

## Cross-Discipline Team Leader Review

<b>Date</b>	October 12, 2017
<b>From</b>	Snezana Trajkovic
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>BLA #</b>	125261
<b>Supplement#</b>	138
<b>Applicant</b>	Janssen Biotech, Inc.
<b>Date of Submission</b>	December 15, 2016
<b>PDUFA Goal Date</b>	October 15, 2017
<b>Proprietary Name / Established (USAN) names</b>	Stelara/ ustekinumab
<b>Dosage forms / Strength</b>	Solution for subcutaneous injection
<b>Proposed Indication(s)</b>	Treatment of adolescent patients 12 to 17 years with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
<b>Recommended:</b>	<i>Approval</i>

### 1. Introduction

Stelara (ustekinumab) injection for subcutaneous use is a marketed biologic product for which the applicant seeks approval in an efficacy supplement for the expansion of the patient population for the psoriasis indication to include treatment of adolescents. Specifically, the applicant proposes 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.” The proposed dose and dosing regimen for Stelara psoriasis is:

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

Stelara for subcutaneous use is supplied as a 45mg/0.5 mL single-dose prefilled syringe; 90mg/mL single-dose prefilled syringe; and 45mg/0.5mL single-dose vial.

Ustekinumab is fully human IgG1k monoclonal antibody that binds to the p40 subunit of interleukin IL-12 and IL-23. IL-12 and IL-23 have been implicated in the pathogenesis of

psoriasis. They are heterodimer cytokines and share the IL-12p40 subunit and immune cell transmembrane receptor subunit IL-12 receptor beta-1 (IL-12R $\beta$ 1). The applicant purports that Stelara neutralizes IL-12 and IL-23 bioactivity by preventing these cytokines from binding to their IL-12 $\beta$ 1 receptor protein expressed on the surface of immune cells.

Stelara was initially licensed in 2009 for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates to phototherapy or systemic therapy. Approval of additional supplements expanded the indication to include:

- Treatment of adult patients (18 years or older) with active psoriatic arthritis.
- 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.

## 2. Background

Stelara was licensed for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy on September 25, 2009. The BLA application did not contain data on the use of Stelara in children, and the Agency recommended the deferral of studies to elevate the safety and efficacy of Stelara in pediatric patients with plaque psoriasis. The Agency's approval letter defined a pediatric post-marketing requirement (PMR) as follows:

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<sup>TM</sup> (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.

## 3. CMC/Device

No new product quality data were included in this efficacy supplement. The marketed presentations will support the proposed dosing.

## 4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were included in this efficacy supplement. There are no outstanding pharmacology/toxicology issues that would preclude approval.

## 5. Clinical Pharmacology/Biopharmaceutics

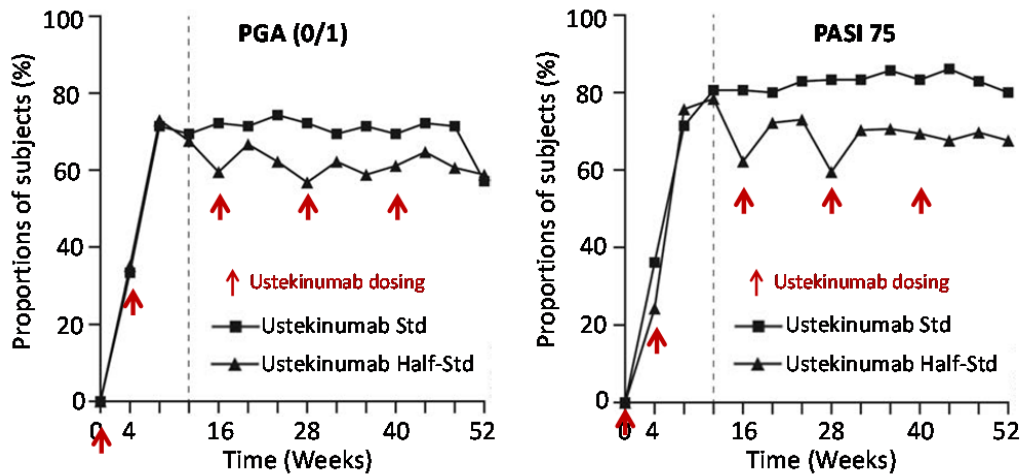
During the conduct of trial CNTO1275PSO3006, the applicant evaluated “standard” and “half-standard” dosage for Stelara, administered subcutaneously at Weeks 0 and 4, then every 12 weeks.

<b>Subjects Body Weight (kg)</b>	<b>Standard Dosage</b>	<b>Half-Standard Dosage</b>
≤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

Conclusions from the clinical pharmacology team included the following:

- Following multiple subcutaneous doses in adolescent subjects, steady-state serum concentrations of ustekinumab were achieved by Week 28. The 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 dosage were generally comparable to those in adults who received labeled dosage regimens.
- In this trial, both the half-standard dosage and the standard dosage of ustekinumab were superior and statistically significant ( $<0.001$ ) to placebo for the primary efficacy endpoint of 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.
- Both ustekinumab standard dosage and half-standard dosages provided significantly higher response rates than placebo for efficacy endpoints of 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.
- The response rates for PGA (0/1) and PASI 75 were generally higher and better sustained in the standard dosage group compared to half-standard dosage group (see Figure 1 below).

**Figure 1: PGA (0/1) or PASI 75 Response Rates through Week 52**



- Loss of treatment response toward the end of the 12-week dosing period was more frequently observed in the half-standard dosage group compared to standard dosage group.
- There was no evidence of dose-response relationship in the occurrence of adverse events (AEs).
- Approximately 8% (9/110) of subjects treated with ustekinumab developed anti-drug antibodies (ADA) by Week 60. Of the ADA positive subjects, 33.3% (3/9) were positive for neutralizing ADA (NAb). The formation of ADA appeared to have negative impact on both serum ustekinumab concentrations and efficacy.

**Overall conclusion and recommendation from the Divisions of Clinical Pharmacology 3 and Pharmacometrics:**

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.

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.

This reviewer agrees with this recommendation.

## 6. Clinical Microbiology

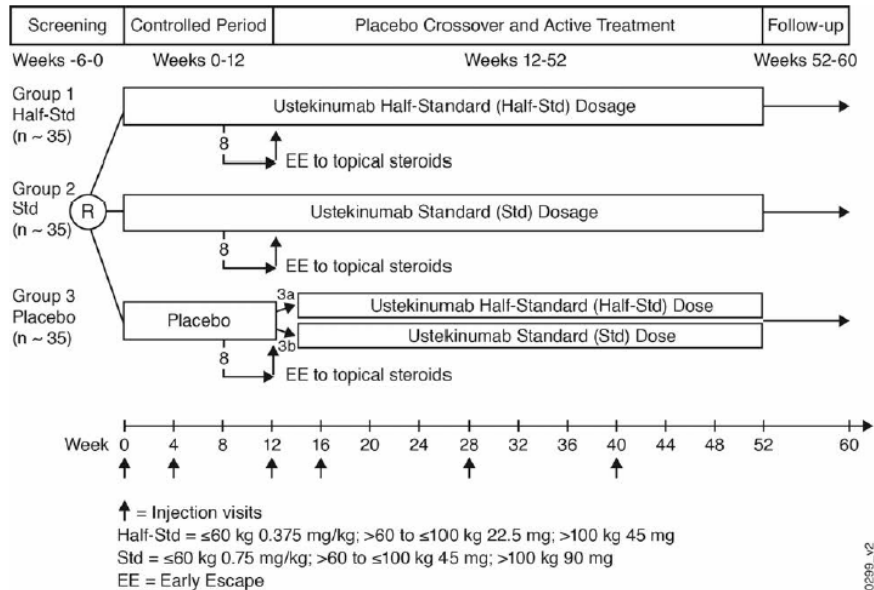
Not applicable.

## 7. Clinical/Statistical- Efficacy

The applicant submitted data from a single Phase 3 trial CNTO1275PSO3006 (3006) to establish the effectiveness of their product in the treatment of moderate to severe psoriasis. This was a randomized, double-blind and placebo-controlled, parallel group, multicenter trial. Adolescent subjects  $\geq 12$  to  $< 18$  years of age with moderate to severe plaque psoriasis, defined by Psoriatic Area and Severity Index (PASI)  $\geq 12$ , Physician's Global Assessment (PGA)  $\geq 3$ , and body surface area (BSA) involvement  $\geq 10\%$ , were enrolled in the trial. Study subjects were treated with Stelara or placebo at Week 0, Week 4, and then every 12 weeks (Q12 w), with the last dose at Week 40. Two weigh-based Stelara dosing was explored in this population:

- Half-standard dosage: intended to provide ustekinumab exposure comparable to half of the approved adult dosage and; allowed better definition of the PK-PD ustekinumab relationship in adolescents:
  - 0.375 mg/kg for subjects  $\leq 60$  kg,
  - 22.5 mg for subjects  $> 60$  kg but  $\leq 100$  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  $\leq 60$  kg,
  - 45 mg for subjects  $> 60$  kg but  $\leq 100$  kg, and
  - 90 mg for subjects  $> 100$  kg.

**Figure 2: Study Schema through Week 60**



Source: Applicant's submission.

Subjects in the placebo group crossed over to receive either half-standard or standard dose of ustekinumab at Week 12 and Week 16, then Q12w doses, with the last dose at Week 40. All subjects were followed for efficacy through Week 52 and for safety through Week 60.

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.

The timepoint for efficacy evaluation was at Week 12.

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.

In this trial, both the half-standard dose and the standard dose of Stelara were superior to placebo at primary efficacy assessment, and the results were statistically significant ( $<0.001$ ). The treatment effects were similar for the two Stelara dosage groups. The results are presented in Table 1 below.

**Table 1: Primary Efficacy Endpoint at Week 12**

	<b>Placebo N=37</b>	<b>Half Standard Dose N=37</b>	<b>Standard Dose N=36</b>
<b>PGA 0 or 1<sup>a</sup></b>	2 (5.4%)	25 (67.6%) <0.001	25 (69.4%) <0.001

a: n (%)

Source: Table 8 from statistical review

For the secondary endpoints of PASI 75 and PASI 90 response at Week 12, Stelara was superior to placebo (results presented in Table 2 below).

**Table 2: Major Secondary Efficacy Endpoints at Week 12**

	<b>Placebo N=37</b>	<b>Half Standard Dose N=37</b>	<b>Standard Dose N=36</b>
PASI 75 <sup>a</sup>	4 (10.8%)	29 (78.4%) <0.001	29 (80.6%) <0.001
PASI 90 <sup>a</sup>	2 (5.4%)	20 (54.1%) <0.001	22 (61.1%) <0.001

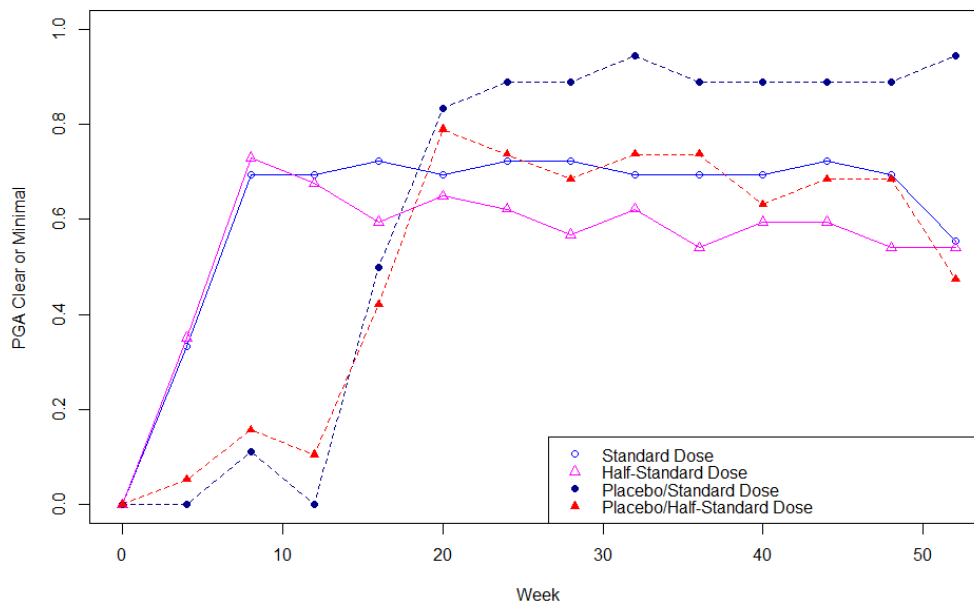
a: n (%)

Source: Table 8 from the statistical review

Secondary endpoint of CDLQI is a patient reported outcome measure that has not be validated prior to use in Phase 3 trial and therefore not eligible for inclusion in labeling.

Subjects were followed for efficacy through Week 52. With continuous dosing every 12 weeks, treatment responses were maintained through Week 52. However, subjects randomized to the standard dosage had higher response rates over time than those randomized to the half-standard dose. The loss in efficacy was also apparent in half standard dose treatment group at the end of the 12-week dosing period. The efficacy decline corresponded with the decline in serum concentrations of Stelara.

**Figure 3: Response Rates over Time for PGA  $\leq$  1 (Clear or Minimal)**



The reader is referred to the Biostatistics review by Kathleen Fritsch, Ph.D., for detailed review of the pivotal trial and additional analyses, including sensitivity analyses. Also refer to review by Clinical Pharmacology/Biopharmaceutics team.

## 8. Safety

The applicant submitted data from a single Phase 3 trial, CNTO1275PSO3006 (3006), to establish the safety and effectiveness of their product in the treatment of plaque psoriasis. Trial 3006 was a randomized, double-blind, placebo-controlled, parallel group, multicenter trial in adolescent subjects  $\geq 12$  to  $< 18$  years of age with moderate to severe plaque psoriasis.

A total of 110 adolescent subjects were treated with ustekinumab for up to one year. Of these, 36 received the standard dosage, which is proposed for marketing, from baseline through one year. Overall exposure to Stelara in terms of dosage, frequency and duration of dosing, and the target population was adequate for evaluation of safety.

One death was reported in study 3006. Subject was a 16 years old female who died from injuries sustained in an automobile accident during the open label portion of the trial (Day 230).

There were no reports of tuberculosis (TB) or opportunistic infection, malignancies, major adverse cardiovascular events (MACE), possible anaphylactic reactions or possible serum



sickness-like reactions, or reversible posterior leukoencephalopathy syndrome (RPLS) or demyelination.

During the placebo-controlled period (Week 0 to Week 12) one serious adverse event (SAE) was reported. A 12 year old male subject in half-standard dosage group was hospitalized because of an exacerbation of psoriasis (pustular psoriasis, “nearly erythrodermic”). The subject was withdrawn from the study due to loss of efficacy. In the opinion of clinical reviewer, Dr. Brenda Carr, this SAE likely represented a rebound phenomenon (i.e. worse than baseline status), not a flare or loss of efficacy, both of which would indicate return to baseline disease severity. I agree with the assessment by Dr. Carr.

Pustular psoriasis and erythrodermic psoriasis are labeled as events that have been reported postmarketing with Stelara treatment.

Five additional SAEs were reported through Week 60: leukopenia; pyelonephritis; acute allergic contact dermatitis; ear infection; death.

The one event of death was discussed above.

Regarding SAEs of pyelonephritis and ear infection, Dr. Carr could not exclude the relationship to the treatment with Stelara. Serious infections are labeled adverse reactions in WARNINGS and PRECAUTIONS section of Stelara labeling.

SAEs of acute allergic contact dermatitis (following hair dye exposure) and, leucopenia (resolved overnight), in the opinion of Dr. Carr were unlikely related to Stelara treatment.

No subject discontinued the trial during the placebo-controlled period through Week 12. Through Week 60, four subjects discontinued the trial: death (discussed earlier); toxoplasma infection (plasma sample obtained prior to randomization revealed antibodies for T. gondi, consistent with prior infection) and two subjects with worsening of psoriasis (both on half-standard dose of Stelara).

Two serious infections (pyelonephritis and ear infection) were reported. These SAEs were discussed above.

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

During the placebo-controlled period (Week 0 to Week 12) three subjects reported AEs of worsening of psoriasis. Two subjects (5.4%) were in placebo group and one subject (2.7%) reported SAE of worsening of psoriasis (discussed above) who in the half-standard dosage group.

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

During the placebo control portion of the trial, the most commonly reported AEs were: headache (half-standard dosage 4 (11%) subjects; standard dosage 3 (8%) subjects; placebo 2 (5%)), and nasopharyngitis (half-standard dosage 5 (14%) subjects; standard dosage 1 (3%) subject; placebo 10 (27%)).

Through Week 60, in the ustekinumab combined group, two most commonly reported AEs were: nasopharyngitis in 38 (34.5%) subjects and headache in 20 (18.2%) of subjects.

## 9. Advisory Committee Meeting

This efficacy supplement was not presented to the Advisory Committee.

## 10. Pediatrics

This supplemental application included data from studies of Stelara in the treatment of moderate to severe plaque psoriasis in subjects  $\geq 12$  to  $< 18$  years of age. The applicant submitted the request for a partial waiver of conducting studies in pediatric patients less than 6 years of age. The applicant cited the reason for partial waiver as (b) (4). The Division did not agree with this stated reason but agreed that partial waiver should be granted because, based on the prevalence data, studies in this age group would be impossible or highly impracticable.

The applicant is currently conducting Phase 3 trial assessing efficacy, safety, and pharmacokinetics of subcutaneously administered Stelara in pediatric subjects  $\geq 6$  to  $< 12$  years of age with moderate to severe chronic plaque psoriasis Stelara in the treatment of plaque psoriasis (CNTO1275PSO3013). As a required pediatric assessment, the applicant should complete this trial.

## 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

## 12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding the contents are ongoing at the time of closure of this review.

### 13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** *Approval*
- **Risk Benefit Assessment:** The applicant established the efficacy and safety of Stelara (ustekinumab) for injection in the treatment of moderate to severe plaque psoriasis in patients 12 years of age and older in one adequate and well-controlled trial, and provided sufficient information in their application to support product labeling.
- **Postmarketing Risk Evaluation and Management Strategies:** Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product.
- **Postmarketing Requirements and Commitments:** As a required pediatric assessment, the applicant should complete the ongoing open label trial CNTO1275PSO3013, assessing the efficacy, safety, and pharmacokinetics of subcutaneously administered ustekinumab in pediatric subjects  $\geq 6$  to  $<12$  years of age with moderate to severe chronic plaque psoriasis.
- **Recommended Comments to Applicant:** None
- **Recommended Comments to Applicant:** None

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SNEZANA TRAJKOVIC  
10/12/2017