Primary Review, Cross-Discipline Team Leader Review, Division Director Summary

Date	See electronic stamp date
From	Raj Nair, MD, Clinical Team Leader, DRTM Suzette Peng, MD, Clinical Reviewer, DRTM Jianmeng Chen, MD, PhD, Clinical Pharmacology Team Leader Nisha Kwatra, PhD, Clinical Pharmacology Reviewer Nikolay Nikolov, MD, Division Director, DRTM
Subject	Cross-Discipline Team Leader Review Division Director Summary
NDA/BLA # and Supplement#	BLA 125261/S-161
Applicant	Janssen Biotech, Inc.
Date of Submission	October 6, 2021
PDUFA Goal Date	August 6, 2022
Proprietary Name	Stelara
Established or Proper Name	Ustekinumab
Dosage Form(s)	Prefilled syringe
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed Dosing Regimen(s)	Weight-tiered dosing at the initial dose, 4 weeks later, then every 12 weeks thereafter. **Weight Range (kilograms)** / **Dosage Regimen** less than 60 kg / 0.75 mg/kg 60 kg or more / 45 mg greater than 100 kg with co-existent moderate-to-severe plaque psoriasis / 90 mg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Pediatric patients 6 years and older with active psoriatic arthritis (PsA)
Recommended Dosing Regimen(s) (if applicable)	Weight-tiered dosing at the initial dose, 4 weeks later, then every 12 weeks thereafter. **Weight Range (kilograms)** / **Dosage Regimen** less than 60 kg / 0.75 mg/kg 60 kg or more / 45 mg greater than 100 kg with co-existent moderate-to-severe plaque psoriasis / 90 mg

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Psoriatic arthritis (PsA) is a chronic progressive inflammatory arthritis associated with psoriasis that may result in permanent joint damage and disability. Pediatric psoriatic arthritis, also referred to as psoriatic juvenile idiopathic arthritis (PsJIA) or juvenile psoriatic arthritis (jPsA), is classified as a subtype of the broader group of childhood inflammatory arthritides, juvenile idiopathic arthritis (JIA). Clinical manifestations of pediatric PsA are similar to adult PsA with peripheral and axial arthritis, enthesitis, dactylitis, psoriasis (PsO), and nail changes. Pediatric PsA comprises between 2 to 11% of children with JIA, and it has a calculated annual incidence of ~3 per million children.[1,2]

Ustekinumab is a first-in-class fully human immunoglobulin G1 kappa monoclonal antibody to human interleukin (IL)-12/23 p40 that binds with specificity to human IL-12 and IL-23 and neutralizes their bioactivity by preventing these cytokines from binding to their IL-12 receptor beta-1 receptor protein expressed on the surface of immune cells. STELARA® was first approved as a treatment for adult psoriasis on September 23, 2009; it has since been approved for adult PsA in September 2013, Crohn's disease in September 2016, ulcerative colitis in October 2019, and pediatric psoriasis (adolescents) in October 2017 and (pediatric patients ages ≥ 6 years) in July 2020.

At the time of approval for adult PsA in September 2013, a full waiver for Pediatric Research Equity Act (PREA)-required pediatric studies was granted due to the rarity of pediatric PsA. The waiver was granted based on the justification that dedicated clinical studies to establish efficacy of products in pediatric PsA would be impossible or highly impracticable to conduct because there are too few children with the disease/condition to study. On October 2, 2019, the FDA/M-CERSI (University of Maryland Center of Excellence in Regulatory Science and Innovation) public workshop, titled "Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)," brought together academia, industry, regulators, and patients to discuss the cumulative experience with drug development for pJIA. From these discussions, the Agency reconsidered the approach to the pediatric assessment for PsA. Specifically, the Agency considered the high degree of similarity between adults with PsA and pediatric patients with PsA to support a scientific rationale for a pediatric extrapolation of efficacy, meaning that efficacy established in adequate and well-controlled studies in adults with PsA could be extrapolated to pediatric patients with PsA based on matching of the pharmacokinetic (PK) exposures between the 2 populations. This extrapolation of efficacy is based on appropriate scientific justification and data provided by the Applicant to support the expectation of similarity in exposure-response (E-R) between the 2 populations which could be product-specific. However, safety and immunogenicity, if relevant, in pediatric patients cannot be extrapolated from the studies in adults and would need to be supported by a reasonable safety database in pediatric patients with PsA or, with appropriate justification, a relevant

[1] Ravelli A and Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007; 369(9563): 767-78.
[2] Stoll ML and Punaro M. Psoriatic juvenile idiopathic arthritis: a tale of two subgroups. *Curr Opin Rheumatol*. 2011; 23(5): 437-443.

pediatric patient population. The Applicant seeks approval of ustekinumab for the treatment of pediatric PsA by providing support in this supplement for this approach to extrapolate efficacy of ustekinumab from adult PsA to pediatric PsA. The supplement includes the following: (1) information to support the similarity of adult PsA and adult PsO with respect to the target, the similarity of adult and pediatric PsO with respect to PK, safety, and response to treatment with ustekinumab, the similarity between adult PsA and pediatric PSA, and the similarity between pediatric PsA and pediatric PsO; (2) justification that the pharmacokinetics (PK) of ustekinumab are expected to be similar in pediatric psoriasis and pediatric PsA and that the therapeutic target and primary mechanism of action are relevant to the 2 indications; (3) rationale for PK bridging (comparable exposure) between adult PsA and pediatric PsA; (4) justification and relevant information to support the extrapolation of efficacy from adult PsA to pediatric PsA; (5) justification of the relevance of the safety data from adult psoriasis, pediatric psoriasis, and adult PsA to pediatric PsA. While ustekinumab is the first-in class product for PsA, additional contextual information on the relevance of the target and mechanism of action is provided by the established efficacy of ustekinumab, at similar exposures, in the related indication of adult and pediatric PsO, further supporting the PK-based extrapolation approach.

Evidence indicates that there are overlapping features of pediatric PsA and adult PsA arthritis and that children with pediatric PsA should respond to treatment similarly to adults with PsA and adults and children with PsO. Thus, the efficacy in pediatric patients with PsA can be extrapolated from adults with PsA where efficacy has been demonstrated in adequate and well-designed clinical trials. To establish the PK bridge to pediatric patients with PsA, PK data in adult PsA, adult PsO, and pediatric PsO were considered. The observed pre-dose (trough) concentrations are generally comparable between adult patients with psoriasis, adult patients with PsA and pediatric patients with psoriasis, and the PK exposure is expected to be comparable between adult and pediatric patients with PsA. This conclusion was also supported by the limited PK information in the 4 patients with pediatric PsA in the two clinical trials in pediatric PsO. By establishing this PK bridge and with the significant disease similarity between pediatric and adult patients with PsA, it is scientifically justified to extrapolate the efficacy established in adults with PsA to pediatric patients with PsA.

Pediatric patients with PsA often have concomitant PsO with a diagnosis of PsO frequently preceding the diagnosis of arthritis. There are no significant disease-specific factors that would be expected to impact safety differently. These considerations along with the expected similar PK exposures support the relevance of safety data from pediatric PsO population to the pediatric PsA population. The safety of ustekinumab in pediatric patients with PsA is supported by the safety observed in 2 studies in pediatric PsO. Study CNTO1275PSO3006 was a multi-center, randomized, double-blind, placebo-controlled study conducted in 110 adolescent patients (≥ 12 to < 18 years-old) with pediatric PsO. A total of 73 adolescent patients received ustekinumab; 36 patients received the standard dosage (approved ustekinumab dose regimen for pediatric PsO) and 37 patients the half-standard dosage. Study CNTO1275PSO3013 was an open-label study conducted in 44 younger patients (≥ 6 to < 12 years-old) with pediatric PsO; all patients received the standard dosage of ustekinumab. The overall safety profile of ustekinumab in pediatric PsO was consistent with the safety in adult PsO and adult PsA. No new safety signals were identified in these studies in pediatric patients (≥ 6 to < 18 years-old) with pediatric PsO.

(b) (4)

(b) (4)

In conclusion, pediatric PsA is a rare and serious disease with high unmet need for new therapies. The Applicant has provided adequate information to inform the benefit-risk assessment of ustekinumab for the treatment of pediatric patients with PsA and support the expansion of the indication for ustekinumab for the treatment of active PsA in patients 6 years of age and older. Approval of ustekinumab will provide additional treatment options in a limited armamentarium in the US for pediatric patients with PsA. Therefore, the review team recommends approval of supplement 161. The Division Signatory agrees with this assessment and recommendation.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Juvenile Idiopathic Arthritis (JIA) is the term used to refer to multiple subtypes of inflammatory arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age. • Pediatric psoriatic arthritis (pediatric PsA), also referred to as psoriatic juvenile idiopathic arthritis (PsJIA) and juvenile psoriatic arthritis (jPsA), is a subtype of JIA and comprises about 2 to 11% of children with JIA. • Clinical manifestations of pediatric PsA are similar to adult PsA with peripheral and axial arthritis, enthesitis, dactylitis, and cutaneous and nail changes.	Pediatric PsA is a serious disabling form of JIA with significant impact on quality of life for patients and families. Pediatric PsA and adult PsA share similar disease manifestations, disease progression, and similar response to treatment; therefore, the similarity of the diseases support the extrapolation of efficacy from adult PsA to pediatric PsA based on bridging of exposure response and PK.
Current Treatment Options	• There are limited treatment options for pediatric patients with PsA. • Recommendations for treatment are based on Expert Consensus Treatment Guidelines, and treatment is determined based on active disease manifestations. • Standard-of-care treatment for pediatric patients with PsA is similar to adult patients. • The 2019 American College of Rheumatology (ACR) Guidelines for the treatment of JIA bases treatment on presentation. Pediatric patients could fall into the categories of polyarthritis, sacroiliitis, or enthesitis. ○ Recommendations for JIA and polyarthritis includes initial treatment with a non-biologic disease modifying anti-rheumatic drug (DMARD), e.g., methotrexate (MTX). For persistent activity,	There is an unmet need for safe and efficacious therapies for pediatric patients with PsA, as there are limited treatments available.

	options include intra-articular glucocorticoid injection(s), increase in DMARD dose, change in DMARD, or addition of a biologic DMARD. ○ Recommendations for JIA and sacroiliitis or enthesitis include initial treatment with NSAIDs. For persistent activity, patients should receive a TNFi. • Current FDA-approved biologic DMARDs for the treatment of pediatric PsA include IV golimumab and secukinumab.	
Benefit	• The efficacy of ustekinumab has been previously demonstrated in adult patients with PsA. Two phase 3 pivotal studies (CNTO1275PSA3001 and CNTO1275PSA3002) supported the approval of ustekinumab for treatment of PsA in adult patients. • The efficacy of ustekinumab has been demonstrated in adult psoriasis (PsO) and pediatric PsO studies. ○ Two phase 3 pivotal studies (C0743T08 and C0743T09) led to the approval of ustekinumab for the treatment of adults with plaque-type moderate to severe PsO. ○ Two phase 3 studies were also conducted in pediatric psoriasis. Study CNTO1275PSO3006 was conducted in pediatric patients ≥ 12 to < 18 years of age, and study CNTO1275PSO3013 was conducted in pediatric patients ≥ 6 to < 12 years of age. There were 7 patients in these pediatric psoriasis studies who had psoriatic arthritis. • The observed pre-dose (trough) concentrations are generally comparable between adult patients with psoriasis, adult patients with PsA and pediatric patients with psoriasis, and the PK exposure is expected to be comparable between adult and pediatric patients with PsA. • The PK exposures with similar doses are similar in (1) adults, adolescents, and children with PsO, (2) adults with PsO and adults with PsA, and (3) adolescents with PsO and adults with PsA.	The efficacy of ustekinumab in pediatric patients ages 6 to < 18 years of age is based on PK-exposure matching and extrapolation from the established efficacy of ustekinumab in adults with PsA in 2 pivotal trials (CNTO1275PSA3001 and CNTO1275PSA3002). This approach is justified based on similarities of disease manifestation and disease progression in adults and pediatric patients with PsA. While ustekinumab is the first-in class product for PsA, additional contextual information on the relevance of the target and mechanism of action is provided by the established efficacy of ustekinumab, at similar exposures, in the related indication of adult and pediatric PsO, further supporting the PK-based extrapolation approach to pediatric PsA.
Risk and Risk Management	• Pediatric PsO is a relevant population to pediatric PsA. Pediatric patients with PsA will often have concomitant psoriasis. In fact, skin lesions frequently precede the onset of arthritis. Approximately, 40-60% of these pediatric patients with PsA have overt psoriasis.	Approximately 40 to 60% of pediatric patients with PsA will have PsO. Therefore, it is reasonable to leverage safety data from studies CNTO1275PSO3006 and CNTO1275PSO3013 in

[redacted]	• The safety database in pediatric patients ages 6 years or older with psoriasis is sufficient to provide a risk assessment for ustekinumab in the pediatric PsA population (studies CNTO1275PSO3006 and CNTO1275PSO3013, reviewed under BLA 125433/s-138 and s-150, respectively). [redacted] (b) (4)	pediatric patients with PsO to patients with PsA ages 6 to 17 years. (b) (4) [redacted]

2. Background

Product Information and the Applicant's Proposal

Ustekinumab is a first-in-class fully human immunoglobulin G1 kappa monoclonal antibody to human interleukin (IL)-12/23 p40 that binds with specificity to human IL-12 and IL-23 and neutralizes their bioactivity by preventing these cytokines from binding to their IL-12 receptor beta-1 receptor protein expressed on the surface of immune cells. STELARA® has been approved as a treatment for adult psoriasis since 2009, adult PsA since 2013, and pediatric psoriasis (ages ≥ 6 years) since 2020. Ustekinumab demonstrated robust efficacy in adults with plaque-type moderate to severe psoriasis (phase 3 studies C0743T08 and C0743T09) and in adults with active PsA (phase 3 studies CNTO1275PSA3001 and CNTO1275PSA3002) which led to approval of ustekinumab for use in these indications. These results further demonstrated the relevance of targeting IL-12/23 in the treatment of both psoriasis and PsA.

The approved dose regimens for ustekinumab for adult psoriasis and adult PsA are essentially the same except that for PsA, only adults weighing > 100 kg with co-existent moderate-to-severe plaque psoriasis can receive a 90 mg dose. See Table 1 below for the dosage regimens for adult psoriasis and adult PsA.

The approval in pediatric psoriasis included two phase 3 studies in pediatric psoriasis (CNTO1275PSO3006 in participants ≥ 12 to < 18 years of age and CNTO1275PSO3013 in participants in ≥ 6 to < 12 years of age) which demonstrated efficacy in the pediatric age range and further demonstrated the relevance of targeting IL-12/23 across a broad age range of patients with psoriasis. The approved ustekinumab dosing in adult and pediatric psoriasis is the same with the exception of weight-based dosing in the smaller children (< 60 kg) in order to achieve a comparable exposure to older children, adolescents, and adults. See Table 1 for the dosage regimen in pediatric psoriasis.

Table 1. FDA-Approved Indications and Dosage Regimens for Ustekinumab

Indication	Dosage Regimen	
Psoriasis	Initial dose, 4 weeks later, then every 12 weeks	
	≤ 100 kg	45 mg SC
	> 100 kg	90 mg SC
Pediatric psoriasis (Ages 6 years or older)	Initial dose, 4 weeks later, then every 12 weeks	
	< 60 kg	0.75 mg/kg SC
	60 to 100 kg	45 mg SC
	> 100 kg	90 mg SC
Psoriatic arthritis	Initial dose, 4 weeks later, then every 12 weeks	45 mg SC
	> 100 kg and co-existent moderate-to-severe plaque psoriasis	90 mg SC
Crohn's disease Ulcerative colitis	Initial IV dosage	
	≤ 55 kg	260 mg IV

	> 55 kg to 85 kg	390 mg IV
	> 85 kg	520 mg IV
	Maintenance SC dosage	90 mg SC 8 weeks later, followed by every 8 weeks

SC = subcutaneous; IV = intravenous

In this supplement, the Applicant proposes the treatment of pediatric patients (b) (4) (b) (4) with psoriatic arthritis. The proposed dosage regimen is similar to the approved regimen for pediatric PsO and adult PsA. Dosing is weight-based in patients < 60 kg (like that of pediatric PsO) and is weight-tiered for patients > 60 kg (like that of adult PsA). Pediatric patients with PsA should be dosed initially, 4 weeks later, and then every 12 weeks, as follows:

- Patients who weigh < 60 kg: 0.75 mg/kg SC
- Patients who weigh ≥ 60 kg: 45 mg SC
- Patients who weigh > 100 kg and have co-existent moderate-to-severe plaque psoriasis: 100 mg SC

No new clinical data are submitted in this supplement. The Applicant proposes that the efficacy in pediatric PsA can be extrapolated from the efficacy data in adult PsA. The utilization of the extrapolation for pediatric PsA is based on the following: (1) the disease similarity of pediatric PsA and adult PsA; (2) the established similarity of PK and E-R of ustekinumab in adults with psoriasis and adolescents and children with psoriasis; (3), the similarity in PK of ustekinumab between adults with psoriasis and adults with PsA, as well as (4) the similarity in PK of adults with PsA and pediatric psoriasis (including participants with pediatric PsA). Overall, the efficacy of ustekinumab in the pediatric PsA population is expected to be similar to that observed in adults with PsA.

PsA in Adults and Pediatrics

PsA is a chronic progressive inflammatory arthritis associated with psoriasis that may result in permanent joint damage and disability. The clinical manifestations of PsA include peripheral and axial inflammatory arthritis. The peripheral arthritis may present as an asymmetric oligoarthritis, a symmetric polyarthritis of the small joints of the hands and feet, arthritis mutilans, or other patterns. Patients with PsA can also have involvement of the tendons, dactylitis, enthesitis, as well as spondyloarthritis.

The International League of Associations for Rheumatology (ILAR) classification system is the currently most widely used classification system to characterize arthritis in children and adolescents.[3] In this system, JIA is the term used to encompass all the included subtypes: systemic-onset JIA, persistent or extended oligoarthritis, rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis, psoriatic JIA, enthesitis-related arthritis, and undifferentiated JIA. Broadly, JIA is defined as arthritis of one or more joints occurring for at

[3] Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004; 31(2): 390-392.

least 6 weeks in a child younger than 16 years of age, where other diagnoses have been excluded. PsA in children can be referred to as psoriatic JIA (PsJIA), juvenile psoriatic arthritis (jPsA), or pediatric PsA. In this review, the condition will be referred to as pediatric PsA or pediatric patients with PsA and will include pediatric patients to the age of 17.

Pediatric PsA comprises 2 to 11% of children with JIA.[4] ILAR criteria for PsA include (1) arthritis and psoriasis or (2) arthritis and at least 2 of the following: dactylitis; nail pitting or onycholysis; psoriasis in a first-degree relative.[3] Exclusions to a classification of PsA include (1) arthritis in an HLA-B27 positive male after age 6; (2) ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis, or a history of one of these in a first-degree relative; (3) presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart; or (4) presence of systemic JIA. The Vancouver criteria for pediatric PsA define definite pediatric PsA by the presence of 2 major criteria (arthritis and psoriasis) or arthritis plus 3-4 minor criteria (dactylitis, nail pitting, family history of psoriasis in a first- or second-degree relative, psoriasis-like lesions).[5] Notably, the presence of skin rash is not required for diagnosis based on either criteria. However, psoriasis occurs in 40 to 60% of patients with pediatric PsA, and nail changes are observed in 50 to 80%.[6] Skin lesions often precede the onset of arthritis in 80% of patients with PsA.[7]

Clinical manifestations of pediatric PsA are similar to those of adult PsA with peripheral and axial arthritis, enthesitis, dactylitis, and cutaneous and nail changes. The age of onset has a biphasic distribution with a peak between ages 2 to 4 years and a second peak at 9 to 11 years of age. Younger patients are more commonly female with a positive ANA and polyarthritis, while older children are more likely to have axial disease and enthesitis.[6,8] The most commonly involved joints are knee and ankle with hip joint disease occurring in up to 20 to 30% of patients.[9] Pediatric PsA can affect the axial skeleton in 10 to 30% of patients.[6] Sacroiliitis is more frequent in patients with older age at onset, who are often positive for the HLA-B27 antigen. Approximately 60% of children in the older subgroup of pediatric PsA have enthesitis, as compared to 22% of younger patients.[5] Dactylitis is observed in 20 to 40% of patients.[5] Chronic painless uveitis occurs in 10 to 15% of children with pediatric PsA, more commonly in younger patients with a positive ANA.[6]

As described, adult PsA and pediatric PsA have similar disease manifestations and progression. Both diseases also appear to have a similar pathogenic pathway. A correlation between *IL-23R* SNP and disease susceptibility has been identified in pediatric PsA but not

[4] Ravelli A and Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007; 369(9563): 767-78.
[5] Southwood TR, Petty RE, Malleson PN. Psoriatic arthritis in children. *Arthritis Rheum*. 1989; 32: 1007-1013.
[6] Stoll ML, Zurakowski D, Nigrovic LE, et al. Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum*. 2006; 54(11): 3564-72.
[7] Lewkowicz D and Gottlieb AB. Pediatric psoriasis and psoriatic arthritis. *Dermatol Ther*. 2004; 17: 364-375.
[8] Zisman D, Gladman D, Stoll M, et al. The juvenile psoriatic arthritis cohort in the CARRA Registry: clinical characteristics, classification, and outcomes. *J Rheum*. 2017; 44(3): 342-351.
[9] Nigrovic P. Psoriatic juvenile idiopathic arthritis: pathogenesis, clinical manifestations, and diagnosis. In: UpToDate, Post TW (ed), UpToDate, Waltham, MA. (Accessed on July 17, 2022.)

other subtypes of JIA.[10,11] Although still theoretical, a similar correlation is noted in adult PsA. This would suggest a common molecular target (i.e., IL-23 and Th17 pathway) in the 2 diseases.

Psoriasis and Psoriatic Arthritis

Ustekinumab is a first-in-class fully human immunoglobulin G1 kappa monoclonal antibody to human interleukin (IL)-12/23 p40 that binds with specificity to human IL-12 and IL-23 and neutralizes their bioactivity by preventing these cytokines from binding to their IL-12 receptor beta-1 receptor protein expressed on the surface of immune cells. While it is the first-in class product for PsA, the additional contextual information on the relevance of the target and mechanism of action is provided by the established efficacy of ustekinumab in the related indications of adult PsO (approved in 2009) and pediatric patients with PsO (adolescents approved in October 2017 and patients ages ≥ 6 years approved in July 2020), further supporting the PK-based extrapolation approach to pediatric patients with PsA.

Psoriasis is a skin condition with multiple subtypes including chronic plaque psoriasis, guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis. Chronic plaque psoriasis is the most common and presents as sharply demarcated plaques overlying silver scale, affecting the scalp, lower back, umbilicus, genitals, and extensor surfaces of the elbows and knees.[12] Amongst psoriasis patients, PsA is diagnosed in 7 to 42% of patients although the numbers may be lower at 15 to 25%.[12] Although psoriasis is not required to diagnose PsA, current classification criteria for pediatric and adult PsA include psoriasis or a family history of psoriasis. Psoriasis may precede arthritis by 8 to 10 years in 67% of patients, and the arthritis may precede psoriasis or occur simultaneously in 33% of patients, particularly in pediatric or older (> 50-years-old) patients.[13]

Many of the systemic treatments overlap for psoriasis and psoriatic arthritis.[12] Specifically, ustekinumab is approved for both PsO (pediatric and adult) and adult PsA. The dose regimens for adult PsO and adult PsA are similar (Table 1) except that patients ≥ 100 kg with moderate-to-severe PsO with or without PsA require higher doses (ustekinumab 90 mg).

Currently Available Treatment for Pediatric Patients with Psoriatic Arthritis

At this time, there are 2 biologic disease-modifying antirheumatic drugs (DMARDs) approved for the treatment of pediatric PsA.

- IV golimumab (SIMPONIA ARIA®) is approved for the treatment of active PsA in patients 2 years of age and older. The basis of approval in September 2020 was the

[10] Hinks A, Martin P, Flynn E, et al. Subtype specific genetic associations of juvenile idiopathic arthritis: *ERAP1* with the enthesitis related arthritis subtype and *IL23R* with juvenile psoriatic arthritis. *Arthritis Res Ther*. 2011; 13: R12.
[11] Zisman D, Stoll ML, Aviel YB, Mellins ED. Juvenile psoriatic arthritis: a report from the GRAPPA 2017 annual meeting. *J Rheumatol Suppl*. 2018; 94: 11-16.
[12] Cunha JS, Quereshi AA, REginato AM. Management of psoriasis and psoriatic arthritis in a multidisciplinary rheumatology/dermatology clinic. *Federal Practitioner*. 2015;
[13] Gilliland W. "Arthritis associated with psoriasis and other skin diseases." In *Rheumatology Secrets, 3rd Edition*, edited by Sterling West, 284-288. Philadelphia: Elsevier, 2015.

extrapolation of efficacy from adult PsA after establishing a PK bridge to pediatric patients with PsA.

- Secukinumab (COSENTYX®) is approved for active PsA in patients 2 years of age and older. Approval in December 2021 was based on a 2-year, 3-part, double-blind, placebo-controlled, event-driven, randomized study in patients between 2 to < 18 years of age with active enthesitis-related arthritis (ERA) or jPsA (n= 34 with jPsA and n = 52 with ERA).

The most recent treatments guidelines for JIA are the 2019 American College of Rheumatology (ACR) and Arthritis Foundation (AF) guidelines[14]; thus, these guidelines preceded the FDA approvals for pediatric PsA. Treatment recommendations are based on active disease manifestations. Patients with pediatric PsA could be treated according to recommendations for polyarthritis (≥ 5 joints ever involved), enthesitis, or sacroiliitis.

- Patients with JIA and polyarthritis, but without systemic arthritis, sacroiliitis, or extra-articular manifestations, may include patients with polyarticular (RF-positive or RF-negative) JIA, extended oligoarticular JIA, ERA, PsA, and undifferentiated arthritis. Initial therapy with a DMARD is strongly recommended over non-steroidal anti-inflammatory drug (NSAID) monotherapy in all patients. For patients with risk factors for disease severity and potentially a more refractory disease course, initial therapy with a DMARD is conditionally recommended over a biologic although initial biologic therapy may be considered in certain circumstances. For patients with moderate/high disease activity on DMARD monotherapy, adding a biologic to the original DMARD is conditionally recommended over changing to a second DMARD or changing to triple DMARD therapy. If a patient has moderate/high disease activity while on a tumor necrosis factor-inhibitor (TNFi) with or without DMARD, switching to a non-TNFi biologic is conditionally recommended over switching to a second TNFi.
- Patients with enthesitis or sacroiliitis most likely include patients with ERA, PsA, and undifferentiated arthritis. Initial therapy with an NSAID is strongly recommended. Addition of a TNFi is strongly recommended in patients with persistent active sacroiliitis despite NSAID therapy and conditionally recommended in patients with persistent active enthesitis over methotrexate or sulfasalazine.

Pertinent Regulatory History

A summary of key regulatory interactions with the Applicant are listed in Table 2 below.

[14] Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesis's. *Arthritis Care Res*. 2019; 71: 717-734.

Table 2: Summary of Regulatory Background for Ustekinumab and Pediatric PsA

Full Pediatric Waiver September 20, 2013	A full waiver of pediatric studies for PsA was granted with approval of BLA 125261/s-103 because necessary studies are impossible or highly impracticable, as the disease occurs in a very small number of pediatric patients.
"Accelerating Drug Development for polyarticular JIA (pJIA)" workshop October 2, 2019	The FDA/M-CERSI (University of Maryland Center of Excellence in Regulatory Science and Innovation) public workshop brought together academia, industry, regulators, and patients to discuss the cumulative experience with drug development for pJIA. From these discussions, the Agency reconsidered the approach to the pediatric assessment for PsA. Specifically, the Agency considered the high degree of similarity between adult and pediatric PsA to support a scientific rationale for a PK extrapolation of efficacy, meaning that efficacy established in adequate and well-controlled studies in adult patients with PsA could be extrapolated to pediatric patients with PsA. This extrapolation of efficacy is based on appropriate scientific justification and data provided by the Applicant to support the expectation of similarity in exposure-response (E-R) between the 2 populations which could be product-specific. However, safety and immunogenicity, if relevant, in pediatric patients cannot be extrapolated from the studies in adults and would need to be supported by a reasonable safety database in pediatric patients with PsA or, with appropriate justification, a relevant pediatric patient population.
Pre-sBLA Meeting April 20, 2021	The Sponsor met with the FDA during a Type B, pre-supplemental BLA meeting to discuss the proposed content and format of a supplemental BLA for the treatment of pediatric subjects (b) (4) (b) (4) with pediatric PsA using an extrapolation-based approach. Agreement was reached on the key components of the proposed supplemental BLA and is the foundation for the extrapolation approach being presented in this submission.

Source: Summary based on meeting minutes (DARRTS)

As stated, no new clinical data are submitted as part of this supplement. However, references are made throughout this review to the completed clinical trials in adult and pediatric PsO and adult PsA. One study in pediatric Crohn's disease has been conducted and will be discussed briefly under the safety assessment. Detailed Agency reviews of these trials can be found under separate applications/supplements that led to approval for these indications. The relevant trials to this submission are described in Table 3.

Table 3. Ustekinumab Clinical Development in Adult and Pediatric Psoriasis, Adult Psoriatic Arthritis, and Pediatric Crohn's Disease

Study Name	Study Description	Sample Size
Adult psoriasis (reviewed under BLA 125261)		
C0743T08 PHOENIX 1	Phase 3, MC, R, DB, PC trial evaluating the efficacy and safety of ustekinumab in the treatment of subjects with **moderate to severe plaque-type psoriasis**	766

C0743T09 PHOENIX 1	Phase 3, MC, R, DB, PC trial evaluating the efficacy and safety of ustekinumab in the treatment of subjects with **moderate to severe plaque-type psoriasis**	1230
C0743T23 LOTUS	Phase 3, MC, R, DB, PC trial evaluating the efficacy and safety of ustekinumab in the treatment of **Chinese** subjects with **moderate to severe plaque-type psoriasis**	321
C0743T25 PEARL	Phase 3, MC, R, DB, PC trial evaluating the efficacy and safety of ustekinumab in the treatment of **Korean and Taiwanese** subjects with **moderate to severe plaque-type psoriasis**	121
CNTO1275PSO3009 PSTELLAR	Phase 3b, R, DB, AC, MC study to evaluate a "subject-tailored" maintenance dosing approach in subjects with **moderate to severe plaque psoriasis**	478
Pediatric psoriasis (reviewed under BLA 125261/s-138 and s-150)		
CNTO1275PSO3006 CADMUS	Phase 3, MC, R, DB, PC study evaluating the efficacy and safety of ustekinumab in the treatment of **adolescent subjects (ages ≥12 to <18 years) with moderate to severe plaque-type psoriasis** Group 1: half-standard dosage regimen (n=37) Group 2: standard dosage regimen (approved dose, n=36) Group 3a: PBO → half-standard dosage regimen at Week 12 (n=19) Group 3b: PBO → standard dosage regimen at Week 12 (approved dose, n=18)	110
CNTO1275PSO3013 CADMUS Jr	Phase 3, OL study to assess the efficacy, safety, and PK of SC ustekinumab in the treatment of **moderate to severe chronic plaque psoriasis in pediatric subjects ≥6 to <12 years of age** All patients received the standard dosage regimen.	44
Adult psoriatic arthritis (reviewed under BLA 125261/s-103 (b) (4))		
CNTO1275PSA3001 PSUMMIT1	Phase 3, MC, R, DB, PC trial of ustekinumab administered SC in subjects with **active psoriatic arthritis**	615
CNTO1275PSA3002 PSUMMIT2	Phase 3, MC, R, DB, PC trial of ustekinumab administered SC in subjects with **active psoriatic arthritis including those previously treated with anti-TNFα agents**	312
Pediatric Crohn's Disease		
CNTO1275CRD1001 UniStar	R,DB PK study of IV ustekinumab induction followed by SC ustekinumab maintenance in **pediatric patients (ages 6 to 17 years) with moderately to severely active Crohn's disease** Induction (IV ustekinumab) Group 1: 3 mg/kg for participants < 40g or 130 mg for participants ≥ 40 kg Group 2: 9 mg/kg for participants < 40g or 390 mg for participants ≥ 40 kg Maintenance (SC ustekinumab) 2 mg/kg participants < 40g or 90 mg for participants ≥ 40 kg	45

3. Clinical Pharmacology

In this application, the Applicant proposes a full extrapolation approach to support the efficacy of ustekinumab in patients with pediatric PsA [redacted] (b) (4) The extrapolation of established efficacy of ustekinumab from adult PsA population is based on PK-exposure matching between adult and pediatric PsA patients. No clinical trials or dedicated PK studies were conducted in pediatric patients with PsA. To support the proposed extrapolation approach for pediatric PsA, the following aspects were considered for extrapolation of efficacy approach:

1. Disease similarity between adult and pediatric patients with PsA
2. PK bridge between adult and pediatric patients
3. Extrapolation of efficacy in pediatric patients from adult PsA patients
4. Justification of the relevance of the safety data from pediatric patients with psoriasis.

The clinical pharmacology review is focused on the PK bridging to support the proposed extrapolation approach and the proposed dosing regimen of STELARA® for the treatment of pediatric patients [redacted] (b) (4) with active pediatric PsA.

Recommendations

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of BLA 125261/s-161 and finds the application acceptable to support approval from a clinical pharmacology perspective. The Division Signatory agrees with this assessment and recommendations.

Table 4: Clinical Pharmacology Recommendations

Review Issue	Recommendations and Comments
Evidence of effectiveness	Efficacy of ustekinumab in pediatric PsA is based on PK-exposure matching and extrapolation of established efficacy of ustekinumab in adult PsA population. Given the similarities in PK exposures in (1) adults, adolescents, and children with psoriasis, (2) adults with psoriasis and adults with PsA, and (3) adolescents with psoriasis and adults with PsA, it is expected that PK will be similar between adult PsA and pediatric PsA.
Evidence of safety	The PK exposure is expected to be similar in pediatric patients with psoriasis and PsA, supporting the relevance of safety data from pediatric psoriasis patients (6- to17- years-old) to the pediatric PsA population in the same age group.

General dosing instructions	Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter: • less than 60 kg: 0.75 mg/kg • 60 kg or more: 45 mg • greater than 100 kg with co-existent moderate-to-severe plaque psoriasis: 90 mg

Is the PK bridging between adults and pediatrics patients adequate to support the extrapolation of efficacy?

Yes. The PK bridge is established to support the extrapolation of the efficacy established in adults with PsA to pediatric patients with PsA.

Extrapolation Framework for pediatric PsA

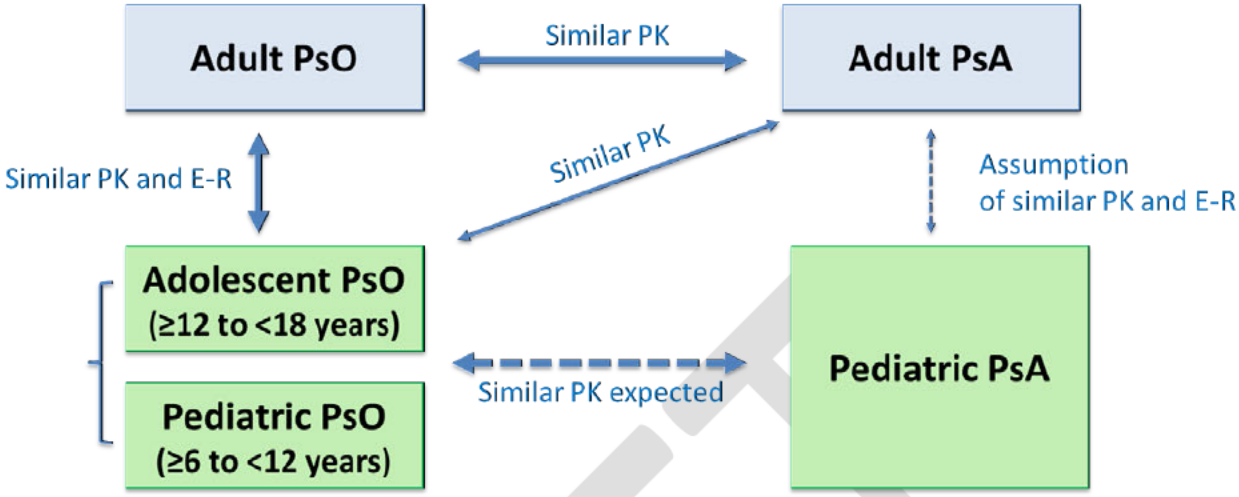
The data from the pediatric subjects with psoriasis as well as data from adult patients with psoriasis and PsA form the basis for the use of extrapolation for this application. In the two pediatric psoriasis studies, there were 7 participants who also had pediatric PsA, 4 of whom received the standard dosage of ustekinumab (approved dosage for pediatric PsO). While very limited, the data from these pediatric PsA subjects provided supportive evidence.

The following PK analyses were performed to support the PK bridge between adult and pediatric patients with PsA:

- Comparisons of ustekinumab PK exposure between pediatric psoriasis and adult psoriasis
- Comparisons of ustekinumab PK exposure between adolescent psoriasis and adult PsA
- Comparisons of ustekinumab PK exposure between adult psoriasis and adult PsA
- Comparisons of ustekinumab PK exposure between pediatric psoriasis (with and without pediatric PsA) and adult PsA

Figure 1 depicts the extrapolation approach for pediatrics with PsA. PK is similar in adult patients with psoriasis and adult patients with psoriatic arthritis; therefore, the disease is not expected to have a significant impact on PK. The PK in pediatric patients with psoriasis and pediatric patients with PsA are expected to be similar. To establish the PK bridge to pediatric patients with PsA, PK in pediatric patients with PsO and adult PsA/PsO were considered. Once the PK bridge is established, borrowing efficacy from adequate and well-controlled studies in adult PsA patients is scientifically justified if the disease is sufficiently similar between the two populations. In addition, safety information from other relevant pediatric populations like PsO can be leveraged. For disease similarity and justification of the relevance of safety data from pediatric PsO, refer to Sections 2 (Background) and 5 (Safety).

Figure 1. Extrapolation Approach to Support the Use of Ustekinumab in Pediatric PsA



Source: FDA Reviewer created version of Figure 2 in Clinical Overview

Similar Exposure-Response Relationship in Pediatric Psoriasis and Adult Psoriasis

At similar exposure, ustekinumab has demonstrated similar efficacy in pediatric patients as in adult patients in the related indication of PsO, which provides contextual information to further support the PK-based extrapolation approach. The exposure-response relationship of ustekinumab in adolescent and adult subjects with psoriasis was explored using data from the adolescent subjects in CNTO1275PSO3006 and the adult subjects in C0743T08/C0743T09 (BLA 125261/s-138). The exposure response-relationship for the primary efficacy analyses of PGA 0/1 and PASI 75 were generally comparable between adolescent and adult subjects with similar response rate at comparable exposure between adult and pediatric PsO patients (Figure 2 and

Figure 3, respectively). For secondary efficacy endpoint such as PASI 90, and PASI 100, the pediatric PsO subjects had better response rates compared to adults (

Figure 3). Similarly, the clinical responses to ustekinumab treatment (at comparable exposures) are similar between adolescents and younger pediatric patients (6-11 year old) with PsO (BLA 125261, s-150 pediatric psoriasis, data not shown).

Overall, these results suggest that the exposure-response relationship is similar between pediatric and adult subjects with psoriasis, further supporting the PK-based extrapolation approach and the expectation that these exposures will result in similar efficacy between adult and pediatric patients with PsA, albeit on different aspects of the disease, i.e. musculoskeletal.

Figure 2. Exposure-response Relationships of PGA 0/1 in Pediatric and Adult Subjects With Psoriasis by Serum Ustekinumab Concentration Quartile Levels at Week 12 (Upper Panel) and Week 28 (Lower panel) (Studies CNTO1275PSO3006 and C0743T08/C0743T09)

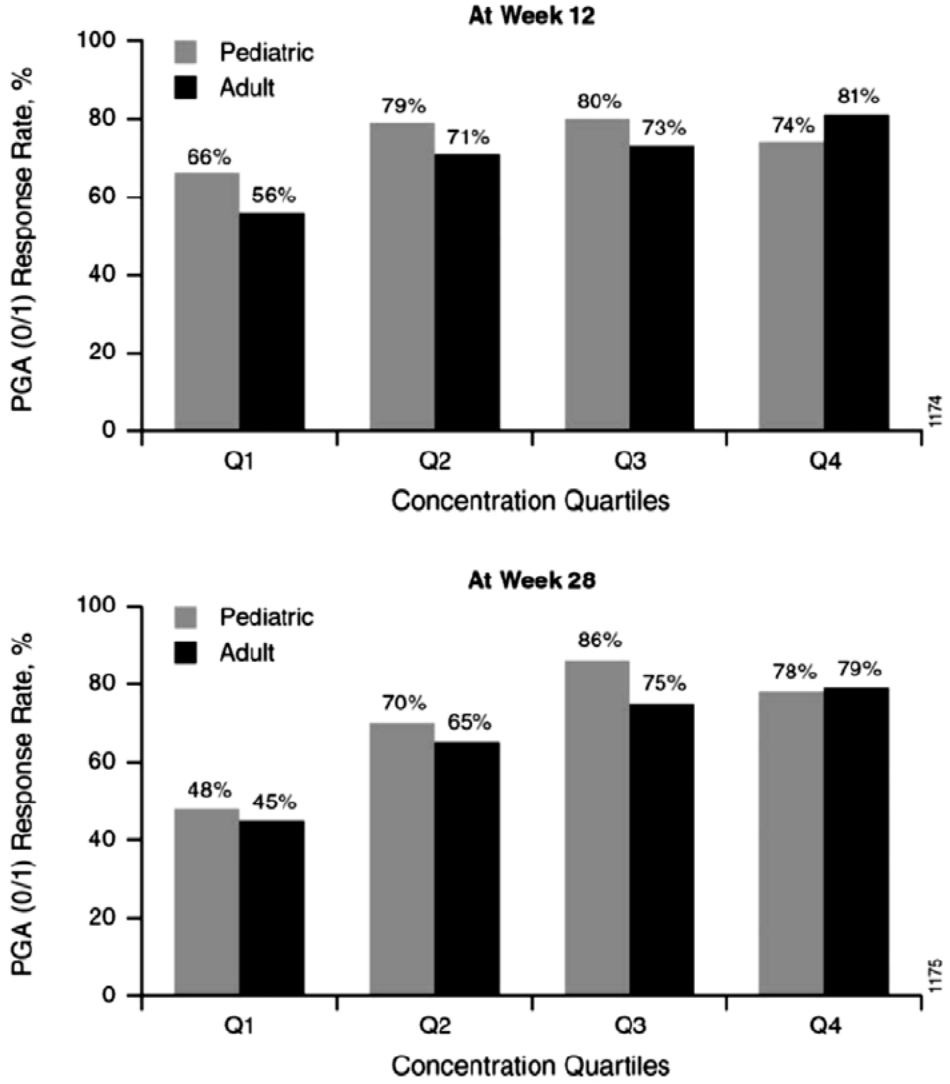
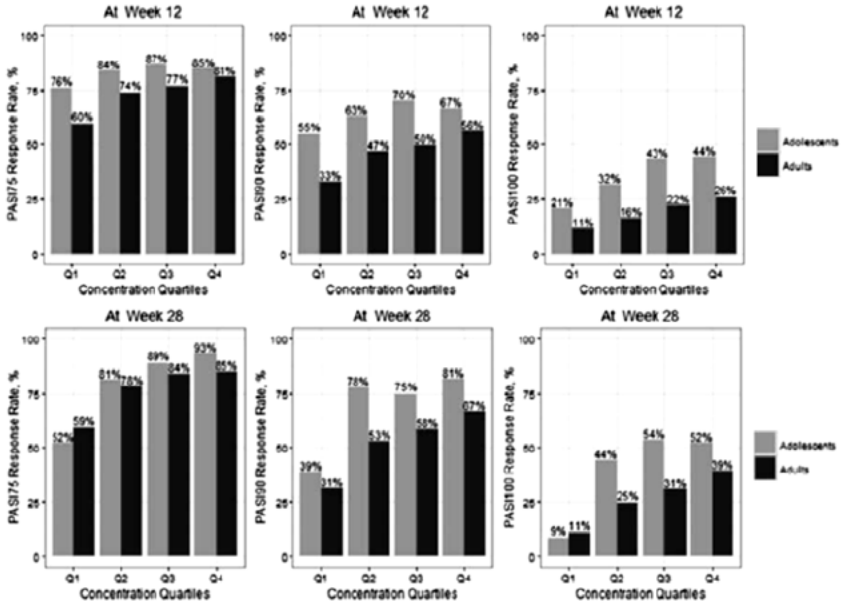


Figure 3. Exposure-response relationships of PASI 75, PASI 90 and PASI 100 of pediatric and adult subjects with ustekinumab concentration quartiles from studies CNTO1275PSO3006, C0743T08, and C0743T09.



Available PK data to support the bridging:

The PK data from the following studies (Table 5) were considered for PK bridging in pediatrics with PsA:

- Ustekinumab demonstrated robust efficacy in adults with plaque-type moderate to severe psoriasis (phase 3 studies C0743T08 and C0743T09) and in adults with active PsA (phase 3 studies CNTO1275PSA3001 and CNTO1275PSA3002) which led to approval of ustekinumab for use in these indications.
- Two phase 3 studies in pediatric psoriasis (CNTO1275PSO3006 in participants ≥ 12 to < 18 years of age and CNTO1275PSO3013 in participants in ≥ 6 to < 12 years of age) which demonstrated efficacy in the pediatric age range and resulted in the approval of ustekinumab for use in pediatric psoriasis patients age 6 years and older.

The approved ustekinumab dosing in adult psoriasis and adult PsA is the same except that for adult PsA, only patients weighing >100 kg with co-existent moderate-to-severe plaque psoriasis can receive a 90 mg dose. Previous studies conducted in patients with psoriasis and PsA that are utilized by the Applicant in the proposed extrapolation approach are summarized in Table 5. Due to a change in the bioanalytical assays used to measure ustekinumab serum concentration in the pivotal phase 3 adult PsO studies compared to the rest of the studies in the ustekinumab clinical development program, other phase 3 studies (C0743T23, C0743T25 and CNTO1275PSO3009) in adult PsO utilizing the same MSD PK assay were also used for PK comparisons.

Table 5: Ustekinumab Psoriasis and Psoriatic Arthritis Phase 3 Studies

Study	Study acronym	Population	PK Assay	Sample size
C0743T08	PHOENIX 1	Adult psoriasis	Bioveris	766
C0743T09	PHOENIX 2	Adult psoriasis	Bioveris	1,230
C0743T23	LOTUS	Adult psoriasis (China)	MSD	321
C0743T25	PEARL	Adult psoriasis (Korea, Taiwan)	MSD	121
CNTO1275PSO3006	CADMUS	Adolescent psoriasis (≥12 to <18 years)	MSD	110
CNTO1275PSO3013	CADMUS Jr	Children with psoriasis (≥6 to <12 years)	MSD	44
CNTO1275PSO3009	PSTELLAR	Adult psoriasis	MSD	478
CNTO1275PSA3001	PSUMMIT 1	Adult psoriatic arthritis	MSD	615
CNTO1275PSA3002	PSUMMIT 2	Adult psoriatic arthritis	MSD	312

Source: Table 4 in Clinical Overview

Pharmacokinetics:

The PK of ustekinumab in adolescents and children with psoriasis as well as in adults with psoriasis and PsA have been previously described in prior submissions (BLA 125261 adult psoriasis, BLA 125261, s-103 (b) (4) adult psoriatic arthritis, BLA 125261, s-138 adolescent psoriasis, and BLA 125261, s-150 pediatric psoriasis). To support the proposed extrapolation approach for pediatric PsA, the following PK analyses were performed:

- Comparisons of ustekinumab PK exposure between pediatric psoriasis and adult psoriasis
- Comparisons of ustekinumab PK exposure between adolescent psoriasis and adult PsA
- Comparisons of ustekinumab PK exposure between adult psoriasis and adult PsA
- Comparisons of ustekinumab PK exposure between pediatric psoriasis (with and without pediatric PsA) and adult PsA

Given the similarities in PK exposures with similar doses seen in (1) adults, adolescents and children with psoriasis, (2) adults with psoriasis and adults with PsA, and (3) adolescents with psoriasis and adults with PsA, it is expected that PK and E-R should be similar between adult PsA and pediatric PsA (**Figure 1**). Additionally, from the pediatric psoriasis PK data in adolescents and children, it is expected that weight-based dosing should provide comparable PK exposures across the age groups from 5 to 17 years. With 2 completed pediatric ustekinumab studies in psoriasis, a closely related disease to PsA, as well as 1 completed pediatric study in Crohn's disease, and further studies in pediatric inflammatory bowel disease pending, the Applicant states that there is an adequate amount of ustekinumab data in pediatric patients and an adequate knowledge about PK exposure to support extrapolation.

Similar PK Exposure in Pediatric Psoriasis and Adult Psoriasis

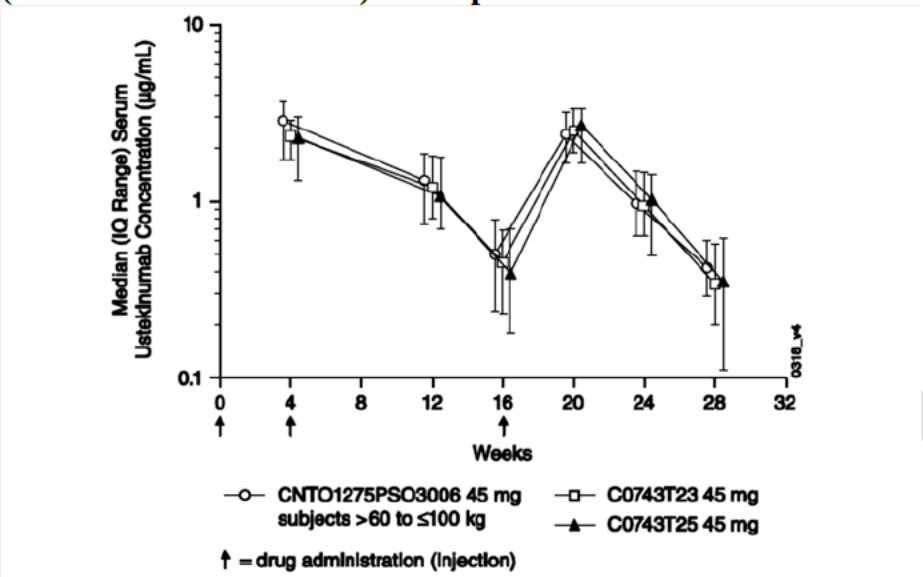
In study CNTO1275PSO3006, a weight-adjusted standard dosage (0.75 mg/kg for participants weighing ≤ 60 kg, 45 mg for participants weighing > 60 kg to ≤ 100 kg, and 90 mg for

participants weighing > 100 kg) and half-standard dosage (0.375 mg/kg for participants weighing ≤ 60 kg, 22.5 mg for participants weighing >6 0 kg to ≤ 100 kg, and 45 mg for participants weighing > 100 kg) were evaluated in adolescent participants with psoriasis. Similar PK was observed between adolescents and adults with psoriasis when compared with adult psoriasis studies C0743T23 and C0743T25 in which the same PK assay method was used for bioanalysis (Figure 3, Panel A). In CNTO1275PSO3013, the same weight-based standard dosage used in CNTO1275PSO3006 was evaluated and provided similar ustekinumab exposure in children ≥ 6 to < 12 years of age as compared with adolescent participants ≥ 12 to < 18 years of age (
Figure 4, Panel B; PedJrPsO/Mod2.7.2/App2).

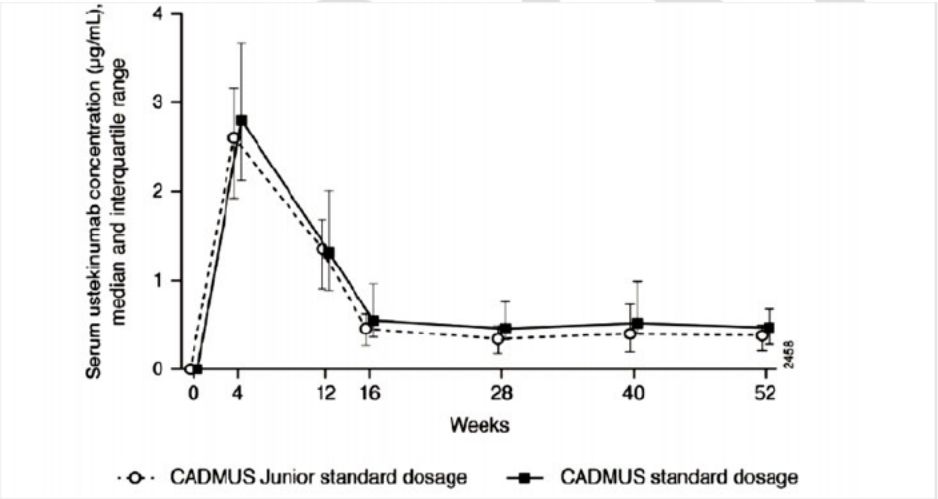
APPEARS THIS WAY ON ORIGINAL

Figure 4. Median (IQ range) Serum Ustekinumab Concentrations Over Time

Panel A: Adolescent (CNTO1275PSO3006; Participants > 60 kg to ≤ 100 kg) and Adult (C0743T23 and C0743T25) Participants With Psoriasis



Panel B: Adolescents (CNTO1275PSO3006) and Children (CNTO1275PSO3013) With Psoriasis



Source: Figure 3 in Clinical Overview

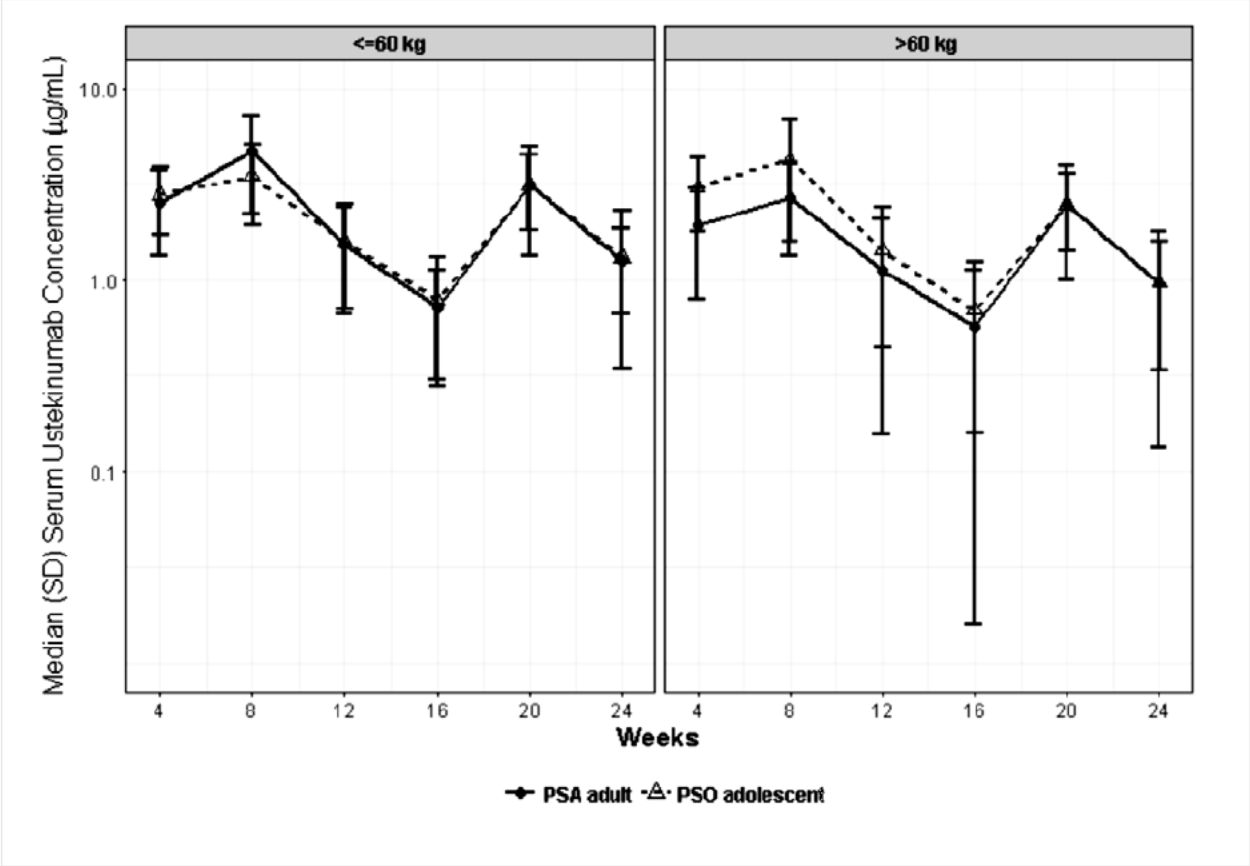
Similar PK Exposure in Adolescent Psoriasis and Adult Psoriatic Arthritis

To evaluate the similarity in PK between pediatric psoriasis and adult PsA, the medians (±SD) of ustekinumab concentrations over time were compared between adolescent participants with psoriasis who received the standard dosage (0.75 mg/kg for participants ≤ 60 kg, 45 mg for

participants > 60 kg but ≤ 100 kg, and 90 mg for participants >100 kg; CNTO1275PSO3006) and adult participants with PsA who received the standard (approved) adult dosage (45 mg for participants ≤ 100 kg, and 90 mg for participants > 100 kg; CNTO1275PSA3001 and CNTO1275PSA3002;
Figure 5). The same PK assay was used to determine the serum ustekinumab concentrations in these studies.

In general, for participants with body weight ≤ 60 kg, serum ustekinumab concentration-time profiles in pediatric participants with psoriasis were similar to those in adult participants with PsA. For participants with body weight > 60 kg, median serum ustekinumab concentrations in pediatric participants with psoriasis appeared to be numerically higher than those in adult participants with PsA. This is likely because pediatric participants with body weight > 60 kg receiving fixed dosages (45 mg or 90 mg) in CNTO1275PSO3006 have an overall lower body weight distribution compared to the participants with body weight > 60 kg in the adult PsA studies. When adolescents and adult participants have similar body weights, similar ustekinumab exposures would be expected following the administration of the same fixed dose (e.g., 45 mg).

Figure 5. Median (±SD) Serum Ustekinumab Concentrations Over Time through Week 24 in Pediatric Participants with Psoriasis (CNTO1275PSO3006) and Adult Participants with PsA (CNTO1275PSA3001, CNTO1275PSA3002)



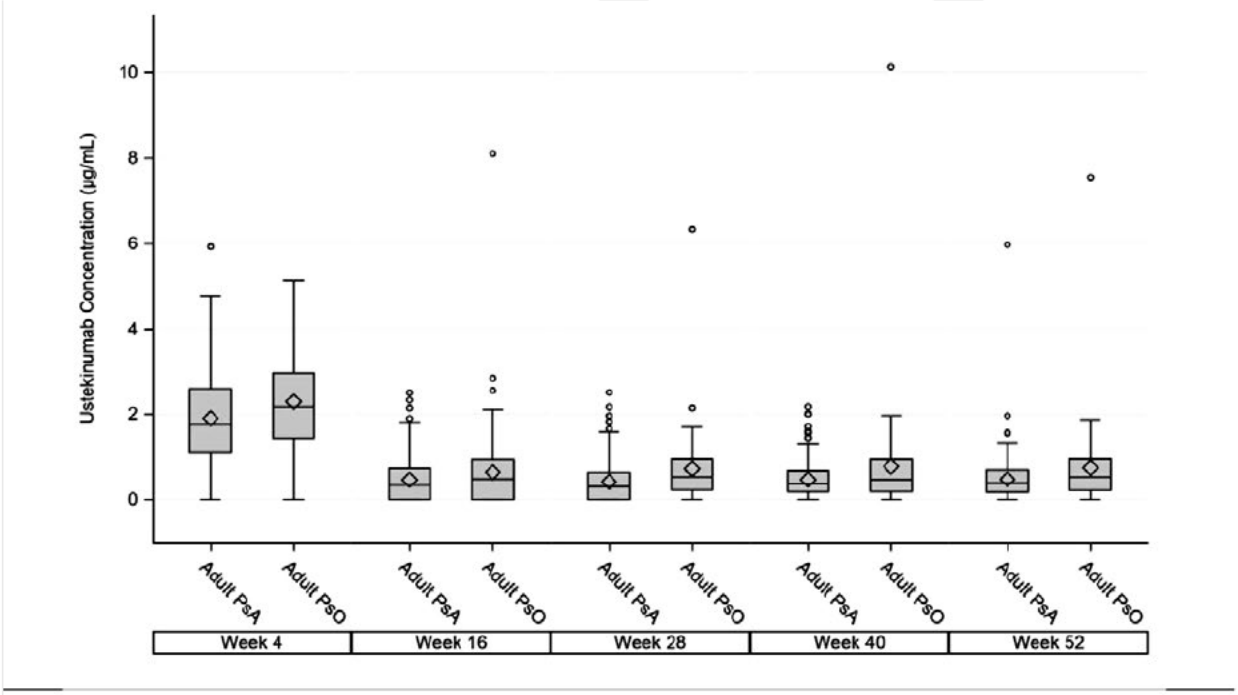
Source: Figure 5 in Clinical Overview

Similar PK Exposure in Adult Psoriasis and Adult Psoriatic Arthritis

Due to differences in the PK assay between the pivotal phase 3 adult psoriasis studies (C0743T08 and C0743T09) and the pivotal phase 3 adult PsA studies (CNTO1275PSA3001 and CNTO1275PSA3002), phase 3 Study CNTO1275PSO3009 (PSTELLAR) was selected to evaluate the similarity in PK between adult psoriasis and adult PsA. The descriptive statistics of ustekinumab concentrations over time are presented in
Figure 6 for adult psoriasis (CNTO1275PSO3009) and adult PsA (CNTO1275PSA3001) who received the standard (approved) adult dosage (45 mg for participants ≤100 kg).

In general, serum ustekinumab concentrations were similar between adult participants with PsA and adult participants with psoriasis.

Figure 6. Box Plot of Steady-State Trough Serum Ustekinumab Concentrations in Adult PsA Subjects from Study CNTO1275PSA3001 and Adult PsO Subjects from Study CNTO1275PSO3009



CNTO1275PSA3001: Only subjects who had the Ustekinumab 45 mg dose.
CNTO1275PSO3009: Only subjects who had the Ustekinumab 45 mg dose.

Source: Figure 6 in Clinical Overview

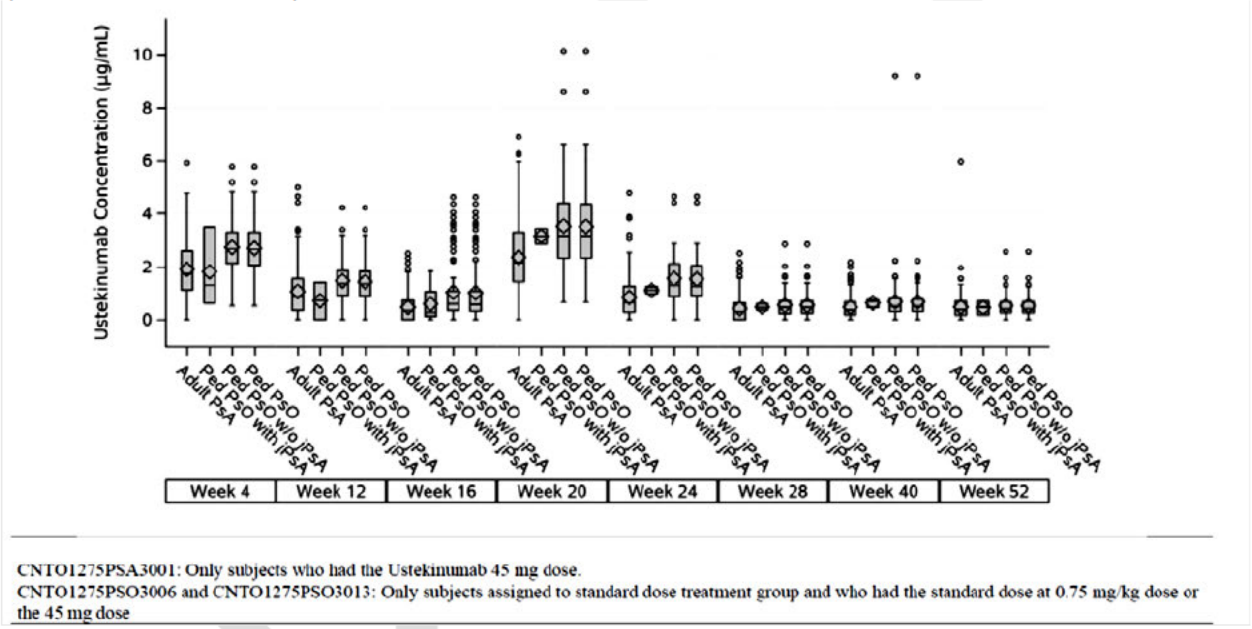
Similar PK Exposure in Pediatric Psoriasis (with and without Pediatric Psoriatic Arthritis) and Adult Psoriatic Arthritis

As seen with the PK data from adolescent psoriasis compared with PK data from adult psoriasis and adult PsA, and with the similarity of PK exposures between adolescents and

children with psoriasis, it is expected that the same weight-adjusted dosing regimen should also result in similar PK exposures in participants with pediatric PsA.

In pediatric psoriasis studies CNTO1275PSO3006 and CNTO1275PSO3013, there were 7 psoriasis participants with pediatric PsA of whom 4 participants received the standard dosage. The ustekinumab concentrations in these pediatric psoriasis participants with pediatric PsA who received the standard dosage (ages 7, 14, 16, and 16 years) were compared with the rest of the pediatric psoriasis patients (age 6 to 17 years) as well as with adult PsA participants from CNTO1275PSA3001 who received the standard dosage (Figure 7). Although the number of pediatric psoriasis participants with pediatric PsA is small, the overlapping steady-state trough serum ustekinumab concentrations through Week 52 support the observation that PK exposure is similar with the pediatric psoriasis, pediatric PsA and adult PsA participants.

Figure 7. Box Plot of Steady-State Trough Serum Ustekinumab Concentrations in Pediatric Participants with Psoriasis with and without Pediatric PsA (CNTO1275PSO3006 /CNTO1275PSO3013) and Adult Participants with PsA (CNTO1275PSA3001)



CNTO1275PSA3001: Only subjects who had the Ustekinumab 45 mg dose.
CNTO1275PSO3006 and CNTO1275PSO3013: Only subjects assigned to standard dose treatment group and who had the standard dose at 0.75 mg/kg dose or the 45 mg dose

Source: Figure 7 in Clinical Overview

(b) (4)

The Applicant proposes (b) (4) the treatment of pediatric psoriasis (6 years and older). (b) (4)

(b) (4)

Source: Figure 8 in Clinical Overview

Overall, based on (1) the disease similarity of pediatric PsA and adult PsA (2) the similarity in PK of ustekinumab between adults with psoriasis and adults with PsA, as well as (3) the similarity in PK of ustekinumab between adults with PsA and pediatric psoriasis (including participants with pediatric PsA), it is expected that PK will be similar between adult PsA and pediatric PsA. Also, the observed PK in the 4 pediatric psoriasis participants with pediatric PsA is comparable to the rest of the pediatric psoriasis participants and to adult PsA, which is consistent with this conclusion. The PK bridge would support the extrapolation of established efficacy of ustekinumab in adult PsA population to pediatric PsA population.

(b) (4)

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen for patients with pediatric PsA is a weight-based dosing recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter:

- less than 60 kg: 0.75 mg/kg
- 60 kg or more: 45 mg
- greater than 100 kg with co-existent moderate-to-severe plaque psoriasis: 90 mg

The proposed dosing regimen for patients with pediatric PsA is similar to that approved for pediatric psoriasis except that for pediatric PsA, only patients weighing >100 kg with co-existent moderate-to-severe plaque psoriasis can receive a 90 mg dose. The approved ustekinumab dosing in adult and pediatric psoriasis is the same except for weight-based dosing in the smaller children (<60 kg) in order to achieve a comparable exposure to older children, adolescents, and adults which is also proposed for the dosing of ustekinumab in patients with pediatric PsA.

Based on the similarity in PK between adult psoriasis and adult PsA and the similarity in PK between pediatric, adolescent, and adult psoriasis, it is expected that the PK in pediatric PsA will be similar to that observed in adult patients with PsA. Therefore, the dosing regimen proposed by the Applicant for pediatric PsA appears reasonable from a Clinical Pharmacology perspective.

Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

A weight-based dosing is proposed for patients with pediatric PsA. In previous studies, when given the same dose, adult subjects with psoriasis or psoriatic arthritis weighing more than 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing 100 kg or less. The median trough serum concentrations of ustekinumab in subjects of higher weight (greater than 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (100 kg or less) in the 45 mg group. However this observation did not warrant dose adjustments in adult patients >100kg with PsA, as discussed in the review of BLA125261/s-103 (Dr. Ping Ji, DAARTS date 8/13/2013) and respectively would not necessitate dose adjustments in pediatric patients with PsA. The proposed weight-based dosing regimen appears reasonable.

4. Clinical/Statistical- Efficacy

No new clinical data are submitted in this supplement. However, the efficacy of ustekinumab in the treatment of pediatric PsA is extrapolated from the efficacy established for ustekinumab in adequate and well-controlled studies in adult PsA (CNTO1275PSA3001 and CNTO1275PSA3002, described in Table 3.), previously reviewed under BLA 125261, s-103 (b) (4) See Section 3 (Clinical Pharmacology) for review of the PK bridge that supports the extrapolation of efficacy. See Section 2 (Background) for discussion of the adult and pediatric

PsA as similar conditions. These form the basis of extrapolation of substantial evidence of effectiveness of ustekinumab in pediatric PsA.

5. Safety

The safety of ustekinumab in pediatric patients with PsA is supported by the safety observed in pediatric psoriasis, approved for patients 6 years of age and older. Pediatric psoriasis is a relevant condition to pediatric PsA, as described in Section 2 (Background); PsO frequently occurs concomitantly with the PsA. Table 3 describes the 2 clinical trials conducted in pediatric psoriasis (studies CNTO1275PSO3006 and CNTO1275PSO3013). The PK exposure is expected to be similar between pediatric PsO and pediatric PsA, supporting the relevance of safety data from pediatric PsO to the pediatric PsA population.

The safety in studies CNTO1275PSO3006 and CNTO1275PSO3013 were reviewed under BLA 125261 s-138 and s-150, respectively, and reflected in the currently approved product labeling. See clinical reviews for those supplements for details regarding the safety database. In general, the safety profile in patients ≥ 6 years to < 18 years with PsO were consistent with that of adults with PsO.

- In study CNTO1275PSO3006 (adolescent patients), one death occurred in a 16-year-old female in the half-standard dosage group who died from injuries in a motor vehicle accident. One serious adverse event (SAE) occurred in the 12-week placebo-controlled period; a 12-year-old male in the half-standard dosage group was hospitalized for an exacerbation in psoriasis. Through Week 60, 4 additional non-fatal SAEs occurred: leukopenia in a 15-year-old female in the half-standard dosage group; pyelonephritis in a 17-year-old female in the half-standard dosage group; acute allergic contact dermatitis in a 17-year-old female in the half-standard dosage group; otitis media in a 16-year-old female in the standard dosage group. No adverse events (AEs) led to discontinuation in the 12-week placebo-controlled period. Through Week 60, there were 3 non-fatal AEs that led to discontinuation (all in the half-standard dosage group): 13-year-old male with toxoplasmosis infection and 2 patients (15-year-old male and 17-year-old males) with worsening in psoriasis. Infections occurred in all treatment arms during the placebo controlled period: urinary tract infection, acute tonsillitis (n=2), and nasopharyngitis in the placebo group; pharyngitis in the half-standard dosage group; pharyngitis streptococcal and urinary tract infection in the standard dosage group. Through Week 60, 28 total patients who received any dose of ustekinumab reported an infection. The types of infections that were reported more than once included pharyngitis (n=5), pharyngitis streptococcal (n=5), pyelonephritis (n=3), tooth abscess (n=3), upper respiratory tract infection (n=3), bronchitis (n=2), and nasopharyngitis (n=2). One injection site reaction (mild, injection site hemorrhage) was reported in a patient in the standard dosage group. The most common AEs during the placebo-controlled period were nasopharyngitis, upper respiratory tract, and headache. These were similar through Week 60.
- In study CNTO1275PSO3013 (pediatric patients ages ≥ 6 to < 12 years-old), no deaths occurred. Three SAEs were reported: left eye tear duct and lower eyelid injury

requiring surgery in a 9-year-old male, attention deficit hyperactivity disorder (ADHD) requiring hospitalization in a 6-year-old female, and infectious mononucleosis in a 6-year-old female. No AEs leading to discontinuation were reported. Infections were reported in 29 patients; the most common of which were nasopharyngitis (n=11), pharyngitis (n=6), and upper respiratory tract infection (n=6). Six patients reported injection-site reactions; all were mild with erythema being the most common (n=6). The most common AEs in study 3013 were similar to that in study 3006: nasopharyngitis (n=11), pharyngitis (n=6), and upper respiratory tract infection (n=6).

As previously discussed, 7 patients with PsA were enrolled in the pediatric PsO clinical trials. Six of these patients reported AEs, and no SAEs were reported. These AEs were consistent with the rest of the pediatric PsO program.

- In study CNTO1275PSO3006, 5 patients with PsA reported AEs. The only AEs deemed to be possibly related to ustekinumab occurred in a patient in the half-standard dosage group who reported bilateral ankle edema, worsening psoriasis, and vasculopathy.
- In study CNTO1275PSO3013, 1 patient with PsA reported AEs, of which several reports of injection-site erythema were determined to be very likely related to ustekinumab.

Additionally, the Applicant summarized the preliminary safety assessment from a pediatric Crohn's disease study in patients ages ≥ 6- to < 18-years-old (study CNTP1275CRD1001, described in Table 3) as being similar to the adult Crohn's disease population.

(b) (4)

6. Advisory Committee Meeting

An advisory committee meeting was not scheduled for this submission. No issues were identified warranting advisory committee input.

7. Pediatrics

This supplement seeks to expand the PsA indication (b) (4) (b) (4) As described in the regulatory history in Section 2 (Background) of this memo, ustekinumab was approved for adult patients with psoriatic arthritis in September 2013. At the time of approval, a study in pediatric patients with PsA was waived because studies necessary to independently establish efficacy in pediatric patients with PsA were considered impossible or highly impracticable, as there are too few children with the disease/condition to study. However, after the FDA/M-CERSI public workshop, the Agency reconsidered its approach to the pediatric assessment for PsA and agreed that information could be provided based on bridging available PK in pediatric patients to support the extrapolation of efficacy from the adult PsA indication and leveraging safety information for other available and relevant pediatric populations. The Applicant was informed of this evolution in approach. See also regulatory history in Section 2 for details regarding the Applicant's subsequent pre-sBLA meeting and submission for pediatric patients with PsA.

The review team notes that the Applicant is planning to conduct study CNTO1275JPA3001, an open-label, PK, efficacy, safety, and immunogenicity study of ustekinumab and guselkumab in pediatric patients ages ≥ 5 to < 18 years, requested by the European Medicines

Agency (EMA). The study will be comprised of 2 cohorts (n=30 in ustekinumab group and n=30 in guselkumab group) for a total treatment duration of 52 weeks. The review team notes that this study may provide clinical experience with ustekinumab and JIA, (b) (4) (b) (4) However, data from this study would not be required for the assessment of the benefit-risk in the current submission which relies on the understanding that pediatric PsA and adult PsA have similar pathophysiology, clinical manifestations, and therapeutic targets. Therefore, efficacy can be extrapolated from adult PsA by bridging exposure response and PK from relevant indications. Safety would also be leveraged from relevant indications.

The Pediatric Review Committee (PeRC) reviewed the submission on June 14, 2022. Understanding that pediatric and adult PsA are similar conditions, the PeRC agreed with the Division that efficacy can be extrapolated from adult to pediatric PsA, and safety and PK can be leveraged from relevant populations such as pediatric patients with psoriasis. The PeRC also agreed with the Division (b) (4) Therefore, the PeRC supported the Division's assessment that that the available information supports the use of ustekinumab for the treatment of psoriatic arthritis in pediatrics 6 years of age and older.

8. Other Relevant Regulatory Issues

This section may include discussion on other issues (if not addressed in previous sections):

- Division of Pediatric and Maternal Health (DPMH)

  DPMH reviewed the efficacy supplement, provided guidance at the meeting with PeRC (described above in Section 7), and recommended revisions to the PI (described below in Section 9).

  In addition, DPMH separately discussed the concept of safety extrapolation (b) (4)

  Applicant's proposed extrapolation approach will support the approval for treatment of PsA in pediatric patients 6- to 17-years-old.

- Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA reviewed the human factors (HF) validation study report and use-related risk analysis (URRA) for the currently approved prefilled syringe. DMEPA concluded that, because of the HF study methodology flaws and the lack of anthropometric data, they could not draw a conclusion regarding whether the user interface supports safe and effective use of the product in the intended user population, including adolescent patients with pediatric PsA who may self-administer the product. DMEPA consulted the Center for Devices and Radiological Health (CDRH) for input on the anthropometric data and force specification for the STELARA® PFS. CDRH deferred acceptability to DMEPA but stated that, "From the CDRH perspective, the sponsor's justification is appropriate, given the limitations on eligible participants given the size of the patient population. The additional mitigation to require determination of the ability to self-administer is given to the treating physician." DMEPA, in turn, deferred the determination to the clinical division (DRTM) as to whether the potential risk associated with the lack of sufficient HF data in pediatric PSA patients (or suitable surrogate pediatric patients) negatively impacts the potential benefits in the proposed user population.

DRTM reviewed and acknowledged the DMEPA's assessment. DRTM has also considered that, irrespective of whether the patient is an adult or child with PsA, it is expected that the patient will only self-administer ustekinumab when willing to do so, having received appropriate training, and having demonstrated the ability to self-inject. The current USPI (Section 2.4 General Considerations for Administration) includes the following statements:

STELARA® is intended for use under the guidance and supervision of a physician. STELARA® should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. The appropriate dose should be determined by a healthcare provider using the patient's current weight at the time of dosing. In pediatric patients, it is recommended that STELARA® be administered by a healthcare provider. If a physician determines that it is appropriate, a patient may self-inject or a caregiver may inject STELARA® after proper training in subcutaneous injection technique. Patients should be instructed to follow the directions provided in the Medication Guide.

Considering the above contextual information, DRTM concludes that no additional HF studies are needed in pediatric PsA or a suitable surrogate pediatric patient population for this application. Current labeling is appropriate and sufficient to ensure the safety and effective use of the PFS in pediatric PsA.

- Any other outstanding regulatory issues

  None.

9. Labeling

The table below presents a high-level summary of labeling revisions.

Section	Labeling Discussions
1 Indications and Usage	(b) (4) indication. The Agency is updating labeling of biologics to omit this statement from the Indication, as it is noninformative. The Agency recommended removal of this statement (b) (4) (b) (4) The Applicant agreed.
2 Dosage and Administration	The Agency agreed with the proposed dosage and administration. The Agency recommended presentation of the weight-tiered dosing in a table format (consistent with the presentation of pediatric psoriasis). The Applicant agreed with the change in presentation.
7 Drug Interactions	The Applicant proposed (b) (4) the following statement:

	(b) (4) (b) (4) The (b) (4) Agency did not agree The Applicant agreed.
8 Use in Specific Populations	In Section 8.4 (Pediatric Use), the Applicant proposed addition of language (b) (4) The Agency recommended the following revised language: *The safety and effectiveness of STELARA® have been established for treatment of psoriatic arthritis in pediatric patients 6 to 17 years old.* *Use of STELARA® in these age groups is supported by evidence from adequate and well-controlled studies of STELARA® in adults with psoriasis and PsA, pharmacokinetic data from adult patients with psoriasis, adult patients with PsA and pediatric patients with psoriasis, and safety data from two clinical studies in 44 pediatric patients 6 to 11 years old with psoriasis and 110 pediatric patients 12 to 17 years old with psoriasis. The observed pre-dose (trough) concentrations are generally comparable between adult patients with psoriasis, adult patients with PsA and pediatric patients with psoriasis, and the PK exposure is expected to be comparable between adult and pediatric patients with PsA.* *The safety and effectives of STELARA® have not been established in pediatric patients less than 6 years old with psoriatic arthritis.* The Applicant agreed with the revisions.
12 Clinical Pharmacology	The Applicant proposed new language in Section 12.3 (Pharmacokinetics) under the specific populations of pediatrics. The Agency recommended revisions (b) (4) (b) (4) and this

	approval is based on assumed comparable PK in pediatric patients with PsA and pediatric patients with psoriasis. The Agency recommended the following revised language: *Overall, the observed steady-state ustekinumab trough concentrations in pediatric patients with psoriasis were within the range of those observed for adult patients with psoriasis and adult patients with PsA after administration of STELARA®.* The Applicant agreed to the revised language. However, they proposed adding the phrase (b) (4) The Agency did not agree with this addition. (b) (4) The Applicant agreed.
14 Clinical Studies	The Applicant proposed inclusion of a statement (b) (4) The Agency noted that this information is not appropriate for Section 14 which should describe clinical trials data; rather, it would be more appropriate for Section (b) (4) (see language described above). The Applicant agreed with removal of this statement.

All labeling revisions have been reviewed by the labeling consultants and agreed upon with the Applicant.

10. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No new risk management plans are submitted as part of this supplement. As no new safety signals have been identified, a Risk Evaluation and Management Strategy (REMS) is not recommended for this product.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The team notes that ustekinumab has been approved for pediatric patients with PsO 6 years of age and older, similar to the age range to be approved for PsA and the benefit-risk of ustekinumab in the patient PsA population can be characterized and described in the product labeling without further assessment with a postmarketing requirement or postmarketing commitment.

11. Recommended Comments to the Applicant

The regulatory action is Approval. There are no comments to be communicated to the 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/

RAJ NAIR
07/29/2022 10:04:11 AM

SUZETTE W PENG
07/29/2022 10:26:07 AM

NISHA V KWATRA
07/29/2022 10:27:42 AM

YOUWEI N BI
07/29/2022 10:32:30 AM

JIANMENG CHEN
07/29/2022 11:13:29 AM

NIKOLAY P NIKOLOV
07/29/2022 11:15:31 AM