BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplement
Application Number(s)	BLA 125118 (b) (4) S-250
Priority or Standard	Standard
Submit Date(s)	December 30, 2022
Received Date(s)	December 30, 2022
PDUFA Goal Date	October 30, 2023
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM)
Review Completion Date	October 27, 2023
Established/Proper Name	Abatacept
Trade Name	Orencia
Pharmacologic Class	Selective costimulation modulator
Applicant	Bristol Myers Squibb Company
Dosage form	Intravenous infusion: 250mg lyophilized powder in a single-dose vial Subcutaneous injection: 50mg/0.4mL, 87.5mg/0.7mL, 125 mg/mL solution in single-dose prefilled syringes; 125mg/mL solution in a single-dose prefilled autoinjector
Applicant proposed Dosing Regimen	(b) (4) • Subcutaneous Use for PsA in Pediatric Patients ≥2 Years Old 10 to <25 kg: 50 mg QW; 25 to <50 kg: 87.5mg QW; ≥50 kg: 125 mg QW
Applicant Proposed Indication(s)/Population(s)	(b) (4) <u>S-250</u> SC: Pediatric patients 2 years of age and older with active PsA.
Recommendation on Regulatory Action	(b) (4) <u>S-250: Approval</u> SC: Pediatric patients 2 years of age and older with active PsA.
Recommended Indication(s)/Population(s) (if applicable)	Patients 2 years of age and older with active psoriatic arthritis (PsA indication expanded to include pediatric patients 2 years of age and older)

Recommended Dosing Regimen	Subcutaneous Use for PsA in Pediatric Patients ≥2 Years Old 10 to <25 kg: 50 mg QW; 25 to <50 kg: 87.5mg QW; ≥50 kg: 125 mg QW

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OPQ=Office of Pharmaceutical Quality
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
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
DHOT	Division of Hematology Oncology Toxicology
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 Conference on Harmonisation
IND	Investigational New Drug
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
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
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

Trade Name:	Orencia
Established Name:	Abatacept
Also Known As:	CTLA-4-Ig
Therapeutic Class:	T-cell costimulation modulator
Chemical Class:	Biologic
Pharmacologic Class:	Fusion protein
Mechanism of Action:	Inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28

Abatacept (Orencia) is a human cytotoxic T-lymphocyte-associated protein 4-Immunoglobulin (CTLA4-Ig) fusion protein that inhibits T cell activation by blocking CD28-mediated costimulation and represents a class of therapeutic agents known as selective costimulation immunomodulators.

Abatacept was first approved by the FDA in 2005 for the treatment of rheumatoid arthritis (RA) as an intravenous (IV) infusion, and a subcutaneous (SC) presentation was approved in 2011. Abatacept was subsequently approved for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) in 2008 (IV) and 2017 (SC), adult active psoriatic arthritis in 2017 (PsA), and prophylaxis of acute graft versus host disease (aGVHD) in patients undergoing hematopoietic stem cell transplant (HSCT) in 2021. Abatacept is available in both intravenous (IV) and subcutaneous (SC) routes of administration in the following presentations:

Intravenous: 250 mg lyophilized powder in a single-dose vial
Subcutaneous: 50 mg/0.4 mL, 87.5 mg/0.7 mL, 125 mg/mL single-dose prefilled syringe and 125 mg/mL solution ingle-dose prefilled ClickJect autoinjectors

Table 1 presents the currently approved indications and dosing regimens for IV and SC abatacept.

Table 1. Currently approved indications and dosing regimens for abatacept

Indication	Route	Weight	Dose	Dosing Regimen
RA; PsA	IV	< 60 kg	500 mg	Admin at 0, 2, and 4 weeks, & q4 weeks after; 30 min infusion
		60-100 kg	750 mg	
		>100 kg	1000 mg	
	SC		• 125 mg SC injection q week • 125 mg/mL solution; single-dose prefilled AI	
pJIA (≥ 6 years)	IV	< 75 kg	10 mg/kg	• Admin at 0, 2, and 4 weeks, & q4 weeks after; 30 min infusion • Max Dose 1,000 mg
		≥ 75 kg	See adult	
pJIA (≥ 2 years)	SC	10 to <25 kg	50 mg	• Weekly • 50 mg/0.4 mL & 87.5 mg/0.7 mL • PFS presentation
		25 - 50 kg	87.5 mg	
		≥ 50 kg	125 mg	
aGVHD (≥ 6 years)	IV		10 mg/kg as 60 min infusion day before transplant, then dose on Days 5, 14, 28 after transplant	
aGVHD (2 to < 6 years)	IV		15 mg/kg as 60 min infusion day before transplant, then 12 mg/kg dose on Days 5, 14, 28 after transplant	

Source: USPI for abatacept (Orencia)

The Applicant, Bristol Myers Squibb (BMS), submitted a 351(a) supplemental biologics license application (BLA 125118 (b) (4)) to expand the indication for PsA to include the treatment of pediatric patients with active psoriatic arthritis (PsA) (b) (4) with the SC routine of administration (ages 2 years and older). (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is approval for SC abatacept for the treatment of pediatric patients age 2 years and older with active psoriatic arthritis. The effectiveness of SC abatacept in pediatric patients 2 to 17 years old with active psoriatic arthritis is based on the extrapolation of efficacy.

For pediatric patients with PsA the following aspects were considered for the 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 JIA with active polyarthritis.

As described in Section 6, the clinical pharmacology review team was able to establish a PK bridge to support the extrapolation of the efficacy established in adults with PsA to pediatric

patients with PsA at the proposed SC abatacept dose. Following the proposed SC dosing regimen, the observed pre-dose (trough) concentrations are generally comparable between adults with RA and PsA and pediatric patients with JIA with active polyarthritis. Also, based on (1) the disease similarity of pediatric PsA and adult PsA, (2) the similarity in PK of abatacept across pediatric and across adult indications, as well as (3) the similarity in PK of abatacept between adults with PsA and children with JIA with polyarthritis, the abatacept systemic exposure in pediatric patients 2 to 17 years of age with active PsA is expected to be comparable to the systemic exposure in adult subjects with active PsA. The PK bridge thus supports the extrapolation of established efficacy of abatacept SC in the adult PsA population to the pediatric PsA population. The safety of SC abatacept in pediatric patients with PsA is supported by the safety data from clinical studies in pediatric patients 2 to 17 years old with JIA with polyarthritis treated with SC abatacept.

(b) (4)

Therefore, the review team recommends approval of S-250 for SC abatacept to expand the indication for PsA to include treatment of patients 2 years of age and older with active PsA. (b) (4)

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and 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 (pediatric PsA), also referred to as psoriatic juvenile idiopathic arthritis or juvenile psoriatic arthritis (jPsA), is 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, and cutaneous and nail changes. Juvenile psoriatic arthritis comprises between 2 to 11% of children with JIA, and it has a calculated annual incidence of ~3 per million children. Without appropriate treatment, JIA, including pediatric PsA, can lead to significant disability. There are four recently FDA-approved treatments for pediatric PsA (golimumab, secukinumab, ustekinumab, and etanercept). However, there remains an unmet need for therapeutic options in this population since not all patients respond to the approved treatments.

Abatacept is a human cytotoxic T-lymphocyte-associated protein 4-Immunoglobulin (CTLA4-Ig) fusion protein. The product was first approved for the treatment of rheumatoid arthritis in 2005 and was subsequently approved for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) in 2008, adult PsA in 2017, and prophylaxis of acute graft versus host disease (aGVHD) in patients undergoing hematopoietic stem cell transplant (HSCT) in 2021. Abatacept is approved in both IV and SC formulations, at the same IV and SC dosing regimens for adults with RA and PsA. Due to the rarity of the disease, a full waiver for any Pediatric Research Equity Act (PREA)-required pediatric studies in psoriatic arthritis was granted at the time of approval of abatacept for PsA in 2017. The waiver was granted based on the justification that dedicated clinical studies to establish the efficacy of products in pediatric PsA would be impossible or highly impracticable because there are too few children with the disease/condition to study. However, based on the cumulative experience with drug development in JIA, as discussed at the FDA/M-CERSI (University of Maryland Center of Excellence in Regulatory Science and Innovation) public workshop on October 02, 2019, titled "Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)," 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 PK exposures between the two 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 between the two populations which could be product-specific. Safety and immunogenicity, if relevant, in pediatric patients could be supported by a reasonable safety database in pediatric patients with PsA or, with appropriate justification, a relevant pediatric patient population. This approach has led to the approvals of golimumab, ustekinumab, and etanercept for pediatric patients with PsA.

No clinical trials or dedicated pharmacokinetic studies were conducted in pediatric patients with PsA in support of this application. The efficacy of SC abatacept in the pediatric patients ages 2 and older with active PsA was extrapolated from adults with PsA where efficacy had been demonstrated in an adequate and well-designed clinical trial (Study IM101332). To support the PK bridge between adults and children with PsA, PK data for SC abatacept were compared in JIA with active polyarthritis from Study IM101301 and in adults with RA and PsA. The PK exposure for SC abatacept in JIA with active polyarthritis was comparable to the exposures in adults with RA and in adults with PsA, and the PK was similar between adult RA and PsA. Respectively, the exposure in pediatric PsA would be expected to be comparable to the exposure in adult PsA patients. This conclusion was also supported by the limited PK information in the pediatric PsA subgroup from Study IM101301. Once this PK bridge is established and given 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.

The PK exposure of SC abatacept is expected to be similar between pJIA and pediatric PsA patients with the same dosing regimen. In addition, there are no significant disease-specific factors that would be expected to impact safety differently. These considerations support the relevance of safety data from JIA with polyarthritis population to the pediatric PsA population. Respectively, the safety of SC abatacept in pediatric patients with PsA is supported by the safety observed in Study IM101301 using dosing that is consistent with the proposed dosing in pediatric patients with PsA. The overall safety profile of abatacept in JIA with active polyarthritis was generally consistent with the safety observed with abatacept in adult RA and PsA patients. Therefore, the safety in pediatric patients 2 years of age and older with active PsA is expected to be similar to the safety in pediatric patients with JIA with polyarthritis and adults with PsA.

(b) (4)

In conclusion, pediatric PsA is a rare and serious disease with unmet need for new therapies. The Applicant has provided adequate information to inform the benefit-risk assessment of SC abatacept for the treatment of pediatric patients with PsA and support the expansion of the indication for SC abatacept for the treatment patients 2 years of age and older with active PsA. Approval of SC abatacept will provide an

additional treatment option in the US for pediatric patients with PsA and will be the first approval for pediatric PsA for this drug class. Therefore, we recommend approval of Supplement 250 to expand the indication of SC abatacept for active PsA to pediatric patients 2 years of age and older. (b) (4)

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. • Psoriatic JIA, also referred to as pediatric psoriatic arthritis (pediatric PsA) and juvenile psoriatic arthritis (jPsA), is a subtype of JIA and comprises between 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 juvenile inflammatory arthritis 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, supporting the similarity of the diseases to support the extrapolation of efficacy from adult PsA to pediatric PsA based on exposure matching.
Current Treatment Options	• There are four currently approved treatments 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 treatment in adult patients and includes initial treatment with NSAIDs, followed by the addition of non-biologic DMARDs, and/or TNF-inhibitors in patients with persistent disease activity.	There is an unmet need for safe and efficacious therapies for pediatric patients with PsA since not all patients respond to currently approved treatments.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	**Supplement 250:** • The efficacy of SC abatacept has previously been demonstrated in adult patients with PsA in Study IM101332, the phase 3 pivotal study of submitted to support the approval of SC abatacept for treatment of PsA in adult patients. • In Study IM101301, 205 pediatric patients ages 2 to 17 years with JIA and active polyarticular disease and an inadequate response to at least one nonbiologic or biologic DMARD received SC abatacept without an IV loading dose once weekly with a weight-tiered dosing regimen. This study supported approval of SC abatacept for the treatment of pJIA. Of note, 5 patients in Study IM101301 were assessed to have pediatric PsA. • The exposures observed in JIA patients with active polyarthritis treated with weekly SC abatacept in Study IM101301 were within the range of exposures observed in adults with PsA in Study IM101332. • Systemic exposures are matched between the adults with PsA and RA and between the adults with RA and pediatric patients with JIA with active polyarthritis, supporting the similarity of exposures in adults and pediatric patients with PsA. (b) (4)	**Supplement 250:** • Efficacy of SC abatacept in pediatric patients with PsA ages 2 years and older is based on PK-exposure matching and extrapolation of established efficacy of SC abatacept in adults with PsA in Study IM101332. • This approach is justified based on similarities of disease manifestations, disease progression, and response to treatment in adults and pediatric patients with PsA, as well as the consistent exposure-response in adults with RA and pediatric patients with JIA. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4)	
Risk and Risk Management	• The PK exposure of SC abatacept is expected to be similar in patients with JIA with polyarthritis and pediatric PsA, supporting the relevance of safety data from JIA patients with active polyarthritis to the expected safety in the pediatric PsA population. • The safety database from Study IM101301 (reviewed under BLA 125118/s211) is sufficient to provide a risk assessment for SC abatacept in the pediatric population of PsA.	• Polyarticular JIA and pediatric PsA are both subtypes of JIA. It is reasonable to leverage the safety data from Study IM101301 in JIA with active polyarthritis. • The overall safety profile of SC abatacept observed in the JIA with active polyarthritis population, 2- to 17-years-old, was generally consistent with the safety observed in SC abatacept in adult RA and PsA patients. There were no new safety signals. • The safety of SC abatacept in pediatric PsA is expected to be similar to that of patients with JIA and adults with PsA.

1.4. Patient Experience Data

No new clinical studies were conducted and therefore, there are no new patient experience data submitted.

2 Therapeutic Context

2.1. Analysis of Condition

Psoriatic arthritis (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, and enthesitis, as well as spondyloarthritis.

The International League of Associations for Rheumatology (ILAR) classification system is the currently accepted classification system used to characterize arthritis in children and adolescents.[1] In this system, Juvenile Idiopathic Arthritis (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 least 6 weeks in a child younger than 16 years of age, where other diagnoses have been excluded. Psoriatic arthritis in children can also be referred to as pediatric PsA, psoriatic JIA, or juvenile psoriatic arthritis (jPsA).

ILAR criteria for psoriatic arthritis include arthritis and psoriasis or arthritis and at least 2 of the following: dactylitis; nail pitting or onycholysis; psoriasis in a first-degree relative.[1] Exclusions to a classification of PsA include arthritis in an HLA-B27 positive male after age 6; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome (reactive arthritis), acute anterior uveitis, or a history of one of these in a first degree relative; presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart; and presence of systemic JIA.[1] The Vancouver criteria for juvenile psoriatic arthritis define definite juvenile psoriatic arthritis 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 first or second degree relative, psoriasis-like lesion).[2] Notably, the presence of skin

[1] 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.
[2] Southwood TR, Petty RE, Malleson PN. Psoriatic arthritis in children. *Arthritis Rheum*. 1989;32:1007–1013.

rash is not required for diagnosis based on either criteria. Psoriatic JIA or juvenile psoriatic arthritis comprises between 2 to 11% of children with JIA.[3,4]

Clinical manifestations of pediatric psoriatic arthritis are similar to those of adult PsA with peripheral and axial arthritis, enthesitis, dactylitis, and cutaneous and nail changes. In children, the age of onset of PsA 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, while older children are more likely to have axial disease and enthesitis.[5,6] In general, the initial presentation is a monoarthritis or oligoarthritis, and the most commonly involved joints are knee and ankle with hip joint disease in up to 20% to 30% of patients.[7] In the absence of effective therapy, the arthritis will often progress to polyarticular disease. Pediatric psoriatic arthritis can affect the axial skeleton in 10% to 30% of patients.[5] 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.[2] Dactylitis is observed in 20 to 40% of patients.[2] Chronic painless uveitis occurs in 10 to 15% of children with pediatric PsA and more commonly in younger patients with a positive ANA.[5] Psoriasis occurs in 40 to 60% of patients with pediatric psoriatic arthritis, and nail changes are observed in 50 to 80%.[5]

In conclusion, adult PsA and pediatric PsA are similar diseases in terms of clinical manifestations and progression. Genetic mapping studies have also shown that adult PsA and pediatric PsA are associated with HLA alleles on the same haplotype, further supporting the similarity of disease.

2.2. Analysis of Current Treatment Options

There are four approved therapies for pediatric patients with PsA. Intravenous golimumab (Simponi Aria) was approved September 29, 2020, for age 2 years and older; secukinumab (Cosentyx) was approved December 22, 2021, for age 2 years and older; ustekinumab (Stelara) was approved July 29, 2022, for age (b) (4) years and older; and etanercept (Enbrel) was approved October 19, 2023, for age 2 years and older, with each approval based on a PK matching and extrapolation methodology.

The American College of Rheumatology (ACR)/Arthritis Foundation (AF) treatment guidelines

[3] Stoll ML, Punaro M. Psoriatic juvenile idiopathic arthritis: a tale of two subgroups. *Curr Opin Rheumatol*.2011;23(5):437-443.
[4] Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007;369(9563):767–78.
[5] Stoll ML, Zurakowski D, Nigrovic LE, et al. Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum*. 2006;54(11):3564-72.
[6] Zisman D, GladmanD, 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.
[7] Nigrovic P. Psoriatic juvenile idiopathic arthritis: pathogenesis, clinical manifestations, and diagnosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on September 17, 2020.)

for children with JIA and polyarthritis, defined as ≥ 5 joints ever involved, may include patients from different ILAR JIA categories.[8] Treatment recommendations are based on active disease manifestations. In patients with JIA and polyarthritis, but without systemic arthritis, sacroiliitis, or extraarticular manifestations, initial therapy with a disease modifying anti-rheumatic drug (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 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. For patients with enthesitis or sacroiliitis, who are most likely to have ILAR categories of psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis, initial treatment 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.

Although these guidelines included anti-TNF biologics, tocilizumab, abatacept, and rituximab, they did not include biologics with other mechanisms of action (e.g., anti-IL-17 and anti-IL-12/23 inhibition) due to a lack of published studies in pediatrics at the time. Notably, these most recent treatment guidelines were published in 2019,[8] prior to the approval dates of golimumab, secukinumab, ustekinumab, and etanercept for pediatric patients with PsA.

Table 2. Summary of treatment armamentarium for pediatric patients with psoriatic arthritis

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments for pediatric patients with PsA					
Ustekinumab	Pediatric patients with PsA	2009/2022	SC formulation: < 60 kg dose is 0.75 mg at Wks 0 and 4 and then q12w thereafter ≥ 60 mg dose is 45 mg at Wks 0 and 4 and then q12w thereafter > 100 kg with co-existent moderate-to-severe	PK-extrapolation using data from adult PsA	Similar to safety profile in adults

[8] Ringold S 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 Enthesitis. Arthritis Care & Res, 2019, 71: 717-734.

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			plaque psoriasis 90 mg at Wks 0 and 4 and then q12w thereafter		
Secukinumab	Pediatric patients with PsA	2016/2021	Children ≥ 2 years: ≥ 15 kg to <50 kg dose is 75 mg SC at Wks 0, 1, 2, 3, and 4 and then q4w thereafter ≥ 50 kg dose is 150 mg SC at Wks 0, 1, 2, 3, and 4 and then q4w thereafter	RW study with fewer flares vs PBO	Similar to safety profile in adults
Golimumab	Pediatric patients with PsA	2009/2020	Children ≥ 2years: IV formulation: 80mg/m^2 IV over 30 minutes at Wks 0 and 4, and then q8w thereafter	PK-extrapolation using data from adult PsA	Similar to safety profile in adults
Etanercept	Pediatric patients with PsA	1998/2023	Children ≥ 2years: 0.8 mg/kg weekly, with a maximum of 50 mg per week	PK-extrapolation using data from adult PsA	Similar to safety profile in adults
FDA Approved Treatments for JIA					
Tofacitinib	Polyarticular Course JIA*	2012/2020	Children ≥ 2 years: 10 to <20 kg: 3.2 mg (3.2mL oral solution) BID; 20 to <40 kg: 4 mg (4 mL oral solution) BID ≥ 40 kg: 5 mg (one 5 mg tablet or 5 mL oral solution) BID	RW study with fewer flares vs PBO	Similar to safety profile in adults
Golimumab	pJIA	2009/2020	Children ≥ 2 years: IV formulation 80mg/m^2 at wks 0, 2, and 4, then q8w	OL, single-arm PK, safety and exploratory efficacy study; PK-extrapolation	Similar to safety profile in adults
Abatacept	pJIA	2005/2008	(b) (4) Children ≥2 years: SC formulation 10 kg to <25 kg: 50 mg qw 25 kg to <50 kg: 87.5 mg qw ≥50 kg: 125 mg qw	(b) (4) OL PK-extrapolation (SC)	Similar to safety profile in adults
Adalimumab	pJIA	2002/2008	Children ≥2years: 10 to <15 kg: 10 mg SC q2w	RW study with fewer flares vs PBO	Infections, hypersensitivity, and ↑CPK

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			15 to <30 kg:20 mg SC q2w ≥30 kg: 40 mg SC q2w		
Etanercept	pJIA	1998/1999	Children ≥2 years: <63 kg: 0.8 mg/kg SC qw ≥63 kg: 50 mg SC qw	RW study with fewer flares vs PBO	Similar to safety profile in adults
Methotrexate	JRA	1953/1993	Starting dose 10 mg/m^2 once weekly; Experience with doses up to 30 mg/m^2/wk	Improvement in PhGA or patient composite over PBO	Similar to safety profile in adults with RA
Sulfasalazine	JRA	1950/2000	Children ≥6 years: initial therapy: 40-60 mg/kg/day, divided into 3 to 6 doses Maintenance: 30 mg/kg/day in 4 divided doses	Approved based on submission of 19 published studies	Leukopenia, ↑LFTs, GI symptoms, hypersensitivity reactions

Abbreviations: CPK=phosphokinase; DB=double-blind; IV=intravenous; JRA=Juvenile Rheumatoid Arthritis; PBO=placebo; PC=placebo-controlled; PhGA=Physician Global Assessment; pJIA=polyarticular juvenile idiopathic arthritis; PsA=psoriatic arthritis; PK=pharmacokinetic; Q2W=every other week; QW=every week; Q4W=every four weeks; Q8W=every eight weeks; R=randomized; RW=randomized withdrawal; SC=subcutaneous; WKs= weeks

***The RWD study of tofacitinib in 225 JIA patients, included 20 and 21 patients, respectively, with diagnosis of JPsA and ERA**

Source: USPI for all listed drugs

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Abatacept was first approved by the Agency on December 23, 2005, as an IV infusion for the treatment of rheumatoid arthritis (RA) in the adult population with an inadequate response to one or more DMARDs. Abatacept SC was approved for the treatment of RA on July 29, 2011. The IV and SC routes of administration of abatacept were approved for active psoriatic arthritis (PsA) in adults on June 30, 2017, and PREA requirements were waived at this time for pediatric patients with psoriatic arthritis because necessary studies were considered impossible or impracticable due to the rarity of the condition.

3.2. Summary of Presubmission/Submission Regulatory Activity

As noted in Section 3.1, PREA requirements were waived for pediatric studies at the time of the approval for abatacept in PsA. Based on the cumulative experience with drug development in JIA, as discussed at the FDA/MCERSI (University of Maryland Center of Excellence in Regulatory Science and Innovation) public workshop on October 2, 2019, titled "Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)", the Agency reconsidered the approach to the assessment of efficacy in pediatric patients with PsA. On November 20, 2020, an advice letter was communicated from the Agency to the Applicant to consider whether extrapolation of efficacy based on PK matching, with appropriate scientific justification, could support an indication for pediatric patients with PsA. Specifically, establishment of efficacy in pediatric PsA could be supported based on information to support the disease similarity between adult and pediatric PsA, adequate justification that the PK would be expected to be similar in the relevant pediatric population in which PK data are available and pediatric PsA, a rationale for PK bridging (comparable exposure) between adult PsA and pediatric PsA, appropriate justification and relevant information to support the extrapolation of efficacy in pediatric PsA patients from adult PsA, and justification of the relevance of the safety data from the relevant pediatric population in which safety data are available.

On May 17, 2022, preliminary pre-sBLA meeting comments were communicated on the proposed package to support a sBLA to expand the PsA indication to the pediatric population based on PK matching and extrapolation of efficacy. The Applicant proposed to submit a data package consisting of the following: (b) (4) The Applicant also proposed to submit efficacy and safety information for six subjects that were diagnosed with pediatric PsA in their JIA studies as evidence of safety and efficacy in this population.

In the preliminary responses, the Agency advised that the efficacy may be extrapolated from adult PsA with appropriate justification and evidence to support the expectation that exposures at effective doses in adults with PsA will provide similar or better response in the pediatric population and that safety would need to be supported by a reasonable safety database for abatacept in pediatric patients with PsA or, with appropriate justification, a relevant pediatric patient population (e.g., pJIA). The Agency noted that the data from the 6 subjects, who met ILAR classification criteria for pediatric PsA, may provide additional supportive information for the use of abatacept in pediatric PsA. However, the primary support for efficacy would be based on PK-matching and extrapolation of efficacy from adults with PsA, and the primary support for safety could be provided by the safety of abatacept in the overall population with pJIA. The Applicant subsequently canceled the scheduled teleconference for May 19, 2022, as they had no further questions.

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

4.1. Office of Scientific Investigations (OSI)

An OSI inspection was not requested as no new clinical studies were included in this submission.

4.2. Product Quality

No changes to the manufacture of the commercial product were included in this submission. Commercial materials or materials comparable to commercial materials were used in the clinical studies, from which results were analyzed to support the additional indication of treatment of pediatric patients age 2 years and older with active PsA. The information provided is adequate from the product quality perspective.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

There are no changes to the approved devices. The device presentations are currently approved for pediatric patients with pJIA, who may have similar disease manifestations to pediatric patients with PsA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical pharmacology or toxicology studies were submitted nor required (b) (4). There is sufficient nonclinical data to support the treatment of pediatric patients with abatacept down to 2 years of age.

6 Clinical Pharmacology

6.1. Executive Summary

On December 30, 2022, the Applicant, Bristol-Myers Squibb, submitted an efficacy supplement under BLA 125118 seeking approval for Orencia (abatacept) for the treatment of pediatric patients 2 years of age and older with active psoriatic arthritis (PsA). (b) (4)

The proposed (b) (4) subcutaneous (SC) dosing regimens are:

(b) (4)

- Subcutaneous Use for PsA in Pediatric Patients ≥2 Years Old

Administer subcutaneously without an intravenous loading dose

Body Weight of Pediatric Patient	**Dose (once weekly)**
10 kg to less than 25 kg	50 mg
25 kg to less than 50 kg	87.5 mg
50 kg or more	125 mg

Abatacept is currently approved for the following indications:

- the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA)
- the treatment of patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA)
- the treatment of adult patients with active PsA
- the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.

The currently approved dosing regimens are listed in **Table 3** below. The proposed (b) (4) SC dosing regimens in pediatric patients with active PsA are the same dosing regimens approved in pediatric patients with moderately to severely active pJIA.

Table 3. Currently approved abatacept dosing regimens

	Intravenous	**Subcutaneous**
Adult RA Adult PsA	at 0, 2, and 4 weeks, and Q4W thereafter <60 kg: 500 mg Q4W 60 to 100 kg: 750 mg Q4W >100 kg: 1000 mg Q4W	125 mg QW
pJIA	**6 years and older:** at 0, 2, and 4 weeks, and Q4W thereafter ≤ 75 kg: 10 mg/kg Q4W (max 750 mg) 75 to 100 kg: 750 mg Q4W >100 kg: 1000 mg Q4W	**2 years and older:** 10 kg to <25 kg: 50 mg QW 25 kg to <50 kg: 87.5 mg QW ≥50 kg: 125 mg QW
aGVHD	**6 years and older:** 10 mg/kg on Day 0, 5, 14, 28 (max 1000 mg) **2 to 5 years old:** 15 mg/kg on Day 0, and 12 mg/kg on Day 5, 14, 28	

Source: USPI for abatacept (Orencia)

(b) (4) the Applicant relied on PK based bridging to support the proposed indication and dosing regimens. No new clinical or PK study data was submitted to support this sBLA. The major clinical pharmacology review findings for this submission are as follows:

- (b) (4)
-

- Following the proposed SC dosing regimen, the observed pre-dose (trough) concentrations are generally comparable between adults with RA and PsA and patients with JIA with active polyarthritis, and the abatacept systemic exposure in pediatric patients 2 to 17 years of age with active PsA was expected to be comparable to the systemic exposure in adult subjects with active PsA. This conclusion was also supported by the limited PK information in the pediatric PsA subgroup from Study IM101301. The PK bridge is established to support the extrapolation of the efficacy established in adults with PsA to pediatric patients with PsA.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM) have reviewed the information submitted under (b) (4) sBLA125118/S-250. The proposed SC dosing regimen for pediatric patients aged 2 years and older is approvable from a clinical pharmacology perspective. (b) (4) The Division Signatory agrees with this assessment and recommendations.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Abatacept, a selective costimulation modulator, inhibits T-cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes. *In vitro*, abatacept decreases T-cell proliferation and inhibits the production of the cytokines TNF alpha (TNFα), interferon-γ, and interleukin-2.

In RA patients, after multiple intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg. Abatacept also exhibited linear pharmacokinetics following subcutaneous administration. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration was 79%. Relative to the RA patients with the same body weight, abatacept clearance in PsA patients was approximately 8% lower, resulting in slightly higher abatacept exposures in patients with PsA.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended SC dosing regimens in pediatric patients with active PsA is:

- Subcutaneous Use for PsA in Pediatric Patients ≥2 Years Old

Administer subcutaneously without an intravenous loading dose

Body Weight of Pediatric Patient	Dose (once weekly)
10 kg to less than 25 kg	50 mg
25 kg to less than 50 kg	87.5 mg
50 kg or more	125 mg

Therapeutic Individualization

None.

Outstanding Issues

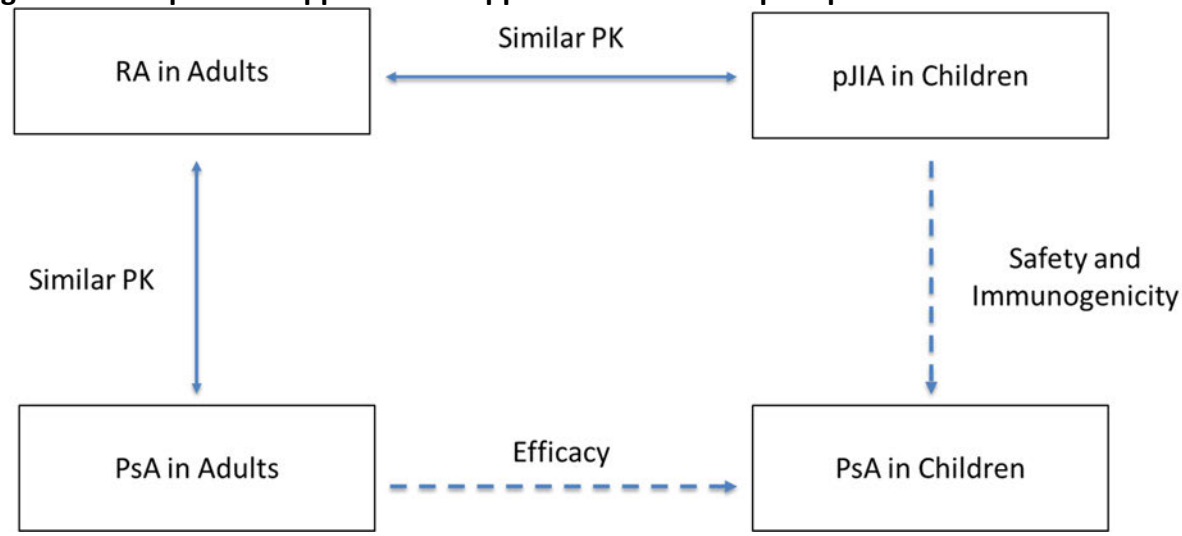
None.

6.3. Comprehensive Clinical Pharmacology Review

For pediatric patients with active PsA the following aspects were considered for extrapolation of efficacy approach:
1. Disease similarity between adult and pediatric patients with active PsA
2. PK bridge between adult and pediatric PsA patients
3. Extrapolation of efficacy in pediatric patients from adult PsA patients
4. Justification of the relevance of the safety data from JIA with active polyarthritis.

The following schematic depicts the extrapolation approach for pediatric patients with PsA (**Figure 1**). Polyarticular juvenile idiopathic arthritis (pJIA) and pediatric patients with PsA are subtypes the broader disease of JIA and their PK are expected to be similar. To establish the PK bridge to pediatric patients with PsA, the PK in JIA with polyarthritis and adult PsA/RA were considered. Once the PK bridge is established, borrowing efficacy from adequate and well-controlled studies in adult PsA patients is scientifically justified, as the disease is sufficiently similar in course between the two populations. In addition, safety information from other relevant pediatric populations like JIA with polyarthritis can be leveraged. For disease similarity and justification of the relevance of safety data in JIA with polyarthritis refer to sections 2 and 8.2.

Figure 1. Extrapolation approach to support use of abatacept in pediatric PsA



Source: FDA Clinical Pharmacology reviewer.

(b) (4)

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(b) (4)

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

Yes. The systemic exposure following the proposed SC dosing regimen in pediatric patients 2 to 17 years old has similar or higher exposure compared to adults with active PsA following the approved dosing regimen.

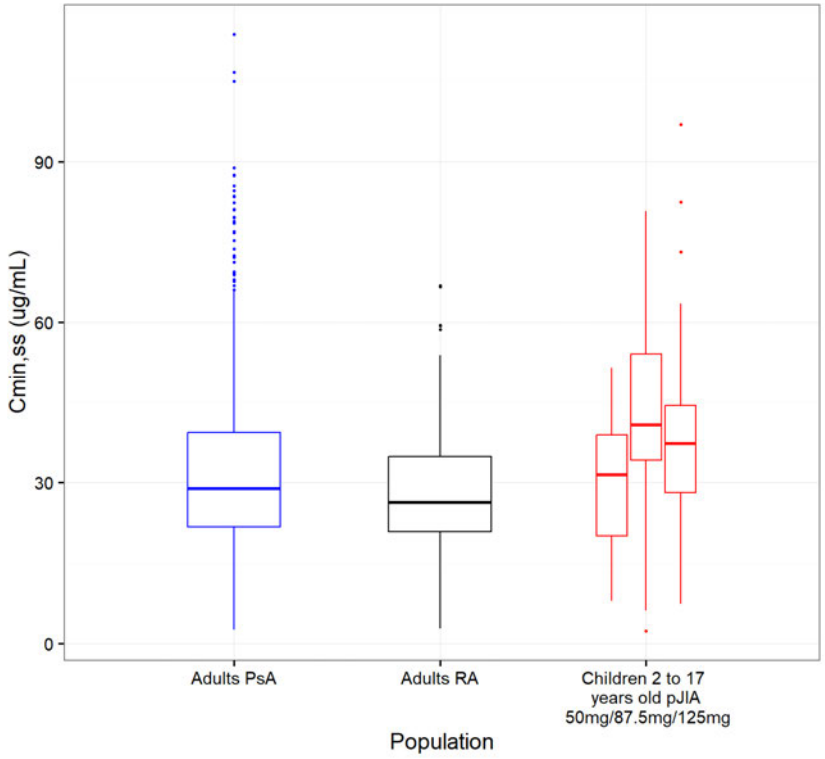
In this sBLA (s250), the Applicant relied on PK data collected from the following studies to support the PK comparison between adults with active PsA and children with active PsA for SC route of administration:

1) RA: Studies IM101167, IM101173, IM101174, IM101185

2) Adult PsA: Study IM101332 was a pivotal phase 3 study that compared the efficacy and safety of abatacept administered subcutaneously to placebo at 24 weeks in adult subjects with active PsA.
3) JIA with polyarthritis: Study IM101301 was 2-period, open-label, PK study in pediatric patients ages 2 to 17 years with active polyarticular disease and an inadequate response to at least one nonbiologic or biologic DMARD

The comparison of observed Cmin,ss between adults with RA, PsA, and pediatric patients with pJIA following SC administration is depicted in **Figure 8**. As the exposures are similar between adults with RA and PsA and there is no impact of disease characteristics on PK, the exposure is expected to be similar between children 2 to 17 years of age with active PsA and adults with active PsA. Following SC administration, the Cmin,ss was slightly higher in pediatric patients 2 to 17 years old with JIA with polyarthritis compared to adults with active PsA. In Study IM101332, five pediatric subjects following SC administration of 125mg was identified as pediatric PsA, the observed Cmin on Day 57 ranged from 20.6 to 71.5 µg/mL.

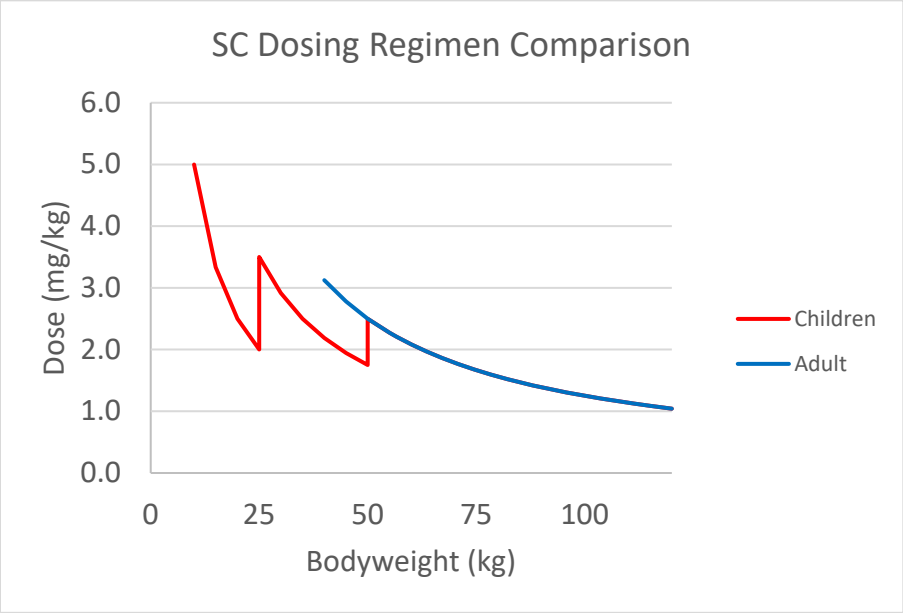
Figure 8. Boxplot of abatacept steady state minimum concentration in adults with RA, PsA, and children with pJIA following subcutaneous administration



Source: Reviewer's analysis

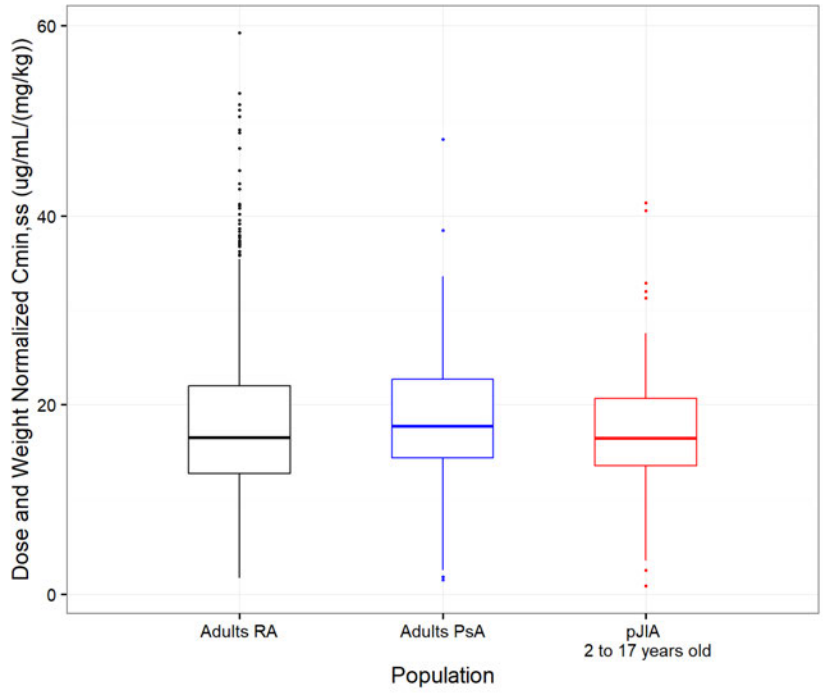
It is noted that the approved SC abatacept dose in adults with active PsA is generally lower than the proposed dose in children with JIA with polyarthritis after adjusting by bodyweight (**Figure 9**). Also, the dose and bodyweight normalized Cmin,ss is similar between adults (RA and PsA) and children with JIA with polyarthritis following SC route of administration (**Figure 10**).

Figure 9. Comparison of SC dosing regimens in adults and children



Source: Reviewer's analysis

Figure 10. Boxplot of dose and bodyweight normalized abatacept steady state minimum concentration in adults with RA, PsA, and children with pJIA following subcutaneous administration



Source: Reviewer's analysis

The higher exposure in children with JIA with polyarthritis following SC administration of

abatacept supports the efficacy of abatacept in children 2 to 17 years of age with PsA. The abatacept exposure is expected to be comparable between pediatric patients with JIA with polyarthritis and pediatric patients with active PsA, which provides adequate support to leverage the safety data observed in the relevant population of children 2 to 17 years of age with JIA with polyarthritis. For safety assessment, see Clinical review in section 8.2.

Overall, the proposed abatacept SC dosing regimen in pediatric patients 2 to 17 years of age with active PsA is approvable from a clinical pharmacology perspective.

What's the bioanalytical methods used in the quantification of abatacept concentration?

The PK data submitted under these sBLAs has been previously reviewed under the original BLA submission for adults with RA by Dr. Anil K. Rajpal and BLA125118/S209 for adults with active PsA following IV and SC route of administration by Dr. Jianmeng Chen, S211 for pJIA following SC route of administration by Dr. Jianmeng Chen. Therefore, the bioanalytical methods for PK assessment were not reviewed in the current review cycle. See the previously archived reviews for details.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

No new clinical studies were conducted to support the BLA supplement (b) (4) S-250).

Table 5. Listing of clinical trials relevant to BLA 125118/ (b) (4) S-250

Trial Identity	Trial Design	Study Population	No. of patients enrolled	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up
(b) (4)						
IM101332	P3, R, PC study to evaluate efficacy and safety of abatacept SC	PsA with active disease despite prior DMARD therapy	424	• Placebo • Abatacept SC 125 mg weekly	ACR 20 response at Day 169 (Week 24)	• 24-week DB period • OL extension received weekly SC abatacept
IM101301	P2, 2-period, OL PK study of SC abatacept	JIA with polyarthritis ages 2 to 17 years with inadequate response to MTX or biologic DMARD	205	• Abatacept SC 50 mg weekly for < 25 kg • Abatacept SC 87.5 mg weekly for 25 to 50 kg • Abatacept SC 125 mg weekly for > 50 kg	• PK • ACRp30/50/70 responses at 4 months	• 4-month short-term period • 20-month LTE
(b) (4)						

(b) (4)

Abbreviations: DB=double-blind; DMARD=disease modifying anti-rheumatic drug; IV=intravenous; LTE=long-term extension; MTX=methotrexate; OL=open-label; OLE=open-label extension; P2=Phase 2; P2b=Phase 2b; P3=Phase 3; PBO=placebo; PC=placebo-controlled; pJIA=polyarticular juvenile idiopathic arthritis; PK=pharmacokinetic; PsA=psoriatic arthritis; R=randomized; RW=randomized withdrawal; SC=subcutaneous
Source: USPI for abatacept (Orencia); Clinical study reports for listed studies

PK data from multiple studies in adult RA (IM101167, IM101173, IM101174, IM101185, (b) (4)) were reviewed as part of the PK analysis to support a PK bridge between adult and pediatric patients with PsA. These studies are not described as part of this review. See Section 6 for a discussion of the PK analysis.

7.2. Review Strategy

No new clinical data were submitted (b) (4). The Applicant provided the following information to support the proposed PK-matching approach to the extrapolation of the efficacy in adult PsA to pediatric patients with PsA.

- Support for the disease similarity of pediatric and adult PsA as discussed in Section 2.1 Analysis of Condition
- Justification that the PK would be expected to be similar in pJIA and pediatric PsA as discussed in Section 6 Clinical Pharmacology
- Justification for the PK bridge between adult PsA and pediatric PsA as discussed in Section 6 Clinical Pharmacology
- Justification and information to support the extrapolation of efficacy of abatacept in pediatric PsA from the efficacy established for abatacept in adequate and well-controlled studies in adult PsA (studies (b) (4) IM101332)
- Justification and information to support the relevance of the safety data in JIA with polyarthritis to pediatric PsA (studies IM101301 (b) (4)

To further support (b) (4), the Applicant also submitted summaries of efficacy and safety in six patients identified in the JIA with polyarthritis clinical studies who were determined by the Applicant to have pediatric PsA.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Information Used to Support Efficacy

(b) (4) IM101332 (b) (4) supported approval of abatacept ((b) (4) SC, (b) (4)) for the treatment of adult PsA. See the review of BLA 125118/S-209 for a discussion of these trials and the data that supported efficacy.

As additional support, the Applicant notes that the studies in pJIA included 6 patients with pediatric PsA. The pJIA studies are described in **Table 5**.

- SC Abatacept
  See the review of BLA 125118/S-211 for details of Study IM101301 including the discussion of efficacy. Study IM101301 was an open-label PK study in patients with JIA with polyarthritis. Five pediatric patients with PsA were enrolled in this study; of these, one patient discontinued the study when the patient's mother could not continue to go to the study site. The other 4 patients were all considered ACRp30 responders consistent with the overall JIA with polyarthritis patient population.

(b) (4)

The extrapolation of efficacy for SC abatacept in pediatric PsA age 2 years of age and older is supported based on the similarity of disease between pediatric PsA and adult PsA, as well as the adequate justification of the PK bridge from adult PsA to pediatric PsA based on comparable PK data from adult patients with RA, adult patients with PsA, and pediatric patients with pJIA, as discussed in Section 6. The small number of subjects with JIA with polyarthritis identified by the Applicant as having pediatric PsA had similar efficacy to the overall population; these results are consistent with the efficacy of SC abatacept in pediatric PsA.

(b) (4)

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of abatacept in pediatric patients with PsA is supported by the safety observed in clinical trials in JIA with polyarthritis that supported approval of SC abatacept in pediatric patients ages 2 and older (Study IM101301, N=205) (b) (4) IM101301 (b) (4) enrolled JIA subjects with polyarthritis and primarily subjects with pJIA. Polyarticular JIA and pediatric PsA are both subtypes of JIA and share similar demographic characteristics, certain clinical features (namely, inflammatory arthritis), and concomitant therapy; thus, the pJIA population, as well as the broader JIA with polyarthritis population, are relevant to pediatric PsA. The PK exposure is expected to be similar between pJIA and pediatric PsA, supporting the relevance of the safety data from pJIA to the pediatric PsA population.

SC Abatacept

Study IM101301 was a phase 3, two-period, open-label study that included 205 JIA patients with active polyarthritis ages 2 to 17 years and an inadequate response to at least one nonbiologic or biologic DMARD where subjects received abatacept SC without an IV loading dose once weekly with a weight-tiered dosing regimen. The safety observed in Study IM101301 was adequate to provide a reasonable risk assessment for abatacept in the JIA population with active polyarthritis. See the clinical review for BLA125118/S-211 for a detailed discussion of safety of Study IM101301.

- There were no deaths.
- A total of 8/173 subjects (5%) in the 6- to 17-year-old cohort experienced 10 serious adverse events (SAEs) during the course of the study. These SAEs included one case each of pyelonephritis, sepsis, anemia, abdominal pain, chest pain, radius fracture, hypomagnesemia, synovitis, ovarian germ cell teratoma (Stage III), and nephrolithiasis. Only the case of nephrolithiasis was classified as severe in intensity.
- A total of 4/173 subjects (2%) in the 6- to 17-year-old cohort discontinued due to adverse events (AEs) including fatigue, sepsis, ovarian germ cell teratoma (Stage III), and exanthemous rash. These AEs are consistent with the known adverse reaction profile of abatacept. Overall, no new safety signals were identified.
- A total of 90/173 subjects (52%) in the 6- to 17-year-old cohort reported an infection during the course of the study with the most common being nasopharyngitis and upper respiratory tract infection. No infection was reported as severe. Opportunistic infections were reported by 2 subjects (herpes zoster and oral candida).
- Infections were reported in 22/32 subjects (69%) in the 2- to 5-year-old cohort with a similar profile to the older cohort. No opportunistic infections were reported.

The overall safety profile of SC abatacept in the JIA population with active polyarthritis was generally consistent with the known safety profile of abatacept in adult RA and PsA patients. No new safety signals were identified.

As additional support of safety, the Applicant highlighted and provided a more detailed assessment of safety in the 5 patients with pediatric PsA in Study IM101301. None of these patients experienced SAEs or AEs leading to discontinuation. All reported AEs were consistent with AEs expected for patients of this age range, disease type, and concomitant medications. For example, the most reported AEs were related to mild or moderate infections, including influenza, conjunctivitis, scarlet fever, tracheitis, laryngitis, gastroenteritis, nasopharyngitis, hand-foot-and-mouth disease, and upper respiratory tract infection. In general, the reported adverse events in these 5 patients were consistent with the overall population of pJIA in Study IM101301.

(b) (4)

8.3. Statistical Issues

As no new clinical data were submitted (b) (4), there are no statistical issues.

[9] Abatacept (ORENCIA) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company, December 2021.

8.4. Conclusions and Recommendations

In the current submission, the Applicant proposes to expand the indication for adult PsA to include the treatment of pediatric patients 2 years and older with active PsA, using a PK-matching approach to extrapolate the efficacy of abatacept in adult PsA to the pediatric population. (b) (4) in S-250, the Applicant proposes SC abatacept for the treatment of pediatric patients 2 years of age and older with active PsA.

Efficacy

There were no new clinical studies conducted or submitted (b) (4). To support the extrapolation of efficacy, the Applicant has provided information to support the disease similarity between adult and pediatric patients with PsA. The similarities between the clinical presentation, disease progression, and responsiveness to therapies of adult and pediatric PsA support the extrapolation of efficacy based on PK-matching.

SC Abatacept

The efficacy of SC abatacept has previously been demonstrated in adult patients with PsA in Study IM101332 (a phase 3 pivotal study of SC abatacept in subjects with active PsA) submitted to support the approval of abatacept for treatment of PsA in adult patients. To support the PK bridge between adults and children with PsA, PK data for SC abatacept were compared in JIA with active polyarthritis from Study IM101301, in adults with RA and PsA, and in adults with RA and pediatric subjects with pJIA. Systemic exposures were matched between the adults with PsA and RA and the pediatric patients with JIA with active polyarthritis, supporting the similarity of exposures in adults and pediatric patients with PsA. The SC abatacept systemic exposure in pediatric patients 2 to 17 years of age with active PsA is expected to be comparable to the systemic exposure in adult subjects with active PsA. Therefore, the Applicant has provided an adequate PK bridge for SC abatacept to support the extrapolation of efficacy of in the adult PsA population to the pediatric PsA population.

(b) (4)

(b) (4)

Safety

The safety of SC abatacept in pediatric patients with PsA is supported by the safety observed in the clinical studies in JIA with polyarthritis. Polyarticular JIA and pediatric PsA are both subtypes of JIA, and the PK exposure of SC abatacept is expected to be similar in patients with pJIA and pediatric PsA, supporting the relevance of safety data from JIA patients with active polyarthritis to the expected safety in the pediatric PsA population. The overall safety profile of SC abatacept observed in the JIA with active polyarthritis population, 2- to 17-years-old, in Study IM101301 was generally consistent with the safety observed in SC abatacept in adult RA and PsA patients.

(b) (4)

There were no new safety signals for SC (b) (4) abatacept in the pediatric JIA population. The safety data in JIA with active polyarthritis provides adequate safety information to support the treatment of pediatric patients ages 2 years and older with active PsA with SC abatacept at the proposed dosing regimen.

In conclusion, the Applicant provided adequate data and information to inform the benefit-risk assessment of SC abatacept for the treatment of pediatric patients 2 years of age and older with active PsA. For SC abatacept, the Applicant was able to establish the PK bridge to support the extrapolation of efficacy established in adults with PsA to pediatric patients with PsA. Supportive safety is leveraged from patients with JIA with polyarthritis (ages 2 to 17 years). Therefore, the efficacy and safety evidence provided in this submission supports a favorable benefit-risk profile of SC abatacept for pediatric patients with PsA 2 years of age and older. The approval of SC abatacept would increase the treatment armamentarium for pediatric patients with PsA for which there are currently a limited number of approved treatment options. The review team recommends approval of S-250 for SC abatacept for the treatment of patients 2 years of age and older with active PsA.

(b) (4)

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee (AC) meeting was not recommended (b) (4).
No issues were identified during the review process that required AC discussion.

10 Pediatrics

At the time abatacept was approved for adult PsA, the Applicant received a full waiver for PREA-required studies in pediatric patients with PsA based on the justification that studies were impossible or highly impracticable because there are too few children with the disease/condition to study. As described in the Regulatory Background (Section 3), the Division has since reconsidered the approach to the pediatric assessment for PsA and agreed that information could be provided based on available PK in pediatric patients to support the extrapolation of efficacy from the adult PsA indication, with assessment of safety based on safety information from other available and relevant pediatric populations (e.g., pJIA).

(b) (4) discussed with the FDA Pediatric Review Committee (PeRC) on September 12, 2023. The PeRC agreed with the assessment for treatment of pediatric patients 2 years of age and older with PsA with the SC route of administration based on the data provided. (b) (4) The PeRC advised the Division that the original waiver for PREA-required studies in pediatric patients with PsA did not need to be modified based on (b) (4) and that the pediatric assessment was complete for PsA in patients 2 years of age and older for the SC formulation, (b) (4) .

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Updates to the prescribing information included the following:

- Changes were made throughout the prescribing information and medication guide to reflect the expansion of the indication for PsA from "adults with active psoriatic arthritis" to "patients 2 years of age and older with active psoriatic arthritis."
- Updates to the dosage and administration information in Section 2 were made to include SC dosing information for pediatric patients with PsA, consistent with the dosage and administration for pJIA.
- (b) (4)
- Section 8.4 Pediatric Use was updated to include establishment of safety and effectiveness of SC abatacept in PsA in pediatric patients 2 years and older and to describe the supportive evidence.
- In Section 8.4, the statement on pediatric patients in which safety and effectiveness was not established was updated to include the following statements:
    - The safety and effectiveness of subcutaneous ORENCIA have not been established in pediatric patients less than 2 years old with PsA.
    - The safety and effectiveness of intravenous ORENCIA in pediatric patients with psoriatic arthritis have not been established.
- (b) (4)

Other Prescription Drug Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) and Division of Medical Policy Programs (DMPP) have reviewed the submitted labeling, and their recommendations which pertain primarily to internal consistency and improving readability and clarity of the labeling, including the instructions for use (IFU), have been considered and conveyed to the Applicant.

All labeling changes were agreed upon with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

No new risk management plans are submitted (b) (4). As no new safety signals have been identified, a Risk Evaluation and Management Strategy (REMS) is not recommended for this product.

13 Postmarketing Requirements and Commitment

There are no potential or new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement or postmarketing commitment.

14 DRTM Associate Director For Therapeutic Review/Signatory Comments

I concur with the review and conclusions by the review team, as detailed in this document. (b) (4) The regulatory action for S-250 for SC abatacept for pediatric patients 2 years of age and older with active psoriatic arthritis is Approval. No postmarketing required studies or commitments are warranted based on this submission.

15 Appendices

15.1. References

Abatacept (Orencia) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company, December 2021

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Stoll ML, Zurakowski D, Nigrovic LE, et al. Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum*. 2006;54(11):3564-72.

Zisman D, GladmanD, 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.

15.2. OCP Appendices (Technical documents supporting OCP recommendations)

15.2.1. Pharmacometrics Review

The Applicant submitted a Population PK analysis to support the comparison of abatacept systemic exposure in children and adults with active PsA for (b) (4) SC routes of administration.

Population Pharmacokinetic Analysis of PsA:
The PPK analysis for abatacept was conducted with 12,962 serum concentration values from 2,244 patients with RA and 493 patients with PsA who received IV infusion and/or SC injection of abatacept. The PPK analysis included the following RA studies: 3 Phase 2 IV studies (IM103002, IM101100, and IM101101); 1 Phase 2 SC study (IM101063); 3 Phase 3 IV studies (IM101102, IM101029, and IM101031); and 4 Phase 3 SC studies (IM101167, IM101173, IM101174 [IM101174 PK substudy is also included], and IM101185), and the following PsA studies: 1 Phase 2b IV study (IM101158 [double-blinded period]), and 1 Phase 3 SC study (IM101332 [double-blinded and open-label periods]). This PPK analysis in adults with RA and PsA has been submitted previously under BLA 125118/S209. See Dr. Jianmeng Chen's review in DARRTS dated 05/27/2017.

Population Pharmacokinetic Analysis of JIA:
The PPK analysis for abatacept was conducted with 12,759 serum concentration values from 2,213 patients with RA and 357 patients aged 6 to 17 years with JIA and 46 patients aged 2 to 5 years with JIA who received IV infusion and/or SC injection of abatacept. The PPK analysis included the following 11 RA studies: 3 Phase 2 IV studies (IM103002, IM101100, and IM101101), 1 Phase 2 SC study (IM101063), 3 Phase 3 IV studies (IM101102, IM101029, and IM101031), and 4 Phase 3 SC studies (IM101167, IM101173, IM101174 [IM101174 PK substudy is also included], and IM101185) and the following 2 JIA studies: 1 Phase 3 IV study (IM101033) and 1 Phase 3 SC study (IM101301 [short-term and open-label periods]). **Table 6** provides the summary statistics of selected demographic characteristics of RA and JIA patients included in the PPK analysis.

Table 6. Summary statistics of covariates used in the PPK model in patients with JIA and RA

Patient Characteristic	Statistic	RA (N = 2213)	JIA 2-5 years old (N = 46)	JIA 6-17 years old (N = 357)	Overall (N = 2616)
Baseline Age [y]	Mean (SD)	51.1 (12.8)	4.1 (1.0)	12.4 (3.0)	45.0 (18.6)
	Median	52.0	4.0	13.0	49.0
	Min, Max	17, 85	2, 5	6, 17	2, 85
Baseline Body Weight [kg]	Mean (SD)	73.96 (19.15)	18.23 (3.52)	44.19 (17.17)	68.91 (22.38)
	Median	71.00	18.00	42.70	68.00
	Min, Max	36.5, 186.8	12.0, 26.0	14.4, 146.3	12.0, 186.8
	Missing N (%)	3 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)
Baseline Albumin [g/dL]	Mean (SD)	4.06 (0.33)	4.54 (0.34)	4.38 (0.40)	4.11 (0.36)
	Median	4.10	4.60	4.40	4.10
	Min, Max	2.7, 5.4	3.8, 5.3	3.0, 5.4	2.7, 5.4
	Missing N (%)	17 (0.8)	0 (0.0)	35 (9.8)	52 (2.0)
Calculated GFR [mL/min/1.73m^2]	Mean (SD)	97.48 (28.52)	134.47 (28.95)	160.90 (74.31)	106.82 (44.10)
	Median	94.64	129.10	133.64	99.19
	Min, Max	25.4, 245.9	85.2, 230.0	65.3, 578.2	25.4, 578.2
	Missing N (%)	10 (0.5)	0 (0.0)	0 (0.0)	10 (0.4)
Baseline Swollen Joint Count	Mean (SD)	18.3 (9.8)	6.6 (5.8)	11.4 (10.0)	17.1 (10.2)
	Median	16.0	4.5	8.0	15.0
	Min, Max	0, 66	0, 27	0, 53	0, 66
	Missing N (%)	52 (2.3)	0 (0.0)	0 (0.0)	52 (2.0)
Gender, N (%)	Male	431 (19.5)	18 (39.1)	90 (25.2)	539 (20.6)
	Female	1782 (80.5)	28 (60.9)	267 (74.8)	2077 (79.4)
Baseline Use of NSAIDS, N (%)	No	1736 (78.4)	16 (34.8)	64 (17.9)	1816 (69.4)
	Yes	477 (21.6)	28 (60.9)	278 (77.9)	783 (29.9)
	Missing N (%)	0 (0.0)	2 (4.3)	15 (4.2)	17 (0.6)

Abbreviations: Max, maximum; Min, minimum; N, number of patients; NSAID, non-steroidal anti-inflammatory drugs; SD, standard deviation.
Source: Table 3-2 in Pharmacometrics Report JPSA 2022

The PK of abatacept in patients with JIA and RA was characterized by a linear 2-compartment PPK model with zero-order IV infusion, first-order SC absorption, and first-order elimination with a combined residual error model (additive and proportional error). Disease effect (JIA versus RA) was a statistically significant covariate in the PPK model. An inverse logit transformation was used to constrain absolute bioavailability ($F1_{Absolute}$) between 0 and 1 with the following equation:

$$F1_{Absolute} = \frac{1}{1 + \exp\left(-F1_{TV} - F1_{IIV}\right)}$$

where F_{TV} is the model estimated typical value for bioavailability prior to transformation, F_{IIV} is the model-estimated interindividual variability for bioavailability prior to transformation.

The covariate effects were described by the following expressions:

$$CL_{TV} = CL_{TV,ref} \times (\frac{BWT_b}{BWT_{ref}})^{CL_{BWT}} \times (\frac{ALB_b}{ALB_{ref}})^{CL_{ALB}} \times (\frac{CGFR_b}{CGFR_{ref}})^{CL_{CGFR}} \times (\frac{BSJC_b + 1}{BSJC_{ref} + 1})^{CL_{BSJC}} \times \exp(SEX \times CL_{SEX} + NSAID \times CL_{NSAID})$$

$$VC_{TV} = VC_{TV,ref} \times (\frac{BWT_b}{BWT_{ref}})^{VC_{BWT}} \times (\frac{AGE_b}{AGE_{ref}})^{VC_{AGE}}$$

$$VP_{TV} = VP_{TV,ref} \times (\frac{BWT_b}{BWT_{ref}})^{VP_{BWT}}$$

The F1 decreased with weight and increased with age, and was higher in patients with JIA.

$$F1_{TV} = F1_{TV,ref} \times (\frac{BWT_b}{BWT_{ref}})^{F1_{BWT}} \times (\frac{AGE_b}{AGE_{ref}})^{F1_{AGE}} \times \exp(DISEASE \times F1_{DISEASE})$$

where $F1_{TV,ref}$ is the typical value of a PK parameter for a reference (ref) patient with RA (BWT_{ref} = 68 kg, AGE_{ref} = 49 y, ALB_{ref} = 4.1 mg/dL, $CGFR_{ref}$ = 99.18 mL/min/1.73m^2, $BSJC_{ref}$ = 15, SEX_{ref} = female, $NSAID_{ref}$ = No).

Table 7 shows a comparison of the parameter estimates from the final abatacept PPK models for PsA and JIA.

Table 7. Parameter estimates of the final PPK model in patients with JIA and RA

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability[a]	
	Estimate	%RSE	Estimate	%RSE
KA: Absorption Rate Constant [1/h]	0.00521	11.0	1.11	24.4
VC: Central Volume [L][b]	3.29	1.57		
$VC_{TV,ref}$: Power of Weight on VC [-][c]	0.603	6.99	0.0464	14.6
VC: Power of Age on VC [-][c]	0.114	23.4		
$CL_{TV,ref}$: Clearance (L/h)[b]	0.0179	1.36		
CL: Power of Weight on CL [-][c]	0.706	2.93		
CL: Power of CGFR on CL [-][c]	0.259	7.19		
CL: Power of Swollen Joint Count on CL [-][c]	0.0742	12.8	0.0637	4.25
CL: Exponent of NSAID use on CL [-][c]	0.102	12.5		
CL: Exponent of Male Sex on CL [-][c]	0.0674	21.4		
CL: Power of Albumin on CL [-][c]	-0.722	9.69		
$VP_{TV,ref}$: Peripheral Volume [L][b]	3.67	3.71	0.154	15.9
VP: Power of Weight on VP [-][c]	0.575	7.20		
Q: Intercompartmental Clearance [L/h]	0.0231	7.25	NE	NA
$F1_{TV,ref}$: Bioavailability of SC Formulation [-][b]	0.770	6.09		
F1: Exponent of JIA on F1 [-][c]	3.08	41.3	0.516	15.0
F1: Power of Weight on F1 [-][c]	-0.506	27.3		
F1: Power of Age on F1 [-][c]	0.487	27.1		
Proportional Residual Error	NA	NA	0.0615	3.29
Additive Residual Error	NA	NA	0.00134	69.3
Minimum Value of the Objective Function = 65061.705				

Source: Table 4.1.2-1 in Pharmacometrics Report JPSA 2022

For a typical adult subject with RA, the estimated bioavailability is

$$F1_{TV} = 0.770 \times (\frac{73.96}{68})^{-0.506} \times (\frac{51.1}{49})^{0.487} = 0.75$$

$$F1_{Absolute} = \frac{1}{1 + \exp(-0.75)} = 67.9\%$$

However, the estimated bioavailability for a typical pediatric subject 6 to 17 years old with JIA is

$$F1_{TV} = 0.770 \times (\frac{44.19}{68})^{-0.506} \times (\frac{12.4}{49})^{0.487} \times \exp(3.08) = 10.67$$

$$F1_{Absolute} = \frac{1}{1 + \exp(-10.67)} = 100\%$$

For a typical adult subject with RA, the estimated CL is

$$\frac{CL_{TV}}{BWT} = 0.0179 \times \left(\frac{73.96}{68}\right)^{0.706} \times \left(\frac{4.06}{4.1}\right)^{-0.722} \times \left(\frac{97.48}{99.18}\right)^{0.259} \times \left(\frac{18.3+1}{15+1}\right)^{0.0742} \times \frac{\exp(19.5\% \times 0.0674 + 21.6\% \times 0.102)}{73.96} = 0.213\, mL/h/kg$$

However, the estimated CL in a typical pediatric subject 6 to 17 years old with JIA is

$$\frac{CL_{TV}}{BWT} = 0.0179 \times \left(\frac{44.19}{68}\right)^{0.706} \times \left(\frac{4.38}{4.1}\right)^{-0.722} \times \left(\frac{133.64}{99.18}\right)^{0.259} \times \left(\frac{11.4+1}{15+1}\right)^{0.0742} \times \exp(25.2\% \times 0.0674 + 77.9\% \times 0.102)\,/44.19 = 0.333\, mL/h/kg$$

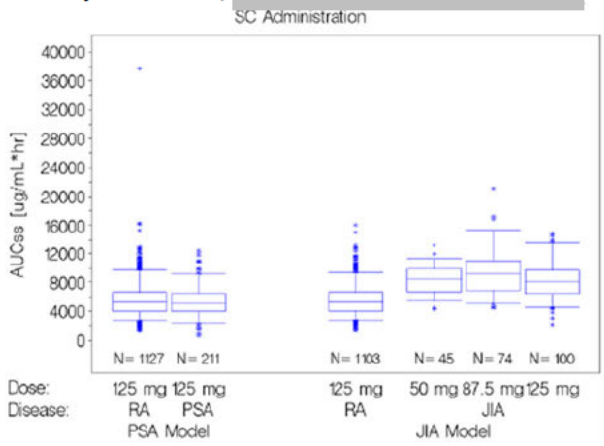
The PPK model in subjects with RA and JIA suggested a significant difference in PK characteristics between these two populations. The reason for this difference remains unclear.

Using the developed PPK model for patients with RA and PsA, the following summary measures of individual abatacept exposure at steady state were obtained and summarized from the final PK model for each patient for whom maximum a posterior Bayesian estimates of the PK parameters were available: trough serum concentration at steady state (Cmin,ss), peak serum concentration at steady state (Cmax,ss), time-averaged serum concentration at steady state (Cavg,ss), and area under the concentration-time curve at steady state (AUCss).

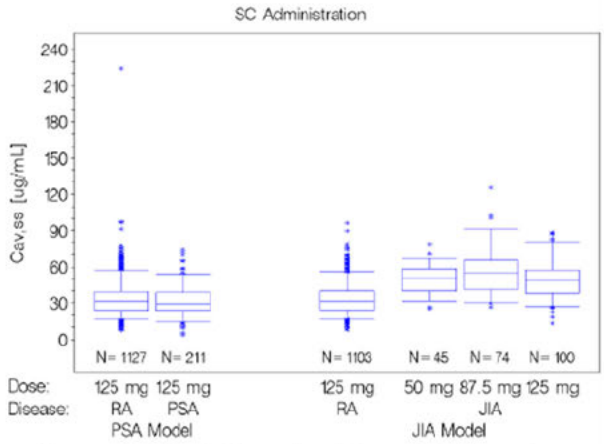
Using the developed PPK model for patients with RA and JIA, simulations of the patients with RA and JIA included in the PPK dataset were performed to obtain exposure measures (Cmin,ss, Cmax,ss, Cavg,ss, AUCss) at steady state (Month 4). The final PPK model and individual patient PK parameters described above were used as a basis for these simulations. The actual dosing history observed in the clinical trials for each patient was used to obtain individual exposure measures.

Boxplots of steady state abatacept exposure measures versus disease (RA, PsA, and JIA), dose, and model are provided Figure 11, (b) (4).

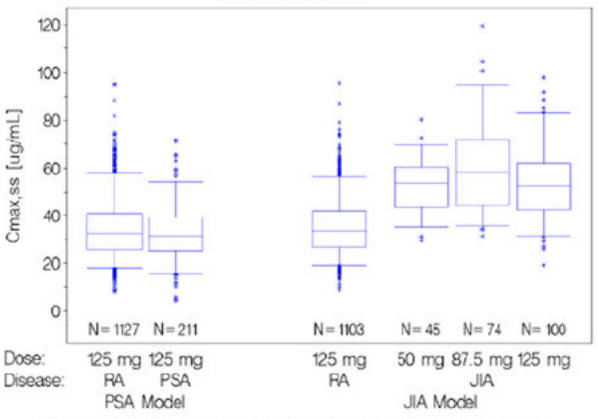
Figure 11. Boxplots of steady-state abatacept exposure measures versus disease (RA, PsA, and JIA) and dose, (b) (4) (b) (4)



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of patients is below each box.

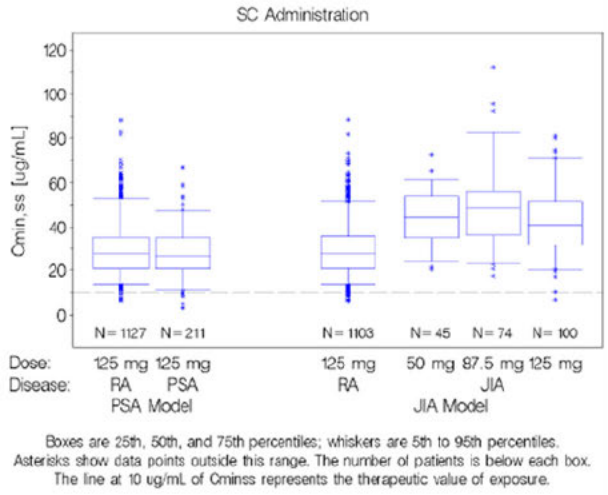


Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of patients is below each box.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of patients is below each box.

(b) (4)



(b) (4)

Source: Figure 5.1.1-1 in Pharmacometrics Report JPSA 2022

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