Clinical Review
Brenda Carr, MD
BLA 125261/S-150
Stelara (ustekinumab)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125261/S-150
Priority or Standard	Standard
Submit Date(s)	09/30/2019
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Division/Office	DDD/OII
Reviewer Name(s)	Brenda Carr, MD
Review Completion Date	06/05/2020
Established/Proper Name	ustekinumab
(Proposed) Trade Name	Stelara®
Applicant	Janssen Biotech Inc.
Dosage Form(s)	solution
Applicant Proposed Dosing Regimen(s)	Administer subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter: less than 60 kg: 0.75 mg/kg; 60 kg to 100 kg: 45 mg; more than 100 kg: 90 mg
Applicant Proposed Indication(s)/Population(s)	treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Ustekinumab is an interleukin (IL)-12/IL-23 antagonist and is marketed under the trade name "Stelara®." It received initial licensure on 09/25/2009 "for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy." The approval letter included Postmarketing Requirement (PMR) #1:

> Conduct studies to evaluate the safety and efficacy of ustekinumab in pediatric subjects with plaque psoriasis.

Supplemental Biologics License Application (sBLA) 138 provided for extension of the psoriasis indication to include treatment of adolescent patients ages 12-17 years and was approved on 10/13/2017. The approval letter for supplement 138 (S-138) included PMR 2331-1:

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

In the approval letter for S-138, the Agency also waived the pediatric assessment for ages under 6 years, because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients under the age of 6 years with psoriasis is so small.

In supplement 150 (S-150), the Applicant proposes extension of the patient population for the psoriasis indication to include treatment of children down to 6 years of age. The Applicant is relying on study CNTO1275PSO3013 (3013) for approval of S-150.

Dosing for the proposed new, younger age group would be the same weight-based approach as is currently labeled for adolescents (12–17 years old) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

With submission of the study report for study 3013, the Applicant has completed the required pediatric assessments. I recommend that PMR #1 and PMR 2331-1 be considered fulfilled.

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.
- treatment of adult patients with moderately to severely active ulcerative colitis.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted the results from an open-label study (3013), which evaluated 44 subjects. As such, the submitted information did not provide substantial evidence of effectiveness. The substantial evidence of effectiveness for the psoriasis indication was provided from studies in subjects ≥ 12 years of age.

1.3. Benefit-Risk Assessment

Following discussion with the team leader, this review does not contain a benefit-risk assessment, as the data is from an open-label, efficacy, safety, and pharmacokinetics study.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints]
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Sec. 6.1.2 Study results
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

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]

2.2. Analysis of Current Treatment Options

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 the therapies may 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 licensed for treatment of psoriasis in patients ages 4 to 17 years who are candidates for systemic or phototherapy. Ixekizumab is licensed for treatment of psoriasis in patients ages 6 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		

[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 and Lara-Corrales I.Update in the management of pediatric psoriasis. *Curr Opin Pediatr* 2017;29:434–442.

Etanercept	TNFα-blocker	serious infections (including TB); malignancy; central nervous system demyelinating disorders; hematologic events (pancytopenia); reactivation of hepatitis B; autoimmunity
Adalimumab	TNFα-blocker	serious infections (including TB); malignancy; reactivation of hepatitis B; demyelinating disease; hematologic reactions (pancytopenia); autoimmunity
Infliximab	TNFα-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.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

See Sec. 1.1 ("Executive Summary").

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant received written responses regarding the planned sBLA in an advice letter dated 06/05/2019 (advice provided under the Applicant's IND: 9590).

Also, see Sec. 1.1.

3.3. Foreign Regulatory Actions and Marketing History

Study 3013 was undertaken to satisfy the remaining elements of the European Paediatric Investigational Plan (PIP) for the psoriasis indication. At the pre-sBLA meeting for the sBLA for the psoriasis indication in patients ages 12 to <18 years (meeting date: 05/04/2016), the Agency

agreed to enrollment of subjects at U.S. sites in study 3013.

The marketing status of ustekinumab in pediatric patients 6 to < 12 years in other jurisdictions is unclear. However, study 3013 was multinational, with sites in Belgium, Canada, Germany, Hungary, the Netherlands, Poland, and the United States.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Inspections were not done for this supplement.

4.2. Product Quality

The Applicant did not submit product quality information for this efficacy supplement.

4.3. Clinical Microbiology

This section is not applicable to this review.

4.4. Nonclinical Pharmacology/Toxicology

The Applicant did not submit any nonclinical information for this efficacy supplement.

4.5. Clinical Pharmacology

Cindy (Liping) Pan, Ph.D. was the clinical pharmacology reviewer for this supplement, and the information in this section is from her review.

Steady-state serum concentrations of ustekinumab were achieved by Week 28, following multiple subcutaneous (SC) injections of the product. At Week 28, the mean ±SD steady-state trough serum ustekinumab concentrations were 0.36 ± 0.26 mcg/mL. Similar serum ustekinumab concentrations were observed for subjects <60 kg at baseline who received 0.75 mg/kg dose and subjects ≥60 kg to ≤100 kg at baseline who received a flat 45 mg dose (only 4 subjects were in the latter group).

The pharmacokinetic (PK) profiles were generally comparable between adolescents (12 to 17 years) and children (6 to 11 years) when treated with the same weight-based dosing regimen that is approved for adolescents and proposed for children. Additionally, population PK analysis suggested that systemic exposures from weight-based dosing in children who received the

weight-based dosing were similar to those in adolescents who received the approved standard dose.

An exploratory exposure-response analysis for the Physician's Global Assessment (PGA) 0/1 suggested that the response was associated with quantifiable steady-state trough ustekinumab levels. Approximately 9.5% (4/42) of subjects developed anti-drug antibodies (ADA) by Week 56, and 2 of these ADA-positive subjects (50%) were positive for neutralizing ADA. Development of ADA generally appeared to be associated with a decrease in serum ustekinumab levels.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) concluded that the Applicant has fulfilled the PREA PMR and recommended approval of the supplement.

4.6. Devices and Companion Diagnostic Issues

This section is not applicable to this review.

4.7. Consumer Study Reviews

This section is not applicable to this review.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2. Table of Clinical Study*

Study Type						
Study ID EudraCT Number First Patient First Visit /Completion date (day Month year) Study Status	Countries: Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
Efficacy and Safety Uncontrolled Clinical Studies						
CNTO1275PSO3013 Synopsis 2016-000121-40 07 June 2016 25 October 2018 Main study (through Week 56): completed LTE (through up to Week 264): ongoing	BEL, CAN, DEU, HUN, NTL, POL,USA:19	Phase 3 Open-label Boys and girls ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis To evaluate the efficacy and safety of ustekinumab in pediatric subjects ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis.	Enrolled: 44	Sterile liquid for SC injection Main Study All subjects received SC ustekinumab 0.75 mg/kg, 45 mg, or 90 mg (body weight of <60 kg, ≥60 kg to ≤100 kg, or >100 kg, respectively) at Week 0 and Week 4 followed by a maintenance dose q12w with the last dose at Week 40. LTE From Week 52 through up to the last dose at Week 262, subjects continue to receive the same dose regimen as per the main study.	All subjects: n=44	Main study: Full report 15 March 2019 EDMS-ERI-165307333 Module 5.3.5.1

Abbreviations:
BEL=Belgium; CAN=Canada; DEU=Germany; HUN=Hungary; NTL=Netherlands; POL=Poland; USA=United States of America.
kg=kilogram; LTE=long-term extension; q12w= every 12 weeks; SC=subcutaneous

*Source: Module 5.2 of the sBLA

5.2. Review Strategy

This review focuses on the single study report provided in the submission.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Phase 3 Open-label Study to Assess the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Ustekinumab in the Treatment of Moderate to Severe Chronic Plaque Psoriasis in Pediatric Subjects ≥6 to <12 Years of Age (CADMUS Jr)

6.1.1. Study Design

Overview and Objective

This was an open-label, multinational study (Europe, Canada, United States) that enrolled subjects 6 to <12 years of age with plaque psoriasis for at least 6 months. Disease was moderate to severe, defined as: Psoriasis Area and Severity Index (PASI) ≥12, Physician's Global Assessment (PGA) ≥3, and body surface area (BSA) ≥10%.

Subjects received SC ustekinumab at Weeks 0 and 4 followed by a maintenance dose every 12 weeks (q12w), with the last dose at Week 40. Subjects were weighed at each visit and the dose of ustekinumab adjusted accordingly. Subjects received one of the following dose levels depending on their weight:

- Weight <60 kg: 0.75 mg/kg
- Weight ≥60 kg to ≤100 kg: 45 mg
- Weight >100 kg: 90 mg.

Visits were every 4 weeks (q4w) through Week 16, then q12w through Week 52. Efficacy was assessed through Week 52, and the final safety follow-up was at Week 56. Following completion of the Week 52 visit, subjects assessed as having had a beneficial treatment response ustekinumab, and who had not yet reached ≥ 12 years of age in countries where marketing authorization for ustekinumab had been granted for treatment of psoriasis in patients 12 to <18 years of age, were permitted to enter a long-term extension (LTE) of the study.

The primary objective was to evaluate the efficacy and safety of ustekinumab in pediatric subjects 6 to <12 years of age with moderate to severe chronic plaque psoriasis.

The secondary objectives were:

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

Trial Design

This was an open-label, multinational study.

Study Endpoints

Primary Endpoint: The proportion of subjects with a PGA of cleared (0) or minimal (1) at Week 12.

Major Secondary Endpoints:

- Serum ustekinumab concentrations over time to assess the PK of ustekinumab.

- The proportions of subjects who achieved a ≥ 75% improvement in PASI from baseline at Week 12.
- The change in Children's Dermatologic Life Quality Index (CDLQI) from baseline at Week 12.
- The proportions of subjects who achieve a ≥ 90% improvement in PASI from baseline at Week 12.

Statistical Analysis Plan

The Applicant did not perform formal hypothesis testing and reported no p-values. Two-sided exact 95% confidence intervals (CI) were provided for the primary and major secondary efficacy endpoints. Subjects who discontinued study treatment due to lack of efficacy, an adverse event of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could affect their psoriasis were considered as treatment failures.

Protocol Amendments

Amendment 1 (05/17/2017) allowed pediatric subjects who demonstrated clinical benefit through Week 52 to continue receiving ustekinumab through Week 264. Per Development Safety Update Report (DSUR) number 9 (submitted 02/20/2020 to IND 9590 as Sequence 856), the subject exposure in this study was 21 subjects.

6.1.2. Study Results

Compliance with Good Clinical Practices

In the study report, the Applicant stated 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.

Financial Disclosure

The Applicant certified that they had not entered into any financial arrangements with clinical investigators.

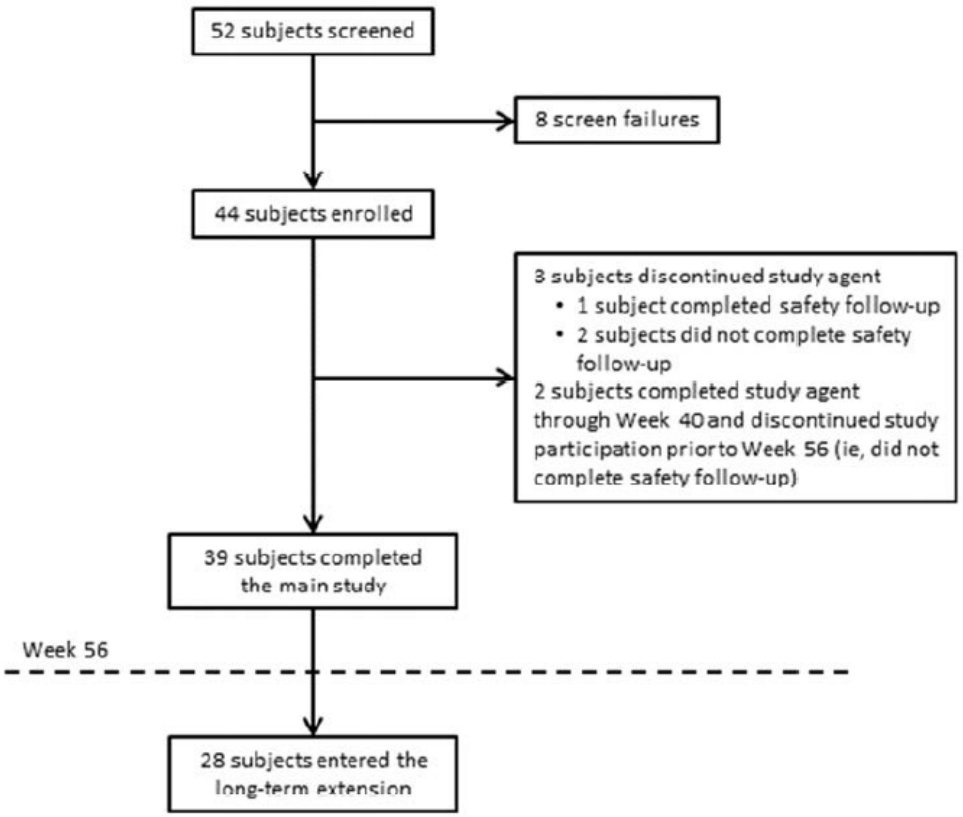
Patient Disposition

A total of 44 subjects was enrolled and treated. Through Week 40 (end of treatment in main study):

- 3 (6.8%) subjects discontinued study treatment,
- 2 (4.5%) subjects discontinued due to protocol violations, and
- 1 (2.3%) subject discontinued due to lack of efficacy.

A total of 39 (88.6%) subjects completed the main study through Week 56 (last follow-up in main study), 28 (63.6%) of whom entered the LTE. A total of 5 (11.4%) subjects discontinued the study through Week 56. Of those who discontinued, 1 (2.3%) subject completed the follow-up at Week 56, and 4 (9.1%) did not. Of the 39 (88.6%) subjects who completed the main study through Week 56, 28 (63.6%) entered the LTE.

Figure 1. Subject Disposition Through Week 56*



*Source: Figure 2 of study report for 3013

Protocol Violations/Deviations

Through Week 56, 3 (6.8%) subjects had at least 1 major protocol deviation:

- 2 subjects had PASI scores below 12 at Week 0 prior to first dose of study drug and were discontinued from the study after 1 dose of study agent.
- 1 subject did not have hepatitis B testing done during screening; the subject tested negative on the subsequent visit and continued in the study.

One subject received a protocol-prohibited concomitant treatment (methylprednisolone aceponate) and was considered a treatment failure.

Demographic Characteristics

A summary of the demographic characteristics at baseline for treated subjects follows:

- 61.4% female
- 90.9% White
- Median body weight was 33.3 kg (90.9% were <60 kg).
- The median age was 9.5 years. All ages across the age range (≥6 to <12 year of age) were represented in the study population.
- The median body mass index (BMI) was 18.0 kg/m^2.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other baseline characteristics are presented below:

- The median duration of psoriasis was 2.9 years.
- The median age at onset of disease was 6.0 years.
- The median percent of BSA involved was 18.0%.
- The 65.9% had PGA scores of 3 (moderate); 34.1% had PGA scores of 4 (marked or severe).
- The median PASI score was 16.1.

Prior therapies for psoriasis included the following:

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

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Most subjects (>90%) received their scheduled ustekinumab administrations through Week 40.

Efficacy Results – Primary Endpoint

The proportion of subjects with a PGA score of cleared (0) or minimal (1) at Week 12, was 77.3% (95% CI: 62.2%; 88.5%).

Table 3. Number of Subjects With a PGA Score of Cleared (0) or Minimal (1) at Week 12; Full Analysis Set *

	Ustekinumab Standard Dosage
Analysis set: Full analysis set	44
PGA of cleared (0) or minimal (1)	34 (77.3%)
95% confidence interval	(62.2%; 88.5%)

*Source: Table 3 of study report for 3013

Data Quality and Integrity

No issues were identified with the data quality or integrity.

Efficacy Results – Secondary and other relevant endpoints

The proportion of subjects with a PASI 75 response at Week 12 was 84.1% (95% CI: 69.9%; 93.4%).

Table 4. Number of PASI 75 Responders at Week 12; Full Analysis Set*

	Ustekinumab Standard Dosage
Analysis set: Full analysis set	44
PASI 75 responders	37 (84.1%)
95% confidence interval	(69.9%; 93.4%)

*Source: Table 4of study report for 3013

Dose/Dose Response

See Sec. 4.5 (“Clinical Pharmacology”).

Durability of Response

This was not a study objective.

Persistence of Effect

This was not a study objective.

Additional Analyses Conducted on the Individual Trial

This section is not applicable to this review.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable to this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

No differences are anticipated regarding how the product was studied and how the product may be used to affect recommendations on a regulatory action or labeling.

7.2.2. Other Relevant Benefits

This section is not applicable to this review.

7.3. Integrated Assessment of Effectiveness

This section is not applicable to this review.

8. Review of Safety

8.1. Safety Review Approach

The safety data from study 3013 were reviewed.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The last dose of study drug was administered at Week 40.

Table 5. Summary of Exposure to Study Agent Through Week 40; Safety Analysis Set *

	Ustekinumab Standard Dosage
Analysis set: Safety analysis set	44
Total number of ustekinumab administrations received	
N	44
Mean (SD)	4.8 (0.89)
Median	5.0
Range	(1; 5)
Total number of ustekinumab administrations received	
1	2 (4.5%)
2	0
3	1 (2.3%)
4	0
5	41 (93.2%)
Total dose of study agent, mg	
N	44
Mean (SD)	142.7 (63.09)
Median	125.6

Range	(27; 405)

*Source: Table TSIEX01 from study report for 3013

8.2.2. Relevant characteristics of the safety population:

See Sec. 6.1.2.

8.2.3. Adequacy of the safety database:

The size of the safety database was adequate for this supplement.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No issues were identified with the data quality or integrity.

8.3.2. Categorization of Adverse Events

Adverse events (AEs) were categorized by the investigator for seriousness, intensity, causality (as assessed by the investigator), duration, and action taken with study agent.

8.3.3. Routine Clinical Tests

Safety was assessed by analyses of rates and type of AEs, serious AEs, reasonably related AEs, injection-site reactions, infections, and AEs of psoriasis. Safety assessments also included analyses of laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry) and rates of markedly abnormal laboratory parameters.

8.4. Safety Results

8.4.1. Deaths

There were no deaths.

8.4.2. Serious Adverse Events

A total of 3 (6.8%) subjects reported SAEs through Week 56:

- A 9 y/o White male sustained an injury to the tear duct and lower eyelid of the left eye, which was surgically repaired.
- A 6 y/o White female experienced attention deficit hyperactivity disorder (ADHD) on

Day 300, for which she was electively hospitalized. She was discharged 8 days later on oral methylphenidate.

- A 6 y/o White female experienced infectious mononucleosis on Day 127. She was hospitalized for approximately 4 days and was considered recovered approximately 3 days post discharge. This was the only serious infection reported in the study.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No subjects discontinued due to an adverse event. See Figure 1 in Sec. 6.1.2.

8.4.4. Significant Adverse Events

The Applicant considered Infections (serious infections and infections treated with oral or parenteral antibiotics), Injection-site reactions, Anaphylactic reactions or serum sickness-like reactions, and Adverse events of psoriasis as "other significant" AEs.

There were no anaphylactic reactions or serum sickness-like reactions reported through Week 56.

Infections

Through Week 56, 29 (65.9%) subjects reported at least 1 AE in the Infections and infestations System Organ Class (SOC). The most common AEs that were considered to be infections were:

- Nasopharyngitis- 11 (25.0%) subjects,
- Pharyngitis- 6 (13.6%) subjects, and
- Upper respiratory tract infection (URTI)- 6 (13.6%) subjects.

The only serious infection has been previously discussed (infectious mononucleosis); see Sec. 8.4.2.

A total of 12 (27.3%) subjects reported at least 1 infection which required oral or parenteral antimicrobial treatment. The events in this category for which there were multiple reports were:

- Otitis media and URTI- 3 (6.8%) subjects each.
- Pharyngitis, Tonsillitis, and Enterobiasis- 2 (4.5%) subjects each.

There were no reports of tuberculosis or opportunistic infection.

Injection-Site Reactions

Injection-site reactions were reported in 6 (13.6%) subjects, and some subjects experienced multiple events. All injection-site reactions were graded as mild in severity and resolved in less

than 24 hours. Erythema was the most common injection-site reaction and was reported in all 6 subjects. There were single reports of all other events: Injection site pruritus, Injection site swelling, and Injection site warmth.

One site in Hungary reported the injection-site reactions for 5 of the 6 subjects who reported such reactions (erythema for all 5 subjects).

A total of 4 subjects were positive for antibodies to ustekinumab, and none reported any injection-site reactions after antibody development.

Adverse events of psoriasis

A total of 3 subjects reported 4 AEs of psoriasis. One subject reported 2 occurrences of Exacerbation of psoriasis, 23 days apart. The onset of the first event was approximately 13 weeks after his last dose of study treatment, and 7 days before he received his next dose; the second report was 16 days after that dose.

The other 2 subjects reported one event each: Exacerbation of psoriasis and Psoriasis aggravated. Both events occurred after the final, Week 40 dose of study treatment. For one subject onset of the event (Exacerbation of psoriasis) was approximately 14 weeks after the last dose of study treatment. For the other subject, the day of onset of the event (Psoriasis aggravated) was not reported on Table LSFAE04 of the study report.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Through Week 56, 34 (77.3%) subjects reported at least 1 treatment emergent adverse events (TEAE). TEAEs were most frequently reported in the Infections and infestations SOC, with 29 (65.9%) of subjects reporting events in this category and with the most frequently reported events being: Nasopharyngitis- 11 (25.0%) subjects and Pharyngitis and URTI- 6 (13.6%) subjects each.

Table 6. Number of Subjects with Treatment-Emergent Adverse Events with Frequency of at Least 5% Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set*

	Ustekinumab Standard Dosage
Analysis set: Safety analysis set	44
Avg duration of follow-up (weeks)	53.15
Avg exposure (number of administrations)	4.77
Subjects with 1 or more AEs	34 (77.3%)
System organ class	

Preferred term	
Infections and infestations	29 (65.9%)
Nasopharyngitis	11 (25.0%)
Pharyngitis	6 (13.6%)
Upper respiratory tract infection	6 (13.6%)
Tonsillitis	4 (9.1%)
Gastroenteritis	3 (6.8%)
Otitis media	3 (6.8%)
General disorders and administration site conditions	9 (20.5%)
Injection site erythema	6 (13.6%)
Gastrointestinal disorders	6 (13.6%)
Abdominal pain	3 (6.8%)
Skin and subcutaneous tissue disorders	5 (11.4%)
Psoriasis	3 (6.8%)

*Source: Table 8 of the study report for 3013
Key: AE = adverse event, Avg = average
Note: Subjects are counted only once for any given event, regardless of the number of times that they actually experienced the event. Adverse events are coded using MedDRA Version 21.0.

8.4.6. Laboratory Findings

The Applicant reported on clinically significant changes in hematology or chemistry parameters.

8.4.7. Vital Signs

The Applicant reported that vital signs (heart rate, respiratory rate, and blood pressure) remained stable over time through Week 52.

8.4.8. Electrocardiograms (ECGs)

ECGs were not done in study 3013.

8.4.9. QT

A thorough QT trial was not conducted.

8.4.10. Immunogenicity

From Dr. Pan's review:

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

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

As described in Section 8.4.4, no antibody-positive subjects reported any injection-site reactions after antibody development, and no anaphylactic reactions or serum sickness-like reactions were reported through Week 56.

8.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified.

8.6. Safety Analyses by Demographic Subgroups

There were 44 subjects in this study. The number of subjects in any subgroup is too small to permit any meaningful assessment.

8.7. Specific Safety Studies/Clinical Trials

The Applicant did not conduct a specific safety study.

Four-month Safety Update (SU)

The submission provided safety information "from Week 56 through 31 October 2019 (the data cut point for this 120-Day Safety Update) for study CNTO1959PSO3013." This period falls within the LTE phase of the study. Per agreement with the Agency, the SU provided for the following from study 3013:

- Listing for all SAEs and discontinuations due to adverse events.
- Full narratives for all deaths, subjects who experienced SAEs and who discontinued due to adverse events (AEs).
- Narrative summaries for events of interest as follows: serious infections (including tuberculosis and opportunistic infections), serious cardiovascular events, and serious neurologic events, and for serious and nonserious malignancy.

The Applicant also provided a summary of the postmarketing experience for ustekinumab.

Study 3013

A total of 28 subjects entered the LTE period of the study.

No deaths occurred. One SAE was reported: A 9 y/o White male with a history of juvenile rheumatoid arthritis experienced arthralgia on Day 679. He was hospitalized, recovered, and was discharged on Day 682. No subjects discontinued treatment due to an AE. No "events of interest" were reported during the reporting period for the SU.

Postmarketing Experience

The Applicant estimated the worldwide exposure to ustekinumab from launch to 12/31/2019 was 1,667,912 person-years. The Applicant did not include any discussion of specific events from the postmarketing environment in the SU.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No malignancies were reported.

8.8.2. Human Reproduction and Pregnancy

No pregnancies were reported.

8.8.3. Pediatrics and Assessment of Effects on Growth

This supplement pertains to a pediatric assessment. However, the study did not assess the effects on growth.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Section 10 of the label ("Overdosage") states:

> Single doses up to 6 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

There were no reports of overdose during study 3013. There is no information suggesting addiction or abuse potential with ustekinumab.

Study 3013 did not include evaluation of disease status following withdrawal of treatment,

including no evaluation for rebound potential.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The Postmarketing Experience section of the label (6.3) includes the following information:

> The following adverse reactions have been reported during post-approval of STELARA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to STELARA® exposure.
>
> *Immune system disorders:* Serious hypersensitivity reactions (including anaphylaxis and angioedema), other hypersensitivity reactions (including rash and urticaria) *[see WARNINGS AND PRECAUTIONS (5.5)]*.
>
> *Infections and infestations:* Lower respiratory tract infection (including opportunistic fungal infections and tuberculosis) *[see WARNINGS AND PRECAUTIONS (5.1)]*.
>
> *Respiratory, thoracic and mediastinal disorders:* Interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia *[see WARNINGS AND PRECAUTIONS (5.9)]*.
>
> *Skin reactions*: Pustular psoriasis, erythrodermic psoriasis.

8.9.2. Expectations on Safety in the Postmarket Setting

The data from children ≥6 to <12 years of age provided in this supplement revealed a safety profile generally similar to that seen in the adolescent and adult psoriasis populations. Based on the available safety data, the expectation is that the postmarketing safety experience for patients aged ≥6 to <12 years may be similar to the experience of those older patients.

8.9.3. Additional Safety Issues From Other Disciplines

There were no safety issues from other disciplines.

8.10. Integrated Assessment of Safety

The data from children ≥6 to <12 years of age provided in this supplement revealed a safety profile generally similar to that seen in the adolescent and adult psoriasis populations. Based on

the available safety data, the expectation is that the postmarketing safety experience for patients aged ≥6 to <12 years may be similar to the experience of those older patients.

9. Advisory Committee Meeting and Other External Consultations

This section is not applicable to this review.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The Medical Officer has reviewed labeling. Labeling negotiations were ongoing as this review was being finalized.

10.2. Nonprescription Drug Labeling

This section is not applicable to this review.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary.

12. Postmarketing Requirements and Commitments

This section is not applicable to this review.

13. Appendices

13.1. References

See footnotes.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): CNTO1275PSO3013

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 20 principal investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRENDA CARR
06/05/2020 01:11:57 PM

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06/05/2020 01:48:54 PM