg at Weeks 0 and 4, thenq12w	Body Weight Based: 0.375 or 0.75 mg/kg at Weeks 0 and 4, then q12w Fixed Dose: 22.5,45 or 90 mg at Weeks 0 and 4, then q12w
Route of administration	SC	SC	SC
No. of samples per subject[1]	10 [2, 11]	7 [2, 9]	9 [4, 10]
Sampling times (weeks)	0, 4, 12, 16, 24, 28, 40, 44, 48 and 52	0, 4, 12, 16, 20, 24 and 28	0, 4, 12, 16, 20, 24, 28, 40, 52 and 60
Bio-analytical method	ECLIA on the BioVeris™ platform	ECLIA on the BioVeris™ platform	ECLIA on the MSD® platform
Lowest quantifiable sample concentration of the assay (µg/mL)	0.1700	0.1700	0.1688

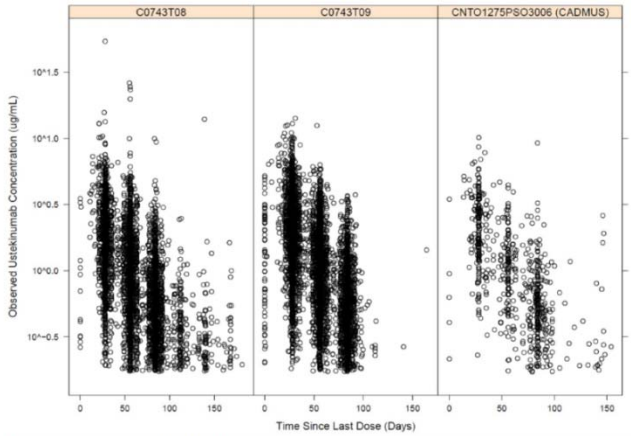
[1] Median [Min, Max]
Abbreviations: SC, subcutaneous; q12w, every 12 weeks

Source: The Applicant's population PK report, Page 13, Table 1

C0743T08 and C0742T09 were the 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 electrochemiluminescent immunoassay (ECLIA) on the BioVeris™ platform, which was discontinued by the vendor. The serum concentrations of ustekinumab in Study CNTO1275PSO3006 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 the current MSD® ECLIA were higher than those generated with the BioVeris™ ECLIA.

A total of 2047 subjects (1937 adults, 110 adolescents) and 10612 non-BQL observations were included in the population PK analysis. M3 method was implemented to evaluate the impact of BQL records for a total of 13068 records from 2047 subjects. Figure 6 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, and 60 prior to drug administration.

Figure 6 Observed ustekinumab concentrations versus time since last dose for all subjects stratified by study



Source: The Applicant's population PK report, Page 23, Figure 2

The majority of the subjects were Caucasian (92.4%). The median age of all subjects was 45 years old (range, 12-84), 67.5% were males, and the median body weight was 88.4 kg (range, 32.0-195). Median body weight for adolescent and adult subjects were 61.6 kg (range, 32.0-174) and 89.8 kg (range, 37.4-195), respectively. Median renal function was 120 mL/min (range, 33.1-371) and 89.2 mL/min (range, 29.2-271) for CrCL and eGFR, respectively. Demographic data for subjects in each of the three studies are shown in Table 11 and Table 12.

Table 11 Demographics and Baseline Characteristics of Pooled Study Data (Categorical Variables)

Study No	C0743T08	C0743T09	CADMUS	Total
N	739	1198	110	2047
Sex, n (%)				
Male	511 (69.1)	817 (68.2)	54 (49.1)	1382 (67.5)
Female	228 (30.9)	381 (31.8)	56 (50.9)	665 (32.5)
Race, n (%)				
Caucasian	694 (93.9)	1099 (91.7)	98 (89.1)	1891 (92.4)
Black	14 (1.9)	26 (2.2)	0 (0)	40 (2.0)
Asian	16 (2.2)	48 (4.0)	6 (5.5)	70 (3.4)
Other	15 (2.0)	25 (2.1)	6 (5.5)	46 (2.2)
Immune Response Positive[1], n (%)				
No	705 (95.4)	1170 (97.7)	108 (98.2)	1983 (96.9)
Yes	34 (4.6)	28 (2.3)	2 (1.8)	64 (3.1)
History of Diabetes Mellitus, n (%)				
No	654 (88.5)	1077 (89.9)	110 (100)	1841 (89.9)
Yes	85 (11.5)	121 (10.1)	0 (0)	206 (10.1)

Key: N, n=number of subjects
[1]EIA Method

Source: The Applicant's population PK report, Page 21, Table 5

Table 12 Demographics and Baseline Characteristics of Pooled Study Data (Continuous Variables)

Study No	C0743T08	C0743T09	CADMUS	Total
N	739	1198	110	2047
Age (years)				
Mean (SD)	45.3 (11.7)	46.2 (12.2)	15.2 (1.65)	44.2 (13.6)
Median [Range]	45.0 [19.0, 76.0]	46.0 [18.0, 84.0]	15.5 [12.0, 17.0]	45.0 [12.0, 84.0]
Weight (kg)				
Mean (SD)	93.8 (23.5)	90.9 (21.1)	65.0 (19.2)	90.5 (22.8)
Median [Range]	91.8 [46.9, 183.]	88.6 [37.4, 195.]	61.6 [32.0, 174.]	88.4 [32.0, 195.]
CrCL (mL/min)				
Mean (SD)	134. (46.0)	125. (37.8)	81.4 (14.2)	126. (41.8)
Median [Range]	126. [39.4, 371.]	121. [33.1, 308.]	79.7 [54.9, 135.]	120. [33.1, 371.]
eGFR (mL/min)[1]				
Mean (SD)	92.9 (19.2)	90.0 (17.9)	77.1 (33.7)	90.3 (19.8)
Median [Range]	91.4 [41.2, 239.]	88.7 [29.2, 180.]	71.5 [31.8, 271.]	89.2 [29.2, 271.]
Serum Albumin (g/dL)				
Mean (SD)	4.36 (0.278)	4.42 (0.297)	4.27 (0.345)	4.39 (0.296)
Median [Range]	4.40 [2.60, 5.10]	4.40 [2.90, 5.40]	4.30 [3.50, 5.50]	4.40 [2.60, 5.50]
Alkaline Phosphatase (U/L)				
Mean (SD)	81.7 (23.8)	79.1 (22.5)	122. (71.0)	82.3 (29.3)
Median [Range]	79.0 [29.0, 262.]	77.0 [23.0, 217.]	102. [43.0, 461.]	78.0 [23.0, 461.]
Psoriasis Area Severity Index				
Mean (SD)	19.6 (8.74)	19.2 (8.01)	21.1 (8.92)	19.4 (8.34)
Median [Range]	17.1 [0.400, 56.4]	17.4 [1.20, 60.3]	18.8 [12.0, 51.0]	17.4 [0.400, 60.3]

Key: N=number of subjects; SD=standard deviation

[1]Abbreviated ("four-variable") Modification of Diet in Renal Disease (MDRD) study equation will be used to estimate glomerular filtration rate: eGFR = 186 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ (× 0.742 if female; × 1.212 if black) [3].

Source: The Applicant's population PK report, Page 21, Table 4

The combined adult and adolescent data were well described by a one-compartment model with first order absorption and elimination. Because the ECLIA assay on the MSD® platform yields markedly higher concentration results than on the BioVeris™ platform, a term for assay bias was incorporated into the base structural model via the relative bioavailability (F1) term. Given the mixture of adult and adolescent 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 two base models, were taken with respect to the modeling of body weight effects on CL/F and V/F using the following allometric equations.

$$CL/F = Typical\ value\ of\ CL \times (Weight/88)^{b1}$$

$$V/F = Typical\ value\ of\ V \times (Weight/88)^{b2}$$

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, eGFR, albumin, alkaline phosphatase, immune response, baseline psoriatic area and severity index (PASI) score, and diabetes co-morbidity, were tested for each base model (FBW or EBW). 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.

The final population PK parameters for the FBW and EBW approaches are presented in Table 13 and Table 14, respectively. Since the M3 method provided more statistically robust estimates than excluding BQL records, the M3 method was implemented in the final models. The CL/F estimates were 83.1% (FBW model) and 72.4% (EBW model) higher for subjects who were positive for IR (immune response, i.e., with positive antibodies to ustekinumab). The CL/F estimates were also higher for subjects with a history of diabetes mellitus (27.4% FBW model; 20.1%, EBW model).

Table 13 Parameter Estimates of Final FBW Model

	Parameter (unit)	Population Mean Estimate	RSE (%)	IIV[1] (%CV)	RSE[2] (%)	Shrinkage (%)
TH 1	CL/F (L/day)	0.322	5.5	43.4	8.03	5.69
TH 2	V/F (L)	10.3	5.51	31.9	15.4	29.6
TH 3	KA (1/day)	0.254	13.5			
TH 4	Prop error (T08/T09)	0.312	2.1			
TH 5	Prop error (CADMUS)	0.315	13.5			
TH 6	Add error (T08/T09) (ug/mL)	0.0001 FIX	-			
TH 7	Add error (CADMUS) (ug/mL)	0.0001 FIX	-			
TH 8	WGT on CL/F[3]	0.75 FIX	-			
TH 9	WGT on V/F[4]	1 FIX	-			
TH 10	Assay bias (F1, T08/T09)[5]	0.654	5.05			
TH11	IRPO on CL/F[6]	0.831	11.2			
TH12	DIAB on CL/F[7]	0.274	12.1			
EPS1	Proportional Error (Variance)	1 FIX	-			

Source: The Applicant's population PK report, Page 28, Table 8

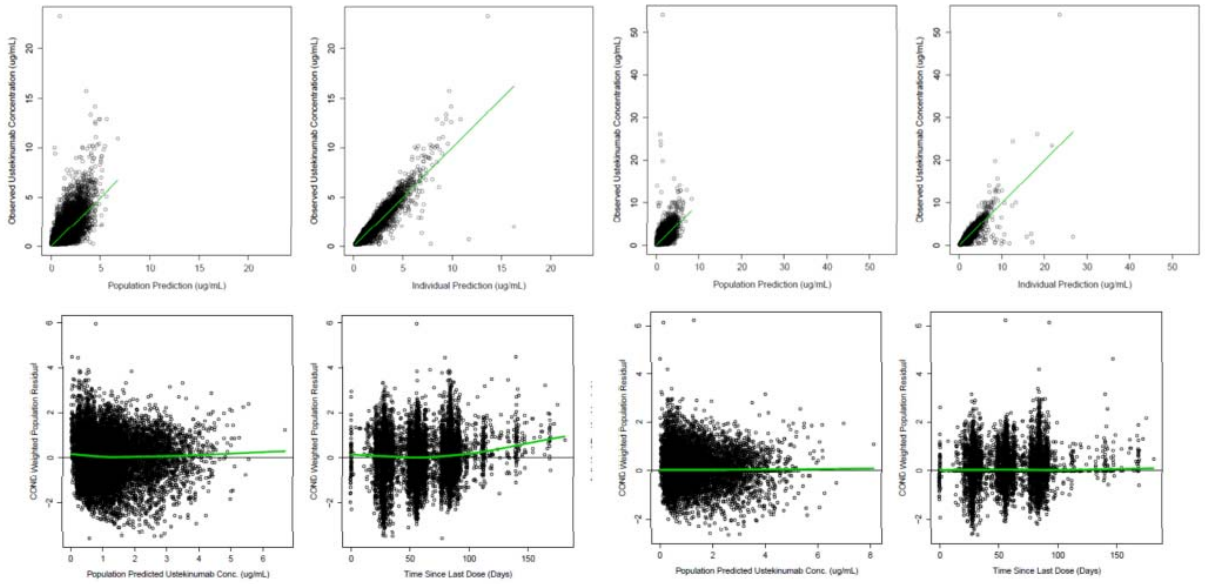
Table 14 Parameter Estimates of Final EBW Model

	Parameter (unit)	Population Mean Estimate	RSE (%)	IIV[1] (%CV)	RSE[2] (%)	Shrinkage (%)
TH 1	CL/F (L/day)	0.323	4.98	42.7	7.86	5.72
TH 2	V/F (L)	10.2	5.02	31.3	15.5	29.3
TH 3	KA (1/day)	0.264	12.5			
TH 4	Prop error (T08/T09)	0.313	2.1			
TH 5	Prop error (CADMUS)	0.319	13.1			
TH 6	Add error (T08/T09) (ug/mL)	0.0001 FIX	-			
TH 7	Add error (CADMUS) (ug/mL)	0.0001 FIX	-			
TH 8	WGT on CL/F[3]	0.988	4.53			
TH 9	WGT on V/F[4]	0.784	5.57			
TH 10	Assay bias (F1, T08/T09)[5]	0.654	4.68			
TH 11	IRPO on CL/F[6]	0.724	13.4			
TH 12	DIAB on CL/F[7]	0.201	17.3			
EPS1	Proportional Error (Variance)	1 FIX	-			

Source: The Applicant's population PK report, Page 29, Table 5

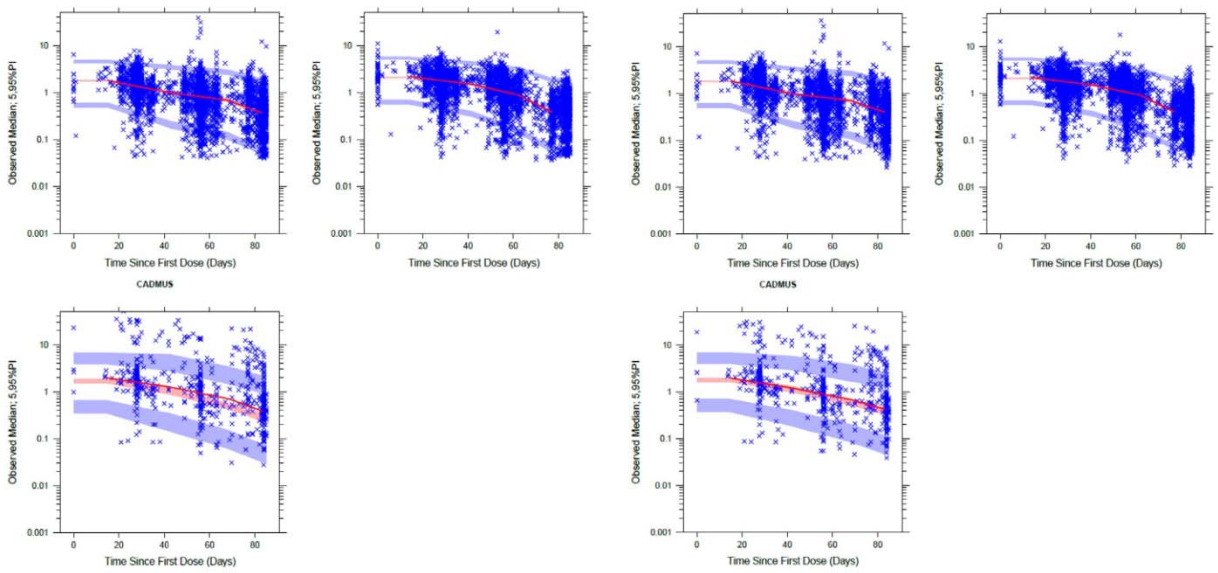
The diagnostic plots for the final FBW and EBW models are shown in Figure 7. The pcVPC (prediction-corrected visual predictive check) in Figure 8 are stratified by study and plotted versus time since last dose ≤ 84 days for the final FBW and EBW models. Both models describe the observed data well and the model predictions were generally within the 90% prediction intervals.

Figure 7 diagnostic plots for the Final FBW (Left) and EBW (Right) Models



Source: The Applicant's population PK report, Page 57-63, Figure 3 and Figure 16, 17, 21, and 22

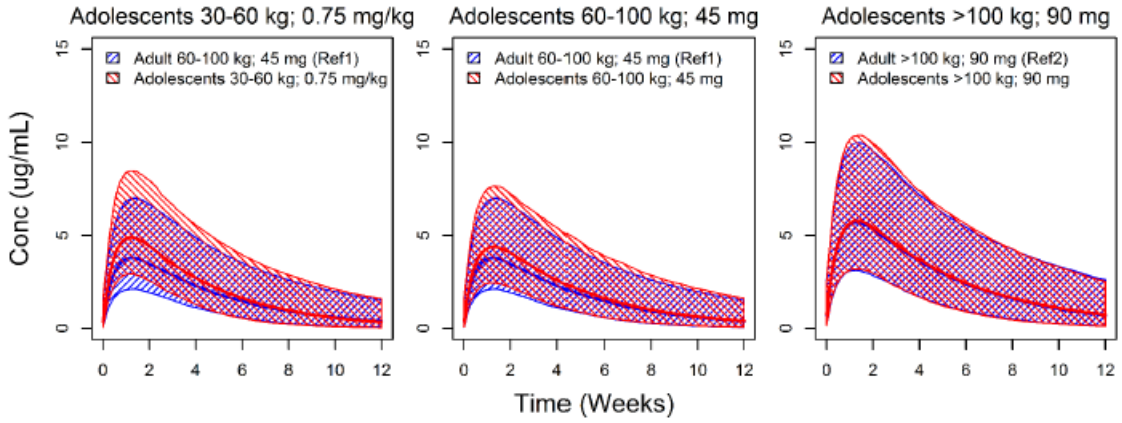
Figure 8 Prediction-Corrected Visual Predictive Check Stratified by Study for the Final FBW (Left) and EBW (Right) Models



Source: The Applicant's population PK report, Page 30 and 32, Figure 3 and Figure 5

Simulations were performed using final FBW model to confirm whether the exposure in adolescent subjects with psoriasis following the proposed dosage regimens were similar to exposures in adult subjects with psoriasis who received ustekinumab at the approved dosage. Figure 9 provides overlay plots for median (90% prediction interval) serum concentration-time profiles of ustekinumab in adolescents and adults in different body weight categories following the proposed/approved dosing regimens.

Figure 9 Comparison of Model FBW predictions of serum concentration-time profiles of ustekinumab in adolescents receiving fixed ustekinumab doses with respective adult reference populations



Lines represent medians of the simulated values. Shaded regions represent the $5^{th} - 95^{th}$ percentile ranges.

Source: The Applicant's population PK report, Page 34, Figure 7

A summary of simulated exposures by population and dosing regimen is presented in Table 15. A similar congruence between the adolescent sub-populations and the respective adult reference populations was observed in the distributions of the model-predicted AUC, Cmax and Ctrough values.

Table 15 Median and 90% prediction intervals of model-predicted PK parameters (Model FBW) by population/dosing scenario

Scenario	AUC (µg·day/mL)	Cpeak (µg/mL)	Ctrough (µg/mL)
Adolescents 30-60 kg; 0.75 mg/kg	170 [87.3, 356]	4.91 [2.93, 8.45]	0.339 [0.0384, 1.58]
Adolescents 60-100 kg; 45 mg	162 [78.5, 350]	4.39 [2.47, 7.67]	0.402 [0.0638, 1.61]
Adolescents >100 kg; 90 mg	236 [109, 483]	5.79 [3.19, 10.4]	0.735 [0.111, 2.52]
Adult 60-100 kg; 45 mg (Ref1)	145 [70.4, 313]	3.8 [2.12, 6.99]	0.388 [0.0579, 1.49]
Adult >100 kg; 90 mg (Ref2)	229 [109, 469]	5.7 [3.13, 10]	0.695 [0.126, 2.61]

Source: The Applicant's population PK report, Page 36, Table 10

***Reviewer's comments**: The reviewer verified the population PK model developed by the Applicant. The model appears to be reasonable in general 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 three studies. This affects the utility of the Applicant's model-based analyses. It should be noted that concentration differences due to change of bioanalytical assays should not be assessed using population PK model as it would not be known if the differences are from study or study populations. Although the current model can well describe the pediatric data, it is more appropriate to conduct population PK analysis using PK data derived from the same bioanalytical assay.

Other than analytical method, the covariate analysis results were consistent with previously developed population PK model based on PK data in adults in Studies C0743T09 and C0743T08. The allometric exposure for body weight on CL/F was estimated to be 0.99 in adolescents (EBW) which was slightly higher than that of 0.84 estimated in adults.

It is noted that none adolescent subject had a history of diabetes mellitus and only 2 adolescent subjects had a positive immune response in the population PK analysis. Thus the inclusion of these two covariates is predominantly based on the PK data in adults which has a considerable number of subjects with a history of diabetes mellitus and subjects who developed anti-drug antibodies. Nonetheless, the current population PK model does not allow for assessing the impact of diabetes mellitus and immunogenicity on PK of ustekinumab in adolescent subjects with psoriasis.

The reviewer conducted an independent analysis to compare individual patient predicted exposures with simulated exposure with doses of 0.75 mg/kg, 45 mg or 90 mg. As shown in Figure 5*, the red shaded area presents the 95% prediction interval of ustekinumab exposure at the 45 mg dose for subjects with body weight of 60-100 kg and at the 90 mg dose for subjects with body weight >100 kg. The result was based on 100 simulations using the population PK model (EBW) developed by Applicant. The individual predicted exposures are overlapping with simulated exposures for the two dose levels with corresponding body weight range. See section 3.3.3 for more information.*

4.2 Exposure-response

The exposure-response (ER) relationship of ustekinumab was evaluated in adolescent subjects with moderate to severe psoriasis. The ER relationship was explored by graphical analysis, followed by a logistic regression modeling approach, using PGA (0/1), PASI 75, PASI 90, and PASI 100 (75, 90 and 100% improvement/reduction in PASI score from baseline, respectively), where PGA stands for Physician's Global Assessment, and PASI stands for Psoriatic Area and Severity Index. The serum ustekinumab concentrations at Week 12 and Week 28 were predicted from population PK model (FBW model) as described above. The Applicant selected Week 12 and Week 28 for the E-R analysis because the data for PK and response variables were available at these time points across the three studies in the database.

Study CNTO1275PSO3006: The study was a Phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter 3-arm study that evaluated the safety and efficacy of ustekinumab in adolescent subjects with moderate to severe chronic plaque psoriasis. See section 3.2.1 for more information. .

Study C0743T08: The study was a Phase 3, multicenter, randomized, placebo-controlled, double-blind, parallel, 3-arm study evaluating the safety and efficacy of ustekinumab for the treatment of adult subjects with moderate to severe plaque psoriasis. A total of 766 subjects were randomized at Week 0. The study was designed to evaluate the safety and efficacy of 2 dose

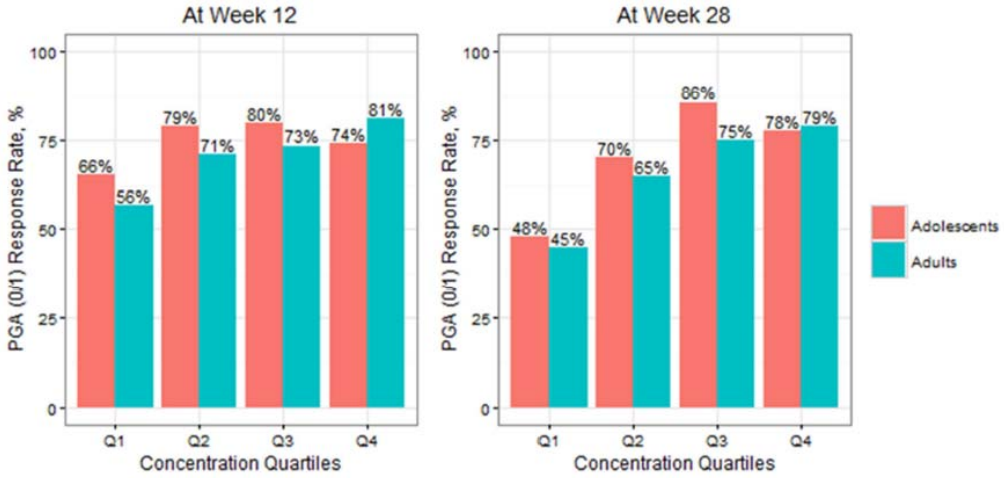
regimens of ustekinumab: (i) 45 mg at Weeks 0 and 4 followed by 45 mg q12w and (ii) 90 mg at Weeks 0 and 4 followed by 90 mg q12w.

Study C0743T09: The study was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel, 3-arm study evaluating the safety and efficacy of ustekinumab for the treatment of adult subjects with moderate to severe plaque psoriasis. A total of 1230 subjects were randomized at Week 0. The study was designed to evaluate the safety and efficacy of 2 dose regimens of ustekinumab: (i) 45 mg at Weeks 0 and 4 followed by 45 mg q12w and (ii) 90 mg at Weeks 0 and 4 followed by 90 mg q12w.

Two datasets (one for Week 12 and the other for Week 28) were used. The two datasets had subject information such as demographics, treatment allocation, and efficacy response variables (PGA (0/1), PASI75, PASI90 and PASI100) from Studies CNTO1275PSO3006, C0743T08 and C0743T09. In the Week 12 dataset, there were 1839 adult subjects in Studies C0743T08 and C0743T09 and 105 adolescents in Study CNTO1275PSO3006. In the Week 28 dataset, there were 1433 adult subjects in Studies C0743T08 and C0743T09 and 105 adolescents in Study CNTO1275PSO3006. The data from doses of 45 mg and 90 mg in adults were combined to provide a wide ustekinumab exposure range for the analysis.

The E-R graphical analysis was performed by comparing the binary responses of PGA (0/1), PASI 75, PASI 90, PASI 100 from CNTO1275PSO3006 (adolescents) and C0743T08/C0743T09 (adults) (Figure 10 and Figure 11).

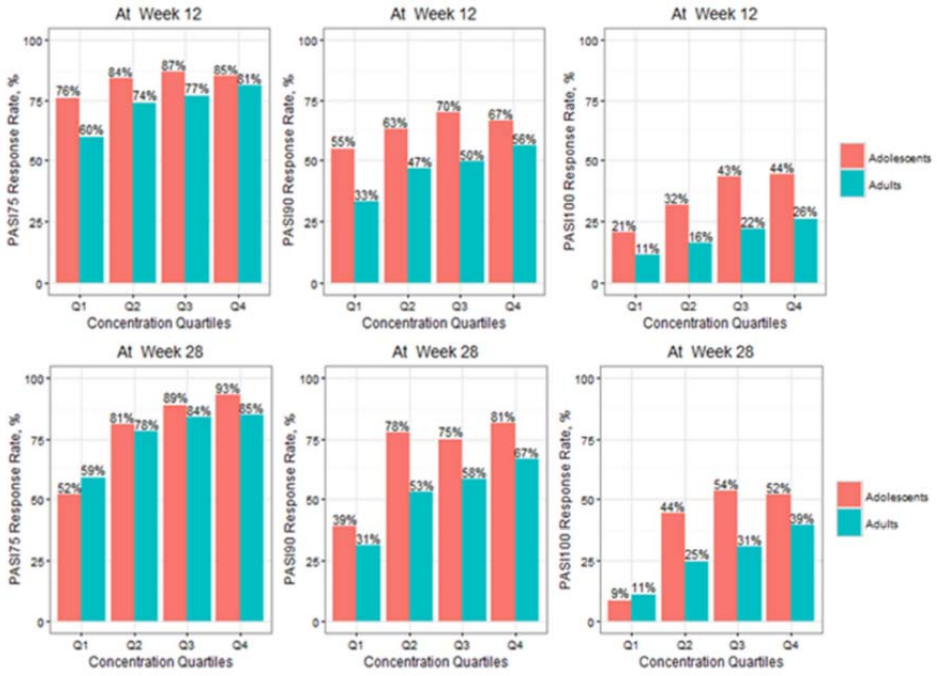
Figure 10 Exposure-response relationships of PGA (0/1) in adolescents and adults



At Week 12, the Q1, Q2, Q3 and Q4 ranges are (0.005, 0.559], (0.559, 0.992], (0.992, 1.620], (1.620, 21.553] µg/mL, respectively. At Week 28, they are (0, 0.157], (0.157, 0.356], (0.356, 0.645], (0.645, 15.503], respectively.

Source: Applicant's Exposure-response analysis report, Page 12, Figure 4

Figure 11 Exposure-response relationships of PASI 75, PAS I90 and PASI 100 in adolescents and adults



At Week 12, the Q1, Q2, Q3 and Q4 ranges are (0.005, 0.559], (0.559, 0.992], (0.992, 1.620], (1.620, 21.553] µg/mL, respectively. At Week 28, they are (0, 0.157], (0.157, 0.356], (0.356, 0.645], (0.645, 15.503], respectively.

Source: Applicant's Exposure-response analysis report, Page 13, Figure 5

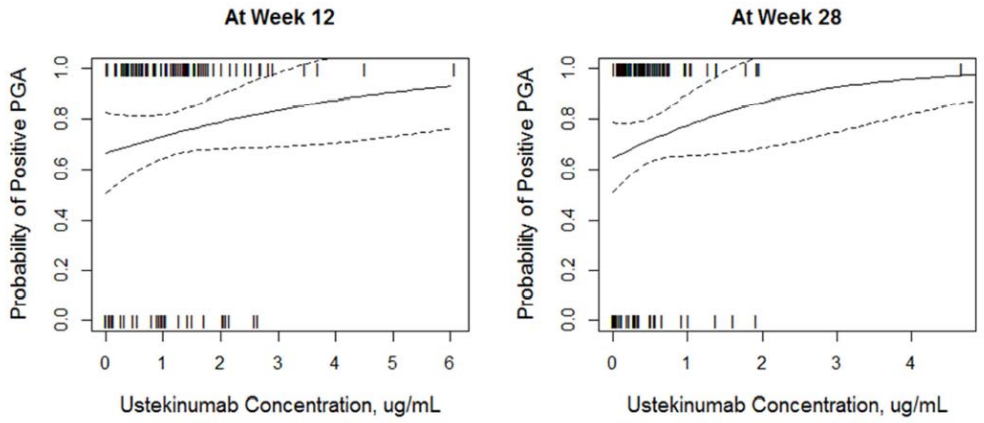
The quartiles of adult individual predicted ustekinumab concentrations from the population PK model were used to evaluate the exposure-response relationship in adolescents. The quartile exposures at Week 12 were (0.005, 0.559], (0.559, 0.992], (0.992, 1.620], (1.620, 21.553] mcg/mL, and 462, 458, 460 and 459 subjects were in each of the quartiles. The number of adolescents whose concentrations fell into each quartile of adults' concentrations at Week 12 was 29, 19, 30, 27 subjects, respectively. Similarly, the quartiles of adult individual predicted ustekinumab concentrations at Week 28 were (0, 0.157], (0.157, 0.356], (0.356, 0.645], (0.645, 15.503] mcg/mL, respectively, and 360, 357, 359, 357 subjects were in each of the quartiles. The number of adolescents whose concentrations fell into each quartile at Week 28 was 23, 27, 28, and 27 subjects, respectively. The Week 12 concentrations are higher than the Week 28 trough concentrations. Note that Week 28 PK samples are from 12 weeks after the prior doseat Week 16, whereas Week 12 PK samples are from 8 weeks after the previous dosing at Week 4.

Figure 12 and Figure 13 demonstrate that relationships exist between ustekinumab concentration quartiles and the PGA- and PASI-derived binary response variables at Week 12 and Week 28 in both adolescent and adult populations. Generally, the proportion of pediatric and adult subjects achieving the clinical endpoints increased with increasing serum ustekinumab concentration.

A logistic regression modeling approach using estimated serum ustekinumab concentration and clinical efficacy measures of PGA (0/1), PASI 75, PASI 90 and PASI 100 at Week 12 and Week

28 was applied to assess the ER relationships in adolescents. The probabilities of the responses were related to estimated concentration using the generalized linear modeling function. The 95% confidence interval was constructed around each predicted logistic regression curve.

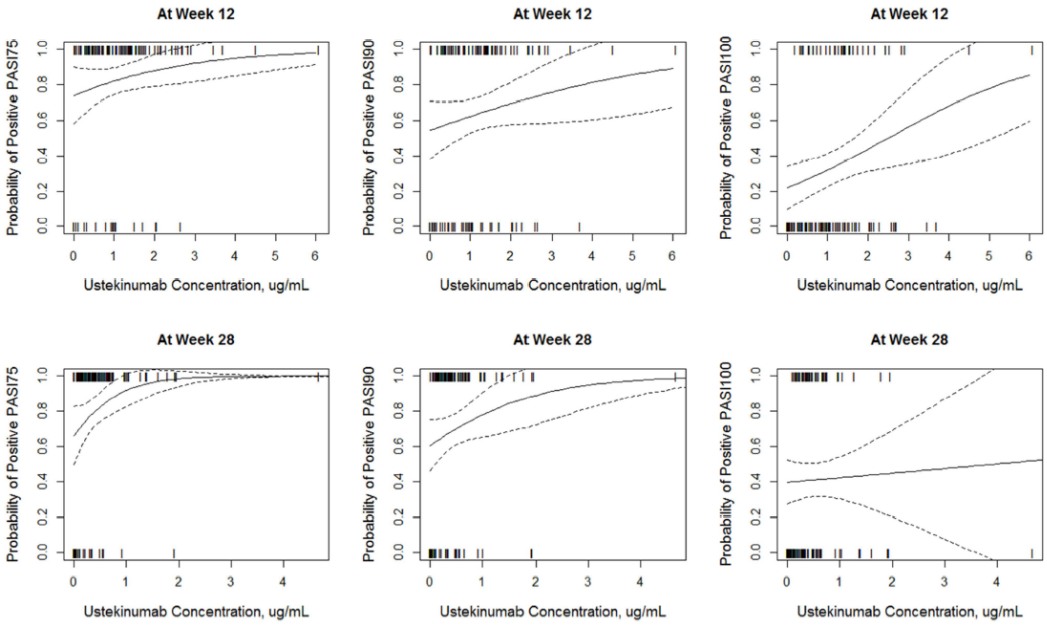
Figure 12 Relationships of probability of positive PGA (0/1) vs. exposure in adolescents with ustekinumab concentrations at Week 12 and Week 28



The solid curve line represents the logistic regression fit with 95% confidence interval (dashed lines). The tick indicates the individual responses at corresponding ustekinumab concentrations.

Source: Applicant's Exposure-response analysis report, Page 16, Figure 8

Figure 13 Relationships of probability of positive PASI 75, PASI 90 and PASI 100 vs. exposure in adolescents with ustekinumab concentrations at Week 12 and Week 28

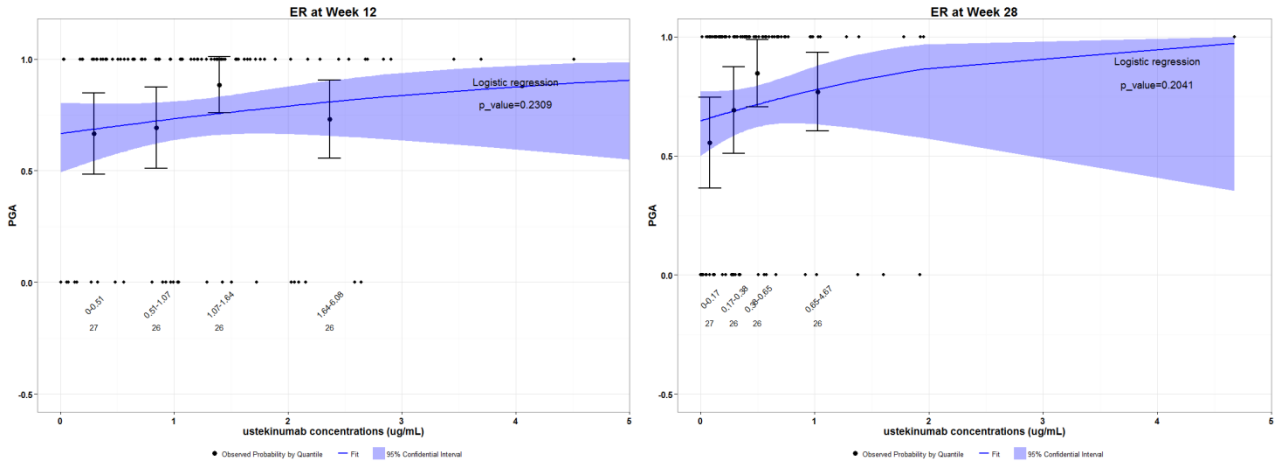


The solid curve line represents the logistic regression fit with 95% confidence interval (dashed lines). The tick indicates the individual responses at corresponding ustekinumab concentrations.

Source: Applicant's Exposure-response analysis report, Page 17, Figure 9

Reviewer's comments: *The reviewer conducted an E-R analysis for PGA (0/1) using observed trough concentrations of ustekinumab at Week 12 which identified a shallow and non-significant E-R relationship (Figure 3). Subjects with higher serum ustekinumab concentrations were associated with higher PGA (0/1) response rates. The reviewer also conducted logistic regression analysis to assess the E-R relationship for PGA (0/1) at Weeks 12 and 28 using model predicted concentrations (Figure 14). These additional analyses identified similar shallow and non-significant relationships between exposure of ustekinumab and PGA (0/1). Further analysis for PASI 75, PASI 90 and PASI 100 resulted in similar findings (data not shown), except for that E-R relationships for PASI 100 at week 12 and PASI 75 at week 28 were statistically significant with p values of 0.025 and 0.043, respectively. Overall, because of the limited number of subjects in the E-R analysis and potential confounding factors (e.g., disease) on both exposure and response, the apparent E-R relationships do not indicate that substantial gains in efficacy would be achieved by further increasing the dose of ustekinumab.*

Figure 14 Logistic regression analysis of ustekinumab for PGA (0/1) in adolescents



Source: Reviewer's independent analysis

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/s/

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