

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125261/S-138
Priority or Standard	Standard
Received Date(s)	December 15, 2016
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Division / Office	DDDP/ODE III
Reviewer Name(s)	Brenda Carr, M.D.
Review Completion Date	August 31, 2017
Established Name	Ustekinumab
Trade Name	Stelara
Therapeutic Class	IL-12/IL-23 antagonist
Applicant	Janssen Biotech, Inc.
Formulation(s)	solution for subcutaneous administration
Dosing Regimen	Weeks 0, 4 then every 12 weeks
Indication(s)	for the treatment of adult patients and adolescent patients (12 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Intended Population(s)	patients (12 years or older)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From my review of the clinical data, I recommend approval of this efficacy supplement.

1.2 Risk Benefit Assessment

Ustekinumab is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines. Current indications include the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. In the efficacy supplement that is the subject of this review, the applicant proposes to extend the psoriasis indication to include treatment of adolescent patients.

Psoriasis is a common, chronic, immune-mediated, inflammatory skin disease that classically presents as sharply-demarcated, scaly, erythematous plaques that are symmetrically-distributed. It affects approximately 2% of the general population, and the frequency is the same in males and females. Onset in childhood is reported by approximately one-third of patients,¹ and plaque psoriasis is the most common presentation in pediatric patients.²

Extent of involvement is one determinant of disease severity. Depending on the site(s) of involvement, psoriasis of limited extent may be considered mild and effectively managed with topical treatment. More extensive psoriasis may constitute moderate to severe disease and require systemic therapy or phototherapy for control. While numerous products (small molecules and biologics) are approved for treatment of moderate to severe psoriasis in adults, only one systemic product has been approved for treatment of disease of this severity in pediatric patients.

Efficacy

The applicant submitted data from one adequate and well-controlled study, 3006, which evaluated ustekinumab in adolescent subjects in the referenced pediatric subgroup. The study evaluated two weight-based dosing regimens of ustekinumab, “half-standard” dosage and “standard” dosage. The primary endpoint was the proportion of subjects who achieved a Physician’s Global Assessment (PGA) score of cleared or minimal at

1 Bronckers IMGJ, Paller AS, van Geel MJ, van de Kerkhof PCM, Seyger MMB. Psoriasis in Children and Adolescents: Diagnosis, Management and Comorbidities. *Pediatr Drugs* 2015;17:373–384.

2 Tangtatco JAA, Lara-Corrales I. Update in the management of pediatric psoriasis. *Curr Opin Pediatr* 2017;29:434–442.

Week 12. Both the half-standard dose and the standard dose of ustekinumab were superior to placebo at primary efficacy assessment, and the results were statistically significant (<0.001). The treatment effects were similar for the two ustekinumab dosage groups.

However, through Week 52, PGA scores of cleared or minimal and psoriasis area severity index (PASI) 75 (a key secondary endpoint) response rates were generally higher and better sustained in the standard dosage group compared to the half-standard dosage group. Additionally, loss of treatment response toward the end of the 12-week dosing interval was more frequently observed in the half-standard dosage group, indicating inadequate exposure during the maintenance phase in this dosage group. Mean \pm SD steady-state trough concentrations at Week 28 in subjects in the standard dosage groups were approximately twice those of subjects who received the half-standard dosage. The observed ustekinumab concentrations in adolescent subjects who received standard dosing were generally comparable to those in adults who received labeled dosing regimens.

Thus, the applicant established that ustekinumab is effective for treatment of moderate to severe plaque psoriasis in adolescent subjects, ages ≥ 12 to < 18 years. The data support the “standard” dosing regimen for adolescents.

Safety

Headache and nasopharyngitis were the most commonly reported adverse events in ustekinumab-treated subjects through Week 12 (the placebo-controlled period) and through Week 60. Adverse events were not worrisome in type or pattern and were generally similar between both ustekinumab treatment groups and placebo during the 12-week placebo-controlled period. No change in the safety profile was apparent with longer-term treatment through Week 40. There was no apparent dose-response in occurrence of adverse events between the half-standard and standard dosage groups with follow-up through Week 60. No new adverse reactions or safety signals were identified in this study.

The applicant established the safety of ustekinumab in the treatment of moderate to severe plaque psoriasis in adolescent subjects.

Conclusions:

Psoriasis may substantially impact the quality of life and psychosocial functioning in all age groups, but may be particularly impactful in children as they are in their developmental years. Because it commonly affects exposed skin, it may result in

bullying and feelings of alienation and insecurity. Quality of life of children with psoriasis has been reported to be worse than epilepsy, enuresis, diabetes, and alopecia.³

There is an unmet medical need for safe and effective treatment for moderate to severe plaque psoriasis in pediatric subjects. Approval of this supplement would add to the very limited armamentarium of approved systemic treatments for this population. It would represent the second approved systemic treatment for psoriasis in adolescents. The applicant has adequately demonstrated that ustekinumab is safe and effective for treatment of plaque psoriasis in adolescent subjects, and the data favor standard dosing for this population. I conclude that the benefits of ustekinumab outweigh its risks for treatment of moderate to severe plaque psoriasis in adolescent patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I recommend routine pharmacovigilance and the product label as methods for postmarket risk evaluation and mitigation. I do not recommend a Risk Evaluation and Mitigation Strategy (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

As a required pediatric assessment, the applicant should 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.

2 Introduction and Regulatory Background

2.1 Product Information

Ustekinumab (Stelara) is an IL-12/IL-23 antagonist that was initially approved on 09/25/2009 “for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.”

In the efficacy supplement that is the subject of this review (sBLA-138), the applicant proposes expansion of the patient population for the psoriasis indication to include treatment of adolescents. Specifically, the applicant proposes the following:

³ Beattie PE and Lewis-Joes MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Bri J Dermatol* 2006;155:145–151.

“STELARA® is indicated for the treatment of adult patients and adolescent patients (12 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.”

Ustekinumab is currently also indicated for:

- treatment of adult patients with active psoriatic arthritis, alone or in combination with methotrexate (MTX).
- treatment of adult patients with moderately to severely active Crohn's disease who have:
 - failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker or
 - failed or were intolerant to treatment with one or more TNF blockers.

Approval of S-138 would represent the first pediatric indication for ustekinumab in the United States.

2.2 Tables of Currently Available Treatments for Proposed Indications

In clinical practice, a recommendation for systemic therapy or phototherapy is based on clinical judgment, and the decision to proceed is one made between caregiver/patient and physician with careful attention to risk-benefit considerations, since all of the therapies carry significant risk. Such considerations are especially important in treatment decisions for moderate to severe psoriasis in pediatric patients, since the majority of treatments would be used off-label.

Etanercept is the only systemic treatment specifically approved for psoriasis in pediatric patients. It is approved in patients ages 4 to 17 years who are candidates for systemic or phototherapy. Therapies presented in the following table are otherwise only approved for use in adults.

Table 1: Approved Systemic Therapies for Psoriasis

Small Molecules		
Product	Class	Warnings/Precautions
Acitretin	Retinoid	teratogen; hepatotoxicity; hyperostosis; lipid effects
Methotrexate	folate antagonist	teratogen; liver fibrosis/cirrhosis; hematologic toxicity; interstitial pneumonitis; opportunistic infections
Cyclosporine	inhibits IL-2	hypertension; nephrotoxicity; serious infections; malignancy
Apremilast	phosphodiesterase 4 inhibitor	depression; weight decrease; drug-drug interactions

Biologics		
Etanercept	TNF α -blocker	serious infections (including TB); malignancy; central nervous system demyelinating disorders; hematologic events (pancytopenia); reactivation of hepatitis B; autoimmunity
Adalimumab	TNF α -blocker	serious infections (including TB); malignancy; reactivation of hepatitis B; demyelinating disease; hematologic reactions (pancytopenia); autoimmunity
Infliximab	TNF α -blocker	serious infections (including TB); malignancy; demyelinating disease; hepatotoxicity
Ustekinumab	interleukin-12 and -23 antagonist	serious infections; malignancy; reversible posterior leukoencephalopathy syndrome
Secukinumab	interleukin-17A antagonist	serious infections; TB, exacerbation of Crohn's disease; hypersensitivity
Ixekizumab	interleukin-17A antagonist	infections; hypersensitivity; inflammatory bowel disease
Guselkumab	interleukin-23 blocker	Infections; TB

Phototherapy

This therapy involves exposures to UVB (including narrowband) or to UVA in combination with the photosensitizer, psoralen, a photochemotherapy regimen that goes by the acronym "PUVA." Long-term phototherapy carries risks of photoaging and skin cancer.

2.3 Availability of Proposed Active Ingredient in the United States

Since approval for the psoriasis indication, ustekinumab has been approved in the United States for (see Section 2.1):

- The psoriatic arthritis indication was approved on 09/20/2013 under S-103.
- The Crohn's disease indication was approved on 09/23/2016 under BLA 761044.

2.4 Important Safety Issues With Consideration to Related Drugs

Guselkumab is an interleukin-23 blocker that was approved for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy on 07/13/2017. The package insert does not describe any safety concerns or adverse reactions that are related to its mechanism of action.

The general risks of biologic therapy are well known and include serious infections, opportunistic infections, malignancy, and immunogenicity. Risks of subcutaneous administration include injection site reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The approval letter communicated deferral of the required pediatric studies as below:

We are deferring submission of your pediatric protocol until December 1, 2022 because pediatric studies should be delayed until additional adult safety and efficacy data have been collected. Pediatric studies are deferred pending analyses of a) safety data from adults in PHOENIX 1 (C0743T08), PHOENIX 2 (C0743T09), the PSOLAR registry, and the Nordic Database Initiative (discussed in items 2, 3, 8, and 9) and b) safety data in pediatric subjects exposed to Stelara™ (ustekinumab) *in utero* or postnatally (described in Items 4, 5, and 6). These safety analyses must establish that there are no safety issues that would preclude study of pediatric subjects. Pediatric studies should not be undertaken until there is agreement with the Agency on the design of such studies.

Pediatric Protocol Submission Date: December 1, 2022.

However, the applicant's European Pediatric Investigational Plan (PIP) required completion of a study in adolescent subjects (ages 12 to <18 years) with moderate to severe plaque psoriasis by 2014. The applicant conducted the Phase 3 clinical study CNTO1275PSO3006 (3006) to address this element of the PIP. Although the applicant submitted the protocol to the IND for informational purposes on 12/02/2009, the agency had no input on the design of study 3006. Study 3006 was conducted in Europe and Canada) and, to date, has been relied on to support approval of the pediatric indication in the European Union (EU), Canada, Russia, Israel, Ukraine, Singapore, Belarus and Taiwan. The applicant submitted the results from 3006 to support the proposed pediatric labeling that is the subject of this review.

The remaining elements of the PIP required the applicant to conduct a second pediatric study in subjects ages 6 to <12 years with moderate to severe plaque psoriasis. Study CNTO1275PSO3013 (3013) is ongoing in this younger pediatric age group. At the pre-sBLA meeting held May 4, 2016, the agency agreed to enrollment of subjects at U.S. sites in study 3013. The agency also agreed to a partial waiver from study of pediatric subjects less than 6 years of age.

At the pre-sBLA meeting, the agency also agreed that the supplement could be filed without an agreed initial pediatric study plan (iPSP) in place, given the pediatric development plan detailed in the approval letter, i.e. granting of deferral of pediatric studies, with submission of the pediatric protocol in December 2022.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

On submission, the application was sufficiently complete and organized, such that necessary data could be accessed and reviewed without difficulty.

3.2 Compliance with Good Clinical Practices

The applicant attested that the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

3.3 Financial Disclosures

A Form 3455 was submitted for the following investigators, all in Canada:

- Kim Papp: site 011008; 5 subjects
- Marc Bourcier: site 011009; 3 subjects
- Yves Poulin: site 011002; 5 subjects
- Vincent Ho; site 011003; 4 subjects
- Ian Landells: site 011004; 3 subjects

Canada enrolled 41 subjects at 10 sites: 13 of 37 in the placebo group and 28 of 73 in ustekinumab groups.

All of these investigators disclosed the following participation in financial arrangements or holding of financial interests: “any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.” All received payments which exceeded \$25,000, excluding the costs of conducting the trial. Examples of the activities for which payment was received included speaker’s bureau, honoraria for advisory board, sponsorship for international meetings.

The applicant appears to have adequately disclosed financial arrangements with clinical investigators. Potential investigator bias was minimized by the randomized, double-blind, placebo-controlled study design. None of the investigators for whom a Form 3455 was submitted enrolled more than five subjects. The study design and the limited number of subjects enrolled by each of the five referenced investigators reasonably mitigated potential bias.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The applicant did not submit CMC information for this efficacy supplement and cross-referenced the Module 3 Quality information previously submitted to the BLA to support the supplement.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The applicant did not submit any preclinical information for this efficacy supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Per section **12.1 Mechanism of Action** of the label:

Ustekinumab is a human IgG1 monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12R β 1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's disease. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

4.4.2 Pharmacodynamics

Per Section **12.2 Pharmacodynamics** of the label

In a small exploratory study, a decrease was observed in the expression of mRNA of its molecular targets IL-12 and IL-23 in lesional skin biopsies measured at baseline and up to two weeks posttreatment in subjects with psoriasis.

4.4.3 Pharmacokinetics

The Divisions of Clinical Pharmacology 3 and Pharmacometrics recommended approval of this supplement.

Study 3006 evaluated “standard” and “half-standard” dosing regimens for ustekinumab, administered subcutaneously at Weeks 0 and 4, then every 12 weeks.

Table 2: Ustekinumab dosages tested in adolescent subjects aged 12 to 17 years with moderate to severe psoriasis in Study CNTO1275PSO3006

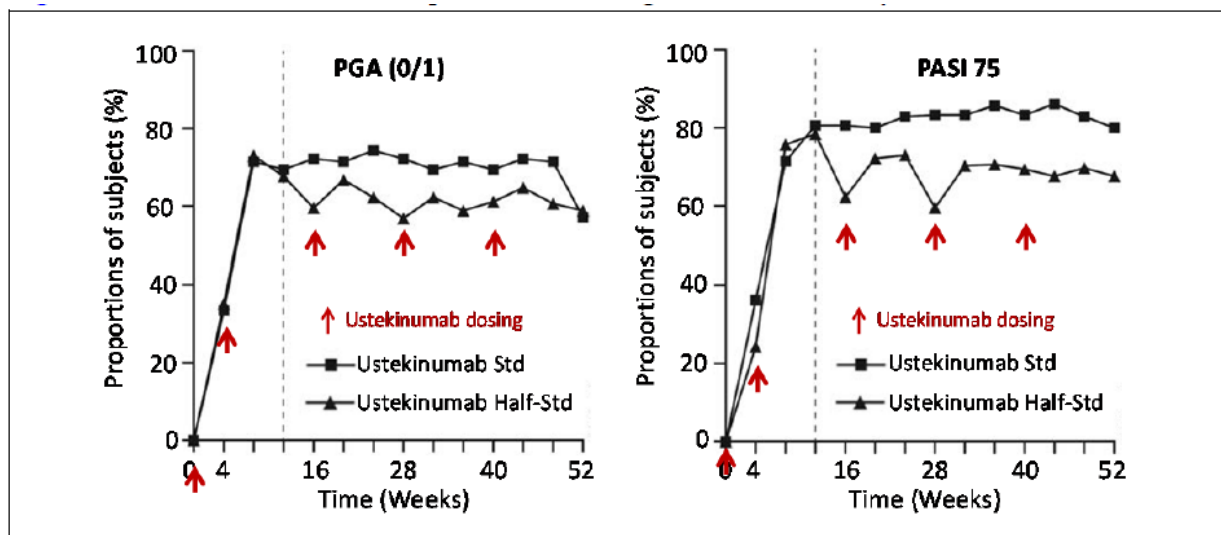
Subjects Body Weight (kg)	Standard Dosage	Half-Standard Dosage
≤60 kg	0.75 mg/kg	0.325 mg/kg
>60 kg to ≤100 kg	45 mg	22.5 mg
>100 kg	90 mg	45 mg

Source: Table 1 Clinical Pharmacology review

Conclusions from the clinical pharmacology team included the following:

- The dose-response relationships for efficacy and safety in study 3006 support that the standard dosage is appropriate for adolescents.
- Through Week 52, PGA (0/1) and PASI 75 response rates were generally higher and better sustained in the standard dosage group compared to half-standard dosage group. See Figure 1.
- Loss of treatment response toward the end of the 12-week dosing interval was more frequently observed in the half-standard dosage group, indicating inadequate exposure during the maintenance phase in this dosage group (Figure 1).
- Mean \pm SD steady-state trough concentrations at Week 28 were 0.54 \pm 0.43 mcg/mL in subjects who received standard dosage and 0.25 \pm 0.26 mcg/mL in subjects who received half-standard dosage. The observed ustekinumab concentrations in adolescent subjects who received standard dosing were generally comparable to those in adults who received labeled dosing regimens. See Table 3.
- There was no evidence of dose-response relationship in the occurrence of adverse events (AEs).

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



Source: Figure 1 Clinical Pharmacology review, sourced from Figure 5 Summary of Clinical Efficacy

Table 3: Trough serum ustekinumab concentrations in adolescent and adult subjects with psoriasis

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

Source: Table 3 of the Clinical Pharmacology review

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Table of Study

Study Type						
Study ID						Type of Study Report
EudraCT Number		Phase		Study Drug(s): Formulation	Number of	Issue Date
First Patient First Visit /Completion date (day Month year)	Countries: Number of Centers	Study Description/Design Study Population Primary Objective(s)	Total Number of Subjects	(Route of Administration) Dose Regimen Duration of Treatment	Subjects Treated (by Treatment Group)	Document ID Number CTD Location of Report or Publication
Study Status						
Efficacy and Safety Controlled Clinical Studies						
CNTO1275PSO3006	BEL, CAN, FRA, DEU, HUN, POR, RUS, SWE, UKR, UK: 36	Phase 3 A multicenter, randomized, double-blind, placebo-controlled study	Randomized: 110 Treated: 110	Sterile liquid for SC injection Group 1: SC ustekinumab 0.375mg/kg, 22.5mg/kg, or 45mg/kg (body weight of ≤60kg, >60-≤100kg, or >100kg respectively) at Weeks 0, 4 and then q12w until Week 40 Group 2: SC ustekinumab 0.75mg/kg, 45mg/kg, or 90mg/kg (body weight of ≤60kg, >60-≤100kg, or >100kg respectively) at Weeks 0, 4 and then q12w until Week 40 Group 3: SC placebo at Weeks 0 and 4 and then crossover to either Group 3a or Group 3b at Week 12 Group 3a: SC ustekinumab 0.375mg/kg, 22.5mg/kg, or 45mg/kg (body weight of ≤60kg, >60-≤100kg, or >100kg, respectively) at	Group 1: n=37 Group 2: n=36 Group 3: n=37 Group 3a: n=19 Group 3b: n=18	Full Report 16 June 2014 EDMS-ERI-85720383 Module 5.3.5.1
Synopsis						
2009-014368-20		Boys and girls ≥12 to <18 years of age with moderate to severe plaque-type psoriasis				
30 March 2010						
03 January 2014						
Completed		To evaluate the efficacy and safety of 2 SC dosages of ustekinumab in pediatric subjects with moderate to severe plaque-type psoriasis				
Study Type						
Study ID						Type of Study Report
EudraCT Number		Phase		Study Drug(s): Formulation	Number of	Issue Date
First Patient First Visit /Completion date (day Month year)	Countries: Number of Centers	Study Description/Design Study Population Primary Objective(s)	Total Number of Subjects	(Route of Administration) Dose Regimen Duration of Treatment	Subjects Treated (by Treatment Group)	Document ID Number CTD Location of Report or Publication
Study Status						
				Weeks 12, 16 and then q12w until Week 40		
				Group 3b: SC ustekinumab 0.75mg/kg, 45mg/kg, or 90mg/kg (body weight of ≤60kg, >60-≤100kg, or >100kg respectively) at Weeks 12, 16 and then q12w until Week 40		
				40 weeks		

5.2 Review Strategy

The applicant cited efficacy and safety data from the psoriasis development program in adults as points of reference for the outcomes in study 3006, principally the five-year, pivotal studies in adults, C0743T08 (T08) and C0743T09 (T09). Study T08 also evaluated treatment withdrawal and retreatment.

The applicant submitted supportive pharmacokinetic (PK) and immunogenicity data from studies C0743T23 (T23) and C0743T25 (T25) from the psoriasis development program in adults and from CNTO1275PSO3009 (3009), which was conducted in adults to address postmarketing requirement #11.

This review will focus on the study conducted in pediatric subjects, 3006. This pediatric study served as the primary source of efficacy and safety data to support the proposed labeling change. This review will provide limited discussion of studies that have been previously reviewed, such as studies from the psoriasis development program in adults.

5.3 Discussion of Individual Studies/Clinical Trials

Title: “A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Ustekinumab in the Treatment of Adolescent Subjects with Moderate to Severe Plaque-type Psoriasis”

Protocol code: CNTO1275PSO3006 (3006)

Study Name: CADMUS

Study Centers: Belgium (3 sites); Canada (10 sites); France (2 sites); Germany (1 site); Hungary (3 sites); Portugal (3 sites); Russia (5 sites); Sweden (2 sites); Ukraine (4 sites); and United Kingdom (3 sites).

Study initiated: March 30, 2010 **Study completed:** January 3, 2014.

Study Objectives:

Primary Objectives: The primary objectives of this study were to evaluate the efficacy and safety of two subcutaneous (SC) dosages of ustekinumab in the treatment of adolescent subjects ≥ 12 to < 18 years of age with moderate to severe chronic plaque psoriasis.

The secondary objectives of this study were to:

1. Evaluate the impact of ustekinumab on physical, social, emotional, and academic functioning as well as dermatologic symptom impact on health-related quality of life in adolescent subjects with moderate to severe chronic plaque psoriasis.
2. Evaluate the pharmacokinetics (PK) and immunogenicity of ustekinumab in adolescent subjects with moderate to severe chronic plaque psoriasis.

The applicant initially planned to randomize 150 subjects, with 50 subjects per treatment group, i.e. ustekinumab half-standard dosage, ustekinumab standard dosage, or placebo. However, the applicant encountered challenges with subject enrollment, and the target sample size in the PIP and statistical analysis plan were revised to 105 subjects.

Methodology

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter three-arm study. The subject population was comprised of adolescent subjects ≥ 12 to < 18 years of age who had a diagnosis of plaque-type psoriasis for at least 6 months prior to first study agent administration and who had moderate to severe disease defined by Psoriatic Area and Severity Index (PASI) ≥ 12 , Physician's Global Assessment (PGA) ≥ 3 , and body surface area (BSA) involvement $\geq 10\%$.

The applicant studied two weight-based ustekinumab dosages in this adolescent population:

- **Half-standard dosage**- intended to provide ustekinumab exposure comparable to half of the approved adult dosage; allowed better definition of the PK-PD ustekinumab relationship in adolescents:
 - 0.375 mg/kg for subjects ≤ 60 kg,
 - 22.5 mg for subjects > 60 kg but ≤ 100 kg, and
 - 45 mg for subjects > 100 kg.
- **Standard dosage**- intended to provide ustekinumab exposure comparable to that in the adult psoriasis population with the approved adult dosage:
 - 0.75 mg/kg for subjects ≤ 60 kg,
 - 45 mg for subjects > 60 kg but ≤ 100 kg, and
 - 90 mg for subjects > 100 kg.

The third treatment group through Week 12 was placebo.

Subjects in all dosage groups received study treatment at Week 0, Week 4 then every 12 weeks (q12w) with the last dose at Week 40.

Subjects in the placebo group crossed over to receive either half-standard or standard dosage ustekinumab at Week 12 and Week 16, then q12w doses of that dosage, with

the last dose at Week 40. Note: “→” symbol denotes crossover to ustekinumab treatment.

All subjects were followed for efficacy through Week 52 and for safety through Week 60.

Subjects were randomized to receive half-standard dosage, standard dosage, or placebo. Randomization was stratified by investigational site and baseline weight (≤ 60 kg or >60 kg). Randomization of subjects in the placebo group to cross-over to either the half-standard dosage or the standard dosage was performed at Week 0 (placebo → half-standard dosage or placebo → standard dosage).

At Week 8, subjects whose PASI scores increased $\geq 50\%$ from their baseline PASI score were allowed early escape use of a moderate to high potency topical corticosteroid through Week 12. These subjects were considered to be non-responders at Week 12. After Week 12, subjects were encouraged to decrease and discontinue use of the moderate to high potency steroid by Week 16. Also, subjects who discontinued treatment due to lack of efficacy or for worsening of psoriasis were handled as treatment failures for the time of the event.

Endpoints

The primary endpoint was the proportion of subjects who achieved a PGA score of cleared or minimal at Week 12.

The major secondary endpoints were:

- PASI 75 response at Week 12
- Change from baseline in Children’s Dermatology Life Quality Index (CDLQI) at Week 12.
- PASI 90 response at Week 12.

The protocol included eight “other secondary endpoints:

- proportion of subjects achieving a PGA score of mild or better (≤ 2) at Week 12
- proportion of subjects achieving a PGA score of cleared (0) or minimal (1) and the proportion of subjects achieving a PGA score of mild or better (≤ 2) will be summarized over time
- proportion of subjects who achieve PASI 50, PASI 75, and PASI 90, and the percent improvement from baseline in PASI will be summarized over time
- change from baseline in CDLQI will be summarized over time
- proportion of subjects with CDLQI = 0 at Week 12
- change from baseline in the total score, psychosocial health summary score, physical health summary score, and each scale of Pediatric Quality of Life Inventory (PedsQL) at Week 12

- change from baseline in the total score, psychosocial health summary score and physical health summary score of PedsQL will be summarized over time
- Subgroup analyses will be performed to evaluate consistency of the primary endpoint over demographics (including weight), baseline disease characteristics, and prior medications

6 Review of Efficacy

Efficacy Summary

The applicant submitted data from one adequate and well-controlled study, 3006, which evaluated ustekinumab in adolescent subjects in the referenced pediatric subgroup. The study evaluated two weight-based dosing regimens of ustekinumab, “half-standard” dosage and “standard” dosage. The primary endpoint was the proportion of subjects who achieved a Physician’s Global Assessment (PGA) score of cleared or minimal at Week 12. Both the half-standard dose and the standard dose of ustekinumab were superior to placebo at the primary efficacy assessment, and the results were statistically significant (<0.001). The treatment effects were similar for the two ustekinumab dosage groups.

However, through Week 52, PGA score of cleared or minimal and PASI 75 (a key secondary endpoint) response rates were generally higher and better sustained in the standard dosage group compared to the half-standard dosage group. Additionally, loss of treatment response toward the end of the 12-week dosing interval was more frequently observed in the half-standard dosage group, indicating inadequate exposure during the maintenance phase in this dosage group. Mean \pm SD steady-state trough concentrations at Week 28 in subjects in the standard dosage groups were approximately twice those of subjects who received the half-standard dosage. The observed ustekinumab concentrations in adolescent subjects who received standard dosing were generally comparable to those in adults who received labeled dosing regimens.

Thus, the applicant established that ustekinumab is effective in the treatment of plaque psoriasis in adolescent subjects, ages ≥ 12 to < 18 years. The data support the “standard” dosing regimen for adolescents.

6.1 Indication

The applicant proposed the following: “STELARA® is indicated for the treatment of adult patients and adolescent patients (12 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.”

6.1.1 Methods

See Section 5.2.

6.1.2 Demographics

The study enrolled 110 subjects. Baseline demographic and disease characteristics were generally similar across treatment groups.

Demographics at Week 0:

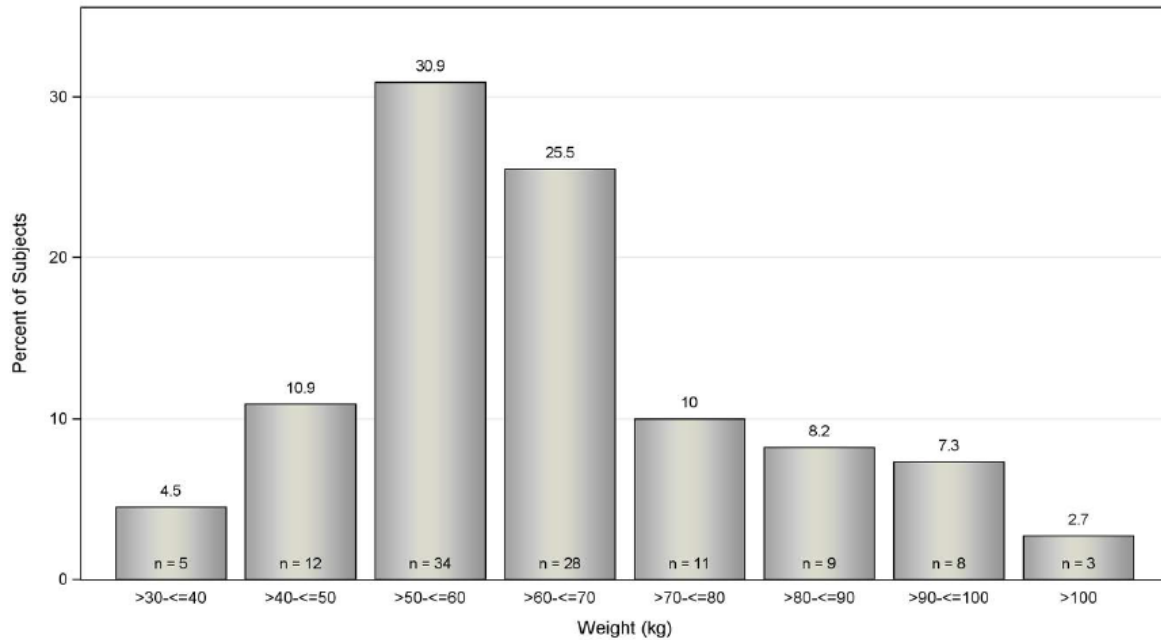
- The study population was approximately half male and half female (49% and 51%, respectively).
- Most subjects were Caucasian (89%).
- The median body weight was 61.6 kg, with most subjects (56.4%) weighing >50 kg to ≤70 kg (Figure 2).
- The median age was 15.5 years, with most subjects (70.0%) being 15 through 17 years of age.

Table 5: Summary of Demographics at Baseline in CNTO1275PSO3006

	Placebo N=37	Half-Standard Ustekinumab N=37	Standard Ustekinumab N=36	Total N=110
<i>Age (years)</i>				
Mean	15.6	15.1	14.8	15.2
12 years	1 (3%)	5 (14%)	5 (14%)	11 (10%)
13 years	3 (8%)	3 (8%)	5 (14%)	11 (10%)
14 years	4 (11%)	3 (8%)	4 (11%)	11 (10%)
15 years	7 (19%)	9 (24%)	6 (17%)	22 (20%)
16 years	7 (19%)	8 (22%)	9 (25%)	24 (22%)
17 years	15 (41%)	9 (24%)	7 (19%)	31 (28%)
<i>Gender</i>				
Female	17 (46%)	19 (51%)	20 (56%)	56 (51%)
Male	20 (54%)	18 (49%)	16 (44%)	54 (49%)
<i>Race</i>				
White	34 (92%)	30 (81%)	34 (94%)	98 (89%)
Black or Afr.-Amer.	--	--	--	--
Asian	2 (5%)	3 (8%)	1 (3%)	6 (5%)
Am. Ind./ AK Native	1 (3%)	1 (3%)	1 (3%)	3 (3%)
Native HI/ Pac. Isl.	--	--	--	--
Other/Unknown	--	3 (8%)	--	3 (3%)
<i>Weight (kg)</i>				
Mean (SD)	64.7 (14.7)	68.2 (24.5)	62.0 (17.1)	65.0 (19.2)
≤ 60 kg	18 (49%)	17 (46%)	16 (44%)	51 (46%)
> 60 to ≤ 100 kg	18 (49%)	19 (51%)	19 (53%)	56 (51%)
> 100 kg	1 (3%)	1 (3%)	1 (3%)	3 (3%)

Sources: Tables 5 and 6 of statistical review

Figure 2: Distribution of Weight (kg) at Baseline; All Randomized Subjects



Source: Figure 3 from 3006 study report

Baseline Disease Characteristics

Baseline disease characteristics for the study population were:

- The median psoriasis duration was 5.29 years.
- The median age at onset of disease was 10.0 years.
- 57.3% of subjects had $\geq 20\%$ of BSA affected with psoriasis.
- The median PASI score was 18.8.
- 61.8% of subjects had PGA scores of moderate and 38.2% had a PGA score of marked or severe.

Table 6 – Baseline Disease Characteristics

	Placebo N=37	Half-Standard Ustekinumab N=37	Standard Ustekinumab N=36	Total N=110
<i>PGA</i>				
Moderate	22 (59%)	22 (59%)	24 (67%)	68 (62%)
Marked	13 (35%)	15 (41%)	10 (28%)	38 (35%)
Severe	2 (5%)	0	2 (6%)	4 (4%)
<i>PASI</i>				
Mean (SD)	20.8 (8.0)	21.0 (8.5)	21.7 (10.4)	21.1 (8.9)
Range	12-44	12-49	12-51	12-51
<i>BSA</i>				
Mean (SD)	27.4 (16.4)	33.6 (21.4)	31.9 (23.2)	30.9 (20.5)
Range	20-79	20-91	10-100	10-100

Source: Table 7 from statistical review

Prior Medications or Therapies for Psoriasis

From review of Appendix 4 of the Summary of Clinical Safety, most subjects (57.3%) had never used a conventional systemic agent (defined as PUVA, MTX, acitretin, and cyclosporine). Most subjects (89%) had never used a biologic (alefacept, efalizumab, infliximab, adalimumab, and etanercept). However, etanercept was the most commonly used biologic, and its use was reported in 9.1% of subjects. UVB was reported to have been used by 35.5% of subjects. Somewhat surprisingly, approximately 11% of subjects reported never having used a topical treatment. Somewhat interestingly, this corresponds to the same percentage of subjects who reported ever having used a biologic.

Additional specifics of the history of prior therapies for study subjects are listed below in descending order of frequency:

- Topical agents: 89.1%
- Conventional systemic agents or biologics: 46.4%
- Conventional systemic agents (PUVA, MTX, acitretin, and cyclosporine): 42.7%
- UVB: 35.5%
- Biologics (alefacept, efalizumab, infliximab, adalimumab, etanercept): 10.9%
- PUVA: 6.4%

Approximately 53% of subjects had a family history of psoriasis, and 5.5% had a history of psoriatic arthritis.

6.1.3 Subject Disposition

A total of 110 subjects were randomized and treated in this study:

- 37 subjects to placebo treatment
- 37 subjects to ustekinumab half-standard dosage

- 36 subjects to ustekinumab standard dosage

No subjects discontinued study treatment through Week 12.

Table 7 – Subject Disposition

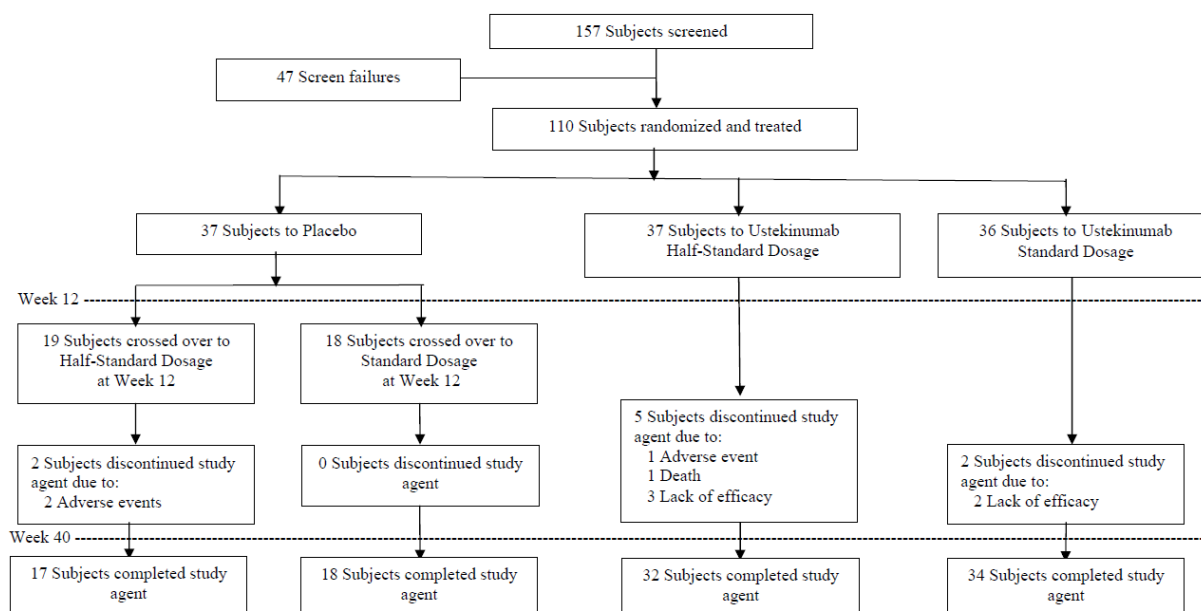
	Placebo/ Half Standard	Placebo/ Standard	Half-Std/ Half-Std	Standard/ Standard
Randomized	19	18	37	36
Discontinued study medication by Week 12	0	0	0	0
Discontinued study medication by Week 40	2 (10.5%)	0	5 (13.5%)	2 (5.6%)
Adverse event	2 (10.5%)	0	1 (2.7%)	0
Lack of efficacy	0	0	3 (8.1%)	2 (5.6%)
Death	0	0	1 (2.7%)	0
Met early escape criteria at Week 8	1 (5.3%)	1 (5.6%)	0	0
Met treatment failure rules by Week 12	2 (10.5%)	0	0	0
Met treatment failure rules by Week 60 ^a	5 (26.3%)	1 (5.6%)	8 (21.6%)	2 (5.6%)
Terminated study participation by Week 60	2 (10.5%)	1 (5.6%)	10 (27.0%)	4 (11.1%)
Withdrawal of consent	2 (10.5%)	1 (5.6%)	5 (13.5%)	1 (2.8%)
Lost to follow-up	0	0	1 (2.7%)	1 (2.8%)
Death	0	0	1 (2.7%)	0
Other ^b	0	0	3 (8.1%)	2 (5.6%)

^a Includes subjects who met treatment failure rules by Week 12

^b Lack of efficacy (2), adverse event (1), relapse (1), and subject convenience (1)

Source: Table 3 from statistical review

Figure 3: Subject Disposition through Week 40



Source: Figure 2 from study report for 3006

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the proportion of subjects who achieved a PGA score of cleared or minimal at Week 12. Both the half-standard dose and the standard dose of ustekinumab were superior to placebo at primary efficacy assessment, and the results were statistically significant (<0.001). The treatment effects were similar for the two ustekinumab dosage groups. The results are presented in Table 8.

Table 2: Primary Efficacy Endpoint (Week 12)

	Placebo N=37	Half Standard Dose N=37	Standard Dose N=36
PGA 0 or 1 ^a (Primary)	2 (5.4%)	25 (67.6%) <0.001	25 (69.4%) <0.001

^a n (%)

^b Mean (SD)

Source: Table 8 from statistical review

6.1.5 Analysis of Secondary Endpoints(s)

The major secondary endpoints were:

- PASI 75 response at Week 12.

- Change from baseline in Children’s Dermatology Life Quality Index (CDLQI) at Week 12.
- PASI 90 response at Week 12.

Table 9: Major Secondary Efficacy Endpoints (Week 12)

	Placebo N=37	Half Standard Dose N=37	Standard Dose N=36
PASI 75 ^a (Secondary)	4 (10.8%)	29 (78.4%) <0.001	29 (80.6%) <0.001
Change in CDLQI ^b (Secondary)	N=32 -1.5 (3.18)	N=35 -5.6 (6.43) 0.003	N=32 -6.7 (5.63) <0.001
PASI 90 ^a (Secondary)	2 (5.4%)	20 (54.1%) <0.001	22 (61.1%) <0.001

^a n (%)

^b Mean (SD)

Source: Table 8 from the statistical review

The agency had no input on any elements of the protocol for study 3006 (see Section 2.5).^{(b) (4)}

^{(b) (4)} Therefore, I do not recommend any labeling claims for the CDLQI.

6.1.6 Other Endpoints

^{(b) (4)}

Kathleen Fritsch, Ph.D. was the statistical reviewer for this application. Dr. Fritsch stated that, “...these endpoints were analyzed in an exploratory manner without multiplicity

adjustments, they may not be appropriate for labeling.”^{(b) (4)}
 .” Given these statistical issues, I would not consider these “other” endpoints to be acceptable for inclusion in the label.^{(b) (4)}

6.1.7 Subpopulations

Across the various subgroups, treatment effects were generally similar between the half-standard and standard dosing groups. Treatment effects in subgroups were generally similar to or slightly higher than overall study results.

Table 10: PGA Success at Week 12 by Age, Gender, Race and Ethnicity

	Placebo N=37	Half-Standard Ustekinumab N=37	Standard Ustekinumab N=36
<i>Age (years)</i>			
12-15 years	1/15 (6.7%)	14/20 (70.0%)	13/20 (65.0%)
16-17 years	1/22 (4.6%)	11/17 (64.7%)	12/16 (75.0%)
<i>Gender</i>			
Female	2/17 (11.8%)	15/19 (79.0%)	15/20 (75%)
Male	0/20 (0%)	10/18 (55.6%)	10/16 (62.5%)
<i>Race</i>			
White	2/34 (5.9%)	21/30 (70.0%)	24/34 (70.6%)
Black or Afric.-Amer.	-	-	-
Asian	0/2 (0%)	2/3 (66.7%)	0/1 (0%)
Am. Ind./ AK Native	0/1 (0%)	0/1 (0%)	1/1 (100%)
Native HI/ Pac. Isl.	-	-	-
Other/Unknown	-	2/3 (66.7%)	-
<i>Ethnicity</i>			
Hispanic or Latino	0/1 (0%)	0/1 (0%)	0/1 (0%)
Not Hispanic or Latino	2/35 (5.7%)	23/33 (69.7%)	25/35 (71.4%)
Not Rep./Unknown	0/1 (0%)	2/3 (66.7%)	-

Source: Table 14 from the statistical review

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

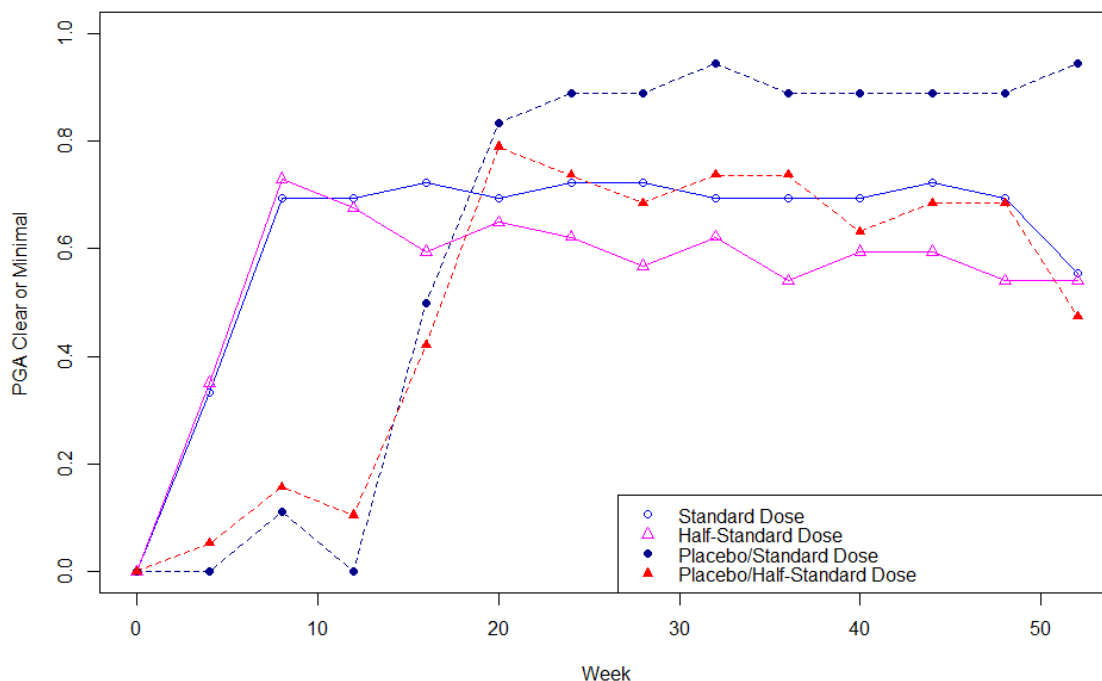
See Efficacy Summary at the beginning of Section 6.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Subjects were followed for efficacy through Week 52 (last dose of study treatment was at Week 40). With continuous dosing every 12 weeks, treatment responses were maintained through one year and were generally maintained in a higher proportion of subjects in the standard dosage groups. See Figure 4. Also, during this maintenance treatment period, a pattern of loss of efficacy nearing the end of the dosing interval was more seen with half-standard dosing. This loss in efficacy corresponded with the

declining serum ustekinumab concentrations late in the 12-week dosing interval. Figure 4 suggests some recapturing of treatment responses following re-dosing. Also see Section 4.4.3.

Figure 4 –Response Rates over Time for PGA ≤ 1 (Clear or Minimal)



Source: Figure 1 from statistical review

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues.

7 Review of Safety

Safety Summary

Headache and nasopharyngitis were the most commonly reported adverse events in ustekinumab-treated subjects through Week 12 (the placebo-controlled period) and through Week 60. Adverse events were not worrisome in type or pattern and were generally similar between both ustekinumab treatment groups and placebo during the 12-week placebo-controlled period. No change in the safety profile was apparent with longer-term treatment through Week 40. There was no apparent dose-response in occurrence of adverse events between the half-standard and standard dosage groups with follow-up through Week 60. No new adverse reactions or safety signals were identified in this study.

The applicant provided sufficient evidence to establish the safety of ustekinumab in subjects. Additionally, the safety profile from the psoriasis program in adults and postmarketing safety data provide supportive information.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety database was from the pediatric study, 3006. The study evaluated the safety of use of ustekinumab in adolescents with psoriasis for up to one year. In supportive safety analyses, the applicant compared the results from study 3006 to pooled data from the pivotal studies in adults with psoriasis, T08 and T09 through Week 12 (placebo-controlled period) and through one year (Week 52 for T08 and T09).

The following safety evaluations were performed only in the adult studies and have been previously reviewed under other submissions to this BLA:

- Evaluation beyond one year (the pivotal adult studies were five years in duration).
- Withdrawal of treatment and retreatment.
- Effect of treatment on vaccine response.

7.1.2 Categorization of Adverse Events

The applicant organized adverse events by system-organ class (SOC) and preferred term (PT) using the version of the Medical Dictionary for Regulatory Activities (MedDRA) that was current at the time of the analyses.

The applicant evaluated safety data for 3006 using the following data categorizations:

- Through Week 12 (placebo-controlled period) by dosage group:
 - Placebo
 - Ustekinumab half-standard dosage
 - Ustekinumab standard dosage
 - Ustekinumab combined
- Through 1 year (Week 60) by dosage group:
 - Placebo → ustekinumab half-standard dosage
 - Placebo → ustekinumab standard dosage
 - Ustekinumab half-standard dosage
 - Ustekinumab standard dosage
 - Ustekinumab combined (events from the first ustekinumab exposure for all treated subjects)

The average duration of follow-up and ustekinumab exposure for subjects in the placebo crossover groups, were approximately 10 weeks less than for subjects who received ustekinumab from Week 0.

Targeted Analyses of Adverse Events

The applicant considered the following to be “targeted events”:

- deaths
- events based on a risk of immunosuppression (e.g., malignancies and serious infections)
- events that represented a population risk of psoriasis (e.g., MACE)
- events that were identified based on observations in clinical studies and/or the postmarketing setting (e.g., serious hypersensitivity reactions including anaphylaxis, angioedema and serum sickness like reactions, and serious neurologic disorders such as RPLS).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 110 adolescent subjects were treated with ustekinumab through one year (58 weeks of follow-up). Of these 110 subjects, 36 received the standard dosage, which is proposed for marketing, from baseline through one year. Table 11 presents the extent of exposure through one year for study 3006 compared to the pivotal adult studies.

Table 11: Summary of Extent of Exposure through 1 Year; Subjects Treated with Ustekinumab in CNTO1275PSO3006 and Pivotal Adult Psoriasis Studies (C0743T08 and C0743T09)

	Pediatric Psoriasis (0-60 weeks) CNTO1275PSO3006 Ustekinumab				Adult Psoriasis (0-52 weeks) C0743T08 and C0743T09 Ustekinumab			
	Placebo * Half- Standard	Placebo → Standard	Half- Standard	Standard	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Treated subjects	19	18	37	36	320	315	664	666
Avg Duration of follow-up (weeks)	45.87	46.87	55.23	58.03	38.92	39.27	49.92	50.11

Source: Table 4 from Summary of Clinical Safety

7.2.2 Explorations for Dose Response

The applicant compared half and standard ustekinumab dosing in the safety analyses; dose response comparisons were inherent in the design of study 3006.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate and included serum chemistry, hematology panels and immunogenicity assessments at scheduled intervals.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

7.3.1 Deaths

One death occurred in study 3006:

Subject 011002-6045 was a 16 y/o female in the half-standard dosage group who died on Day 230 of injuries (“poly-trauma”) sustained in an automobile accident.

7.3.2 Nonfatal Serious Adverse Events

Through Week 12 (Placebo-controlled Period)

One SAE was reported through Week 12:

Subject 032001-6131 was a 12 y/o male in the half-standard dosage group whose psoriasis was diagnosed at 6 years of age. He was hospitalized with an exacerbation of psoriasis (pustular psoriasis, “nearly erythrodermic”) on study Day 83. He was treated with topical therapy while in the hospital. His last dose of study product prior to the flare was on Day 30. He continued study treatment as the flare was presumed to reflect a loss of efficacy. The exacerbation was resolved on Day 104. He was again hospitalized for a disease flare on Day 141, and treatment included methotrexate. The exacerbation reported as resolved on Day 148. He was withdrawn from the study on Day 141 due to loss of efficacy.

In my opinion, development of pustular psoriasis or erythroderma more represents a rebound phenomenon (i.e. worse than baseline status), than a flare or loss of efficacy, both of which I would consider to indicate return of disease of baseline severity. Pustular psoriasis and erythrodermic psoriasis are labeled as events that have been reported postmarketing with ustekinumab.

Through Week 60

Five additional SAEs were reported through Week 60:

Subject 007001-6123: leukopenia

This 15y/o female was in the half-standard dosage group. On Day 281, her white blood cell (WBC) count was found to be 1.62 giga/L (normal: 4.35-13.15 giga/L). She received her final dose of study treatment (Week 40) that same day. She was hospitalized on Day 286 for leukopenia. The following day (Day 287), her WBC count had increased to 5.41 giga/L, and she was discharged that same day. The leukopenia coincided “with two separate cases of herpes simplex labialis.” Herpes simplex labialis was reported for this subject on Days 58, 154, 272, 287, 339, and 399.

Given her overnight recovery from the leukopenia only five days after having received ustekinumab, I consider it unlikely that this event was related to study treatment.

Subject 011002-6045: death

This subject was previously discussed.

Subject 033004-6050: pyelonephritis

This 17 y/o female was in the half-standard dosage group. She received her Week 40 dose of study treatment on Day 285. She presented to the emergency department on Day 297 with fever, abdominal pain, and right lumbar back pain. Urine culture was positive for *E. coli*. She was treated with triple IV antibiotic therapy for 4 days and was discharged on oral antibiotic therapy (discharge date not provided). The event was considered to be resolved on Day 309. She was withdrawn from the study on Day 387 due to worsening of psoriasis.

I cannot exclude a role for ustekinumab in this serious infection.

Subject 036003-6119: acute allergic contact dermatitis

This 17 y/o female was in the half-standard dosage group and was hospitalized on Day 263 due to an acute allergic contact dermatitis due to black hair dye. She was discharged on Day 268, and the event was considered resolved on the same day.

I conclude that this event was unlikely to be related to ustekinumab treatment.

Subject 038008-6059: ear infection

This 16 y/o female was in the standard dosage group. She was hospitalized on Day 109 for “acute catarrhal otitis media of both ears” and received parenteral antibiotics. She was discharged on Day 119, and the event was considered to be resolved on the same day. Study treatment was not interrupted. The most recent dose of study treatment before the event was on Day 85 (Week 16), and she received study treatment on Day 120 (Week 28).

I cannot exclude a role for ustekinumab in this serious infection of bilateral acute otitis media in a 16 y/o subject. Acute otitis media is most prevalent between the ages of 6 and 24 months, with a declining incidence thereafter.⁴ Data are unavailable to determine the incidence of AOM in an adult population.⁵ However, the subject was treated and fully recovered in the setting of uninterrupted ustekinumab treatment.

4 Klein J.O. & Pelton S (2017), Acute otitis media in children: Epidemiology, microbiology, clinical manifestations, and complications. In Kaplan S.L. & Isaacson G.C. (Ed), *UpToDate*, from https://www.uptodate.com/contents/acute-otitis-media-in-children-epidemiology-microbiology-clinical-manifestations-and-complications?source=search_result&search=catarrhal%20otitis%20media&selectedTitle=4~150.

5 Limb C.J., Lustig L.R. & Klein J.O. (2017), Acute otitis media in adults. In Deschler D.O. (Ed),

7.3.3 Dropouts and/or Discontinuations

Through Week 12 (Placebo-controlled Period)

No subject discontinued study agent due to an AE through Week 12.

Through Week 60

Through Week 60, four subjects (3.6%) in the ustekinumab combined group discontinued treatment due to an AE. All of these subjects were in the half-standard dose group. The following AEs led to discontinuation of treatment:

Subject 032001-6019: Toxoplasmosis infection

This subject was a 13 y/o male who was diagnosed with a toxoplasmosis infection on Day 252, following weeks of fatigue. He had no signs of disseminated disease, neurological symptoms or ocular findings. Testing of a serum sample obtained prior to randomization and receipt of any study treatment revealed antibodies to *T. gondi*, consistent with prior infection.

Subject 011002-6045: Death

This subject has been previously discussed.

Subject 046001-6014: worsening of psoriasis

This subject was a 17 y/o male who was diagnosed with psoriasis at eight years of age. Moderate worsening of psoriasis was reported on Day 190. He received his last dose of ustekinumab on that same day. He received placebo treatment through Day 84, was crossed over to half-standard ustekinumab treatment and received his first dose on Day 84.

Subject 011012-6053: worsening of psoriasis

This subject was a 15 y/o male who was reported to have had psoriasis for 15 years (diagnosed at age "0"). He received half-standard dose at Weeks 0 and 4, and 45mg at Week 16 (his last dose of study treatment). Worsening of psoriasis was reported on Day 195 and again on Day 205. Details of the flare were not provided.

7.3.4 Significant Adverse Events

Infections Requiring Antimicrobial Treatment:

Through Week 12 (Placebo-controlled Period)

UpToDate, from

https://www.uptodate.com/contents/acute-otitis-media-in-adults?source=search_result&search=catarrhal%20otitis%20media&selectedTitle=1~150.

During this period, seven subjects were reported to have had infections which required oral or parenteral antimicrobial treatment. “Urinary tract infection” was the only infection for which there were multiple reports (two). Occurrences of infections in this category per treatment group were as follows:

- 10.8% (4) in the placebo group: Urinary tract infection, Acute tonsillitis, Nasopharyngitis, and Tonsillitis
- 2.7% (1) in the half-standard dosage group: Pharyngitis
- 5.6% (2) in the standard dosage groups: Pharyngitis streptococcal and Urinary tract infection

Through Week 60

Through Week 60, 28 subjects in the ustekinumab combined group (25.5%) reported at least one infection which required oral or parenteral antimicrobial treatment. The types of infections for which there were multiple reports (in decreasing order of frequency) were:

- Pharyngitis: 5 subjects (4.5%)
- Pharyngitis streptococcal, pyelonephritis, tooth abscess, and upper respiratory tract infection: 3 subjects for each event (2.7%)
- Bronchitis and nasopharyngitis: 2 subjects each (1.8%)

Two serious infections occurred, and both cases have been previously discussed (see Section 7.3.2).

Injection-site Reactions:

One injection site reaction was reported through Week 60, and it was of mild severity. The event was “injection site hemorrhage,” and the subject was in the standard dosage group. The subject was positive for antibodies to ustekinumab.

Adverse Events of Psoriasis:

Through Week 12 (Placebo-controlled Period)

Three subjects reported at least one AE of psoriasis: 2 (5.4%) in the placebo group and 1 (2.7%) in the half-standard dosage group. The subject who reported a serious adverse event of psoriasis is discussed in Section 7.3.2.

Through Week 60

Through Week 60, 7 (6.4%) subjects reported one or more AEs of psoriasis. Five subjects in the half-standard dosage groups and two subjects in the standard dosage groups reported worsening of psoriasis.

Targeted Events:

Through Week 60 in study 3006, there were no reports of TB or opportunistic infection, malignancies, major adverse cardiovascular events (MACE), possible anaphylactic reactions or possible serum sickness-like reactions, or RPLS or demyelination. The one death that occurred in this study has been previously discussed.

7.3.5 Submission Specific Primary Safety Concerns

No submission specific primary safety concerns were identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Through Week 12 (Placebo-controlled Period)

In all treatment groups, AEs were most commonly reported in the Infections and infestations SOC. Overall, headache and nasopharyngitis were the two most commonly reported PTs in the placebo and combined ustekinumab groups. PTs for which there was more than one report in the combined ustekinumab group are presented in Table 12.

Per the approved label, nasopharyngitis, upper respiratory tract infection, and headache were the top three most commonly reported adverse reactions during the placebo-controlled period in the adult psoriasis program.

Table 12: Number of Subjects with 1 or More Treatment-emergent Adverse Events through Week 12 by MedDRA Preferred Term; Treated Subjects

	Ustekinumab			
	Placebo	Half-Standard Dosage	Standard Dosage	Combined
Analysis set: subjects treated	37	37	36	73
Avg duration of follow-up (weeks)	12.17	12.17	12.40	12.28
Avg exposure (weeks)	4.16	4.19	4.09	4.14
Subjects with 1 or more adverse Preferred term	21 (56.8%)	19 (51.4%)	16 (44.4%)	35
Headache	2 (5.4%)	4 (10.8%)	3 (8.3%)	7 (9.6%)
Nasopharyngitis	10 (27.0%)	5 (13.5%)	1 (2.8%)	6 (8.2%)
Pharyngitis	0	3 (8.1%)	1 (2.8%)	4 (5.5%)
Upper respiratory tract infection	2 (5.4%)	1 (2.7%)	3 (8.3%)	4 (5.5%)
Diarrhea	0	0	2 (5.6%)	2 (2.7%)
Dysmenorrhea	0	0	2 (5.6%)	2 (2.7%)
Fatigue	2 (5.4%)	1 (2.7%)	1 (2.8%)	2 (2.7%)

Source: Appendix 6 from Summary of Clinical Safety

Through Week 60

Through Week 60, 90 subjects (81.8%) in the ustekinumab combined group reported \geq one AE. The proportions of subjects reporting AEs were generally similar across treatment groups. AEs were again most commonly reported in the Infections and infestations SOC, with 75 of subjects (68.2%) in the ustekinumab combined group reporting AEs in this SOC. Overall, headache (20 subjects; 18.2%) and nasopharyngitis (38 subjects; 34.5%) were also the two most commonly reported AEs through Week 60 in the ustekinumab combined group.

7.4.2 Laboratory Findings

Markedly Abnormal Changes in Hematology:

Through Week 12 (Placebo-controlled Period)

One subject in the standard dosage group experienced markedly abnormal postbaseline eosinophil values on more than one occasion.

Through Week 60

Two subjects experienced markedly abnormal postbaseline hematology laboratory values on more than one occasion through Week 60. Both subjects were in the standard dosage group. The affected elements were: abnormal lymphocytes (one

subject on two occasions had markedly abnormally low counts) and eosinophils (one subject on three occasions had markedly abnormally high counts).

Markedly Abnormal Changes in Chemistry:

Through Week 12 (Placebo-controlled Period)

No subjects reported more than one markedly abnormal chemistry value.

Through Week 60

One subject reported a markedly abnormal postbaseline chemistry laboratory value more than once through Week 60. The subject was in the standard dosage group and had three markedly abnormally high total bilirubin values; ALT and AST remained within normal ranges.

7.4.3 Vital Signs

Vital signs (heart rate, respiratory rate, and blood pressure) were comparable between treatment groups during the study.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not done in study 3006.

7.4.5 Special Safety Studies/Clinical Trials

The applicant did not conduct any special safety studies.

7.4.6 Immunogenicity

From the clinical pharmacology review:

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.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Assessments of dose dependency of adverse events were inherent in the design of study 3006 (parallel dosing of half-standard and standard dosing). No pattern for dose dependency for adverse events was observed.

7.5.2 Time Dependency for Adverse Events

No pattern for time dependency for adverse events was observed over the 60-week course for study 3006.

7.5.3 Drug-Demographic Interactions

The applicant analyzed AEs in study 3006 by the following subgroups: age (≤ 15 years or > 15 years), gender (male or female), and weight (≤ 60 kg or > 60 kg). There were no consistent trends or patterns in discontinuations due to an AE or the occurrence of AEs for any of the subgroups.

7.5.4 Drug-Disease Interactions

No trends were observed in discontinuations due to an AE or the occurrence of AEs for baseline disease severity (by BSA, PGA or PASI).

7.5.5 Drug-Drug Interactions

The applicant has not performed a formal drug-drug interaction study has not been conducted with ustekinumab.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No malignancies were reported in study 3006.

From the approved ustekinumab label:

5.4 Malignancies

STELARA is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA in clinical

studies [see *Adverse Reactions (6.1)*]. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy [see *Nonclinical Toxicology (13)*].

The safety of STELARA has not been evaluated in patients who have a history of malignancy or who have a known malignancy. There have been post-marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving STELARA who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving STELARA should be monitored for the appearance of non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment should be followed closely [see *Adverse Reactions (6.1)*].

6.1 Clinical Trials Experience

Malignancies

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years, representing 8998 subject-years of exposure), 1.7% of STELARA -treated subjects reported malignancies excluding non-melanoma skin cancers (0.60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of STELARA -treated subjects (0.52 per hundred subject-years of follow-up) [see *Warnings and Precautions (5.4)*]. The most frequently observed malignancies other than non-melanoma skin cancer during the clinical studies were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in STELARA -treated patients during the controlled and uncontrolled portions of studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender and race).

7.6.2 Human Reproduction and Pregnancy Data

One pregnancy was reported in study 3006 (Subject 011009-6039); it was ended by elective abortion.

Through the cutoff date for safety analyses for this efficacy supplement, 139 pregnancies were documented across ustekinumab clinical development programs (psoriasis, psoriatic arthritis, Crohn's disease): 70 maternal exposure; 69 paternal exposure. One (unspecified) congenital anomaly/birth defect was reported among the 71 live births, and it occurred in a pregnancy with paternal exposure from treatment in the psoriasis program. Additional information on pregnancy outcomes is presented in Tables 13 and 14. The applicant found that the outcomes from pregnancies with ustekinumab exposure to be similar to outcomes in the general population.

Table 13: Pregnancy Outcomes for Medically Confirmed Ustekinumab Cases with Maternal Exposure Cumulatively through 31 Dec 2015

Pregnancy Outcome	Clinical Trial				
	PSO	PsA	CD	Other ^a	Total
Live birth	15	0	11	2	28
<i>Congenital anomaly/birth defect</i>	0	0	0	0	0
<i>Other AE</i>	2	0	0	0	2
<i>No AE/Congenital anomaly/birth defect</i>	13	0	11	2	26
Elective abortion	10	1	4	1	16
Spontaneous abortion	5	0	3	0	8
Premature birth	1	0	0	0	1
Abortion (unspecified)	0	0	0	1	1
Ectopic pregnancy	1	0	0	0	1
Induced abortion	0	0	1	0	1
Neonatal demise	0	0	0	0	0
Not reported/Continuing	9	1	2	2	14
Total	41	2	21	6	70

AE=adverse event; CD=Crohn's disease; PsA=psoriatic arthritis; PSO=psoriasis.

^a Other indications include: erythrodermic psoriasis, guttate psoriasis, pustular psoriasis, pyoderma gangrenosum, relapsing-remitting multiple sclerosis, and dual indications (rheumatoid arthritis and crohn's disease reported in single case).

Source: Table 11 from Summary of Clinical Safety

Table 14: Pregnancy Outcomes for Medically Confirmed Ustekinumab Cases with Paternal Exposure Cumulatively through 31 Dec 2015

Pregnancy Outcome	Clinical Trial				
	PSO	PsA	CD	Other ^a	Total
Live birth	35	0	4	4	43
<i>Congenital anomaly/birth defect</i>	1	0	0	0	1
<i>Other AE</i>	4	0	0	1	5
<i>No AE/Congenital anomaly/birth defect</i>	30	0	4	3	37
Elective abortion	2	0	1	0	3
Spontaneous abortion	3	1	1	0	5
Neonatal death	0	0	0	0	0
Premature birth	5	0	0	0	5
Not reported/Continuing	6	2	2	3	13
Total	51	3	8	7	69

AE=adverse event; CD=Crohn's disease; PsA=psoriatic arthritis; PSO=psoriasis.

^a Other includes case where the study was a pharmacokinetic study and indication exposure via body fluid.

Source: Table 12 from Summary of Clinical Safety

The following is from the Pregnancy section (8.1) of the approved label:

Risk Summary

Limited data on the use of STELARA in pregnant women are insufficient to inform a drug associated risk [see Data]. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the human exposure at the maximum recommended human subcutaneous dose (MRHD).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Human Data

Limited data on use of STELARA in pregnant women from observational studies, published case reports, and postmarketing surveillance are insufficient to inform a drug associated risk.

The label also advises of a pregnancy registry that monitors pregnancy outcomes in women exposed to ustekinumab during pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

The efficacy supplement principally relied on a trial (3006) conducted in pediatric subjects with psoriasis, who were ≥ 12 to < 18 years of age. Thus, the safety and efficacy of ustekinumab in this adolescent population are discussed throughout this review.

At the time of this supplement review, a Phase 3 trial evaluating ustekinumab for treatment of plaque psoriasis in pediatric subjects ≥ 6 to < 12 years of age was ongoing (CNT01275PSO3013 or "3013"). This is an open-label study to assess the efficacy, safety, and PK of ustekinumab in the treatment of moderate to severe chronic plaque psoriasis in the referenced pediatric age group. The applicant plans to ^{(b) (4)}

and the FDA agreed to enrollment of subjects at U.S. sites at the pre sBLA meeting, held for the efficacy supplement that is the subject of this review. Also see Section 2.5 of this review.

At the pre-sBLA meeting, the agency agreed to a partial waiver from study of pediatric subjects less than 6 years of age. The applicant submitted the request for a partial waiver to the BLA on 06/30/2017. Their cited basis for the request was a (b) (4)

” Consistent with divisional practices, I recommend that the partial waiver in patients ages less than 6 years be granted because studies are impossible or highly impractical.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reports of overdose during study 3006. There is no information suggesting addiction or abuse potential with ustekinumab.

Study 3006 did not include evaluation of disease status following withdrawal of treatment, including no evaluation for rebound potential. However, one of the Phase 3 trials in the adult program (T08) included a randomized withdrawal period, and no tendency for disease rebound was noted (the applicant defined rebound as a PASI of 125% of baseline, of new generalized pustular, erythrodermic or more inflammatory psoriasis occurring within 3 months of stopping therapy).

7.7 Additional Submissions / Safety Issues

(b) (4)

(b) (4)

(b) (4)

Deaths and Other Serious Adverse Events

No deaths occurred in any of the seven ongoing studies for the time period covered in the safety update. There were no events of RPLS, demyelination, or suicidal ideation or behavior.

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)

The information provided in the update did not change the risk-benefit assessment for use of ustekinumab for treatment of adolescent patients with moderate to severe plaque psoriasis. No new adverse drug reactions were identified in the analyses for the 120-Day Safety Update. However, that five of the seven studies were blinded at the time of the analyses for the update limits the conclusions that may be drawn from the data.

8 Postmarket Experience

The applicant estimated the worldwide exposure to ustekinumab from product launch to 12/31/2015 to have been (b) (4) person-years. The applicant has identified no new safety signals in their postmarket safety surveillance program.

The applicant provided updates and information pertaining to several registries conducted as postmarketing requirements, as discussed below.

PSOLAR

The applicant is evaluating the long-term safety of ustekinumab in the Psoriasis Longitudinal Assessment and Registry (PSOLAR). PSOLAR is a multicenter, prospective, observational study that enrolled (b) (4) patients who were eligible for or were receiving systemic treatment for psoriasis (enrollment is complete). Through the data cutoff of 08/23/2015, (b) (4) patient-years of follow up had been accrued.

Of the (b) (4) enrolled subjects, more than (b) (4) received ustekinumab at some point, and approximately (b) (4) ustekinumab-exposed patients have at least (b) (4) years of follow-up.

No new safety signals have been identified in PSOLAR.

Nordic Database Initiative (CNT01275PSO4005)

The Nordic Database Initiative is a prospective, observational study of AEs observed in patients exposed to ustekinumab in actual clinical practice in Sweden and Denmark, based on data from national registries in those countries. Approximately (b) (4) patients have been exposed to ustekinumab. No new safety signals have been identified in the study.

Pregnancy Registries

The applicant is evaluating pregnancy outcomes in a U.S. registry and in an initiative based in certain countries in Europe:

- The Stelara Pregnancy Exposure Registry (OTIS Autoimmune Disease in Pregnancy Project; CNTO1275PSO4037) is the U.S. pregnancy registry; as of 12/31/2015, (b) (4) ustekinumab-exposed patients had been enrolled.
- The Pregnancy Research Initiative is a review of birth outcomes from the Swedish, Danish, and Finnish birth registers; (b) (4) patients had been exposed through the differing cut-off dates for the various countries.

The data are too limited to permit meaningful conclusions regarding the safety of ustekinumab during pregnancy.

9 Appendices

9.1 Literature Review/References

See footnotes for references.

9.2 Labeling Recommendations

I have reviewed all labeling (that was available as the review was closing); labeling negotiations with the applicant were pending as the clinical review was being finalized. Labeling recommendations have been incorporated into the draft label.

9.3 Advisory Committee Meeting

Not applicable.

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/s/

BRENDA CARR
08/31/2017

SNEZANA TRAJKOVIC
09/01/2017