# NDA/BLA Multi-Disciplinary Review and Evaluation

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| **Application Type** | sBLA |
| **Application Number(s)** | 103795/S5595 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | December 20, 2022 |
| **Received Date(s)** | December 20, 2022 |
| **PDUFA Goal Date** | October 20, 2023 |
| **Division/Office** | Division of Rheumatology and Transplant Medicine (DRTM) |
| **Review Completion Date** | October 18, 2023 |
| **Established/Proper Name** | Etanercept |
| **(Proposed) Trade Name** | Enbrel |
| **Pharmacologic Class** | A tumor necrosis factor (TNF) blocker |
| **Applicant** | Amgen |
| **Dosage form** | •25 mg/0.5 mL clear, colorless solution in a single-dose prefilled syringe<br>•50 mg/mL clear, colorless solution in a single-dose prefilled SureClick autoinjector<br>•25mg/0.5 mL clear, colorless solution in a single-dose vial<br>•25 mg lyophilized powder in a multiple-dose vial for reconstitution<br>•50 mg/mL clear, colorless solution in Enbrel Mini single-dose prefilled cartridge for use with the AutoTouch reusable autoinjector only |
| **Applicant proposed Dosing Regimen** | 50 mg administered by subcutaneous injection weekly for pediatric patients weighing 63 kg (138 pounds) or more; 0.8 mg/kg administered by subcutaneous injection weekly for pediatric patients weighing less than 63 kg (138 pounds) |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment of active juvenile psoriatic arthritis (JPsA) in patients 2 years and older |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | Treatment of active juvenile psoriatic arthritis (JPsA) in pediatric patients 2 years of age and older. |
| **Recommended Dosing Regimen** | 0.8 mg/kg administered weekly via subcutaneous injection in children weighing less than 63 kg (138 pounds), or 50 mg administered weekly via subcutaneous injection in children weighing 63 kg (138 pounds) or more |

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# Reviewers of Multi-Disciplinary Review and Evaluation

| | |
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OPQ=Office of Pharmaceutical Quality
OPMA=Office of Pharmaceutical Manufacturing Assessment
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs

## Signatures

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| Product Quality Review Chief | Joanna Zhou, PhD | OBP/DBRR1 | Sections: 4.2 | **Select one:**<br>___ Authored<br>_x__ Approved |
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# Glossary

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|---|---|
| AE | adverse event |
| AGSD | Amgen Global Safety Database |
| AS | ankylosing spondylitis |
| BIW | twice a week |
| BLA | biologics license application |
| CBER | Center for Biologics Evaluation and Research |
| CFR | Code of Federal Regulations |
| CIDP | chronic inflammatory demyelinating polyneuropathy |
| DIIP | Division of Immune and Inflammation Pharmacology |
| DMARDs | disease-modifying antirheumatic drugs |
| DPV | Division of Pharmacovigilance |
| E-R | exposure-response |
| FDA | Food and Drug Administration |
| HLGT | high-level group terms |
| ILAR | International League of Associations for Rheumatology |
| IND | Investigational New Drug |
| JIA | juvenile idiopathic arthritis |
| JPsA | juvenile psoriatic arthritis |
| JRA | juvenile rheumatoid arthritis |
| LLOQ | lower limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTX | methotrexate |
| NEC | not elsewhere classified |
| NSAIDs | nonsteroidal anti-inflammatory agents |
| OCP | Office of Clinical Pharmacology |
| OLE | open-label extension |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PeRC | pediatric review committee |
| PI | prescribing information |
| PK | pharmacokinetics |
| PREA | Pediatric Research Equity Act |
| PsA | psoriatic arthritis |
| PsO | plaque psoriasis |
| PSUR | Periodic Safety Update report |
| QW | once weekly |
| RA | rheumatoid arthritis |
| REMS | risk evaluation and mitigation strategy |
| RF | rheumatoid factor |

| | |
|---|---|
| SAE | serious adverse event |
| sBLA | supplemental biologics license application |
| SC | subcutaneous |
| TNF | tumor necrosis factor |
| TNFi | tumor necrosis factor inhibitor |
| TNFR | tumor necrosis factor receptor |

# 1 Executive Summary

## 1.1. Product Introduction

Etanercept (Enbrel®) is a biologic fusion protein that is a member of the tumor necrosis factor inhibiting (TNFi) class of agents. It exerts its activity by blocking the binding of both TNF-alpha and –beta (lymphotoxin alpha) to their respective cell surface receptor sites. Etanercept was first licensed in the United States (U.S.) in 1998 for the treatment of rheumatoid arthritis (RA). It has been subsequently approved in the U.S. for the treatment of the following autoimmune disorders: polyarticular juvenile rheumatoid arthritis (now known as juvenile inflammatory arthritis) in pediatric patients 4 years of age and older in 1999 that was extended down to 2 years of age in 2006, adults with psoriatic arthritis (PsA) in 2002, adults with ankylosing spondylitis (AS) in 2003, adult plaque psoriasis (PsO) in 2004, and pediatric patients ages 4 to 17 years old with PsO who are candidates for systemic therapy or phototherapy in 2016. The approved etanercept dosage presentations for subcutaneous administration include:

- 25 mg/0.5 mL clear, colorless solution in a single-dose prefilled syringe
- 50 mg/mL clear, colorless solution in a single-dose prefilled SureClick autoinjector
- 25mg/0.5 mL clear, colorless solution in a single-dose vial
- 25 mg lyophilized powder in a multiple-dose vial for reconstitution
- 50 mg/mL clear, colorless solution in Enbrel Mini single-dose prefilled cartridge for use with the AutoTouch reusable autoinjector only

The Applicant, Amgen Inc., has submitted a 351(a) supplemental biologics license application (sBLA) seeking to expand etanercept's marketing approval to include the treatment of pediatric patients age 2 years and older with active juvenile psoriatic arthritis (JPsA). This application does not fulfil a Pediatric Research Equity Act (PREA) post-marketing required (PMR) pediatric assessment related to the approval of the adult indication for PsA, since PREA was not enacted until 2003 following the January 15, 2002, approval for BLA 103795/S-5024 Enbrel (etanercept) as a treatment of adults with active PsA.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is approval for etanercept (Enbrel) for the treatment of pediatric patients age 2 years and older with JPsA. This recommendation is based on the extrapolation of efficacy established in adults with PsA.

This application is in response to a November 2020 Advice letter issued by the Agency informing the Applicant that it had reconsidered its approach to the pediatric assessment of PsA and PREA waivers historically in place for pediatric patients with psoriatic arthritis based on public discussions at a 2019 workshop held at the University of Maryland Center for Regulatory

Science and Innovation (FDA/M-CERSI).[1] In the November 2020 Advice letter, the Agency communicated to the Applicant that the high degree of similarity between adults with psoriatic arthritis and pediatric patients with psoriatic arthritis could support a scientific rationale for a pediatric extrapolation of efficacy and safety based on a demonstration of pharmacokinetic comparability between the adult and pediatric populations with psoriatic arthritis. Support of the safety of etanercept in JPsA could be provided by a reasonable safety database in pediatric patients with PsA, or by a relevant pediatric population with an appropriate justification. However, safety and immunogenicity, if relevant, in pediatric patients cannot be leveraged from the studies in adults and would need to be supported by a reasonable safety database in pediatric patients with psoriatic arthritis or, with appropriate justification, a relevant pediatric population.

Juvenile idiopathic arthritis (JIA), formerly known as juvenile rheumatoid arthritis (JRA), is a broad term used to describe a heterogeneous group of inflammatory disorders characterized by arthritis of one or more joints of unknown etiology persisting for 6 or more weeks that begins before 16 years of age.[2] Juvenile psoriatic arthritis is a rare subtype of JIA involving the peripheral joints and axial skeleton that is associated with psoriasis. Since JPsA and adult PsA share many of the same disease characteristics and clinical manifestations (peripheral and axial arthritis, enthesitis, dactylitis, psoriasis, and nail changes), it has been suggested that they may be a spectrum of the same disease. Currently, there are three biologic therapeutic agents approved for the treatment of JPsA. However, an unmet medical need exists for additional therapeutic options for pediatric patients with JPsA since not all patients respond to these approved treatments which can result in significant and permanent disability.

In view of the available data with etanercept in adults with PsA, PsO, and RA, as well as children with polyarticular JIA and PsO, and considering the rarity of JPsA, the Applicant has undertaken a pharmacokinetics (PK)-bridging approach with full extrapolation of efficacy and leveraging of safety from existing etanercept studies in support of this application.

As described in Section 6, the clinical pharmacology review team were able to establish a PK bridge to support the extrapolation of the efficacy established in adults with PsA to pediatric patients with JPsA at the proposed etanercept dose of 0.8 mg/kg. Overall, based on (1) the disease similarity of JPsA and adult PsA (2) the similarity in PK of etanercept across pediatric and across adult indications, as well as (3) the similarity in PK of etanercept between adults with PsA and PsO and children with PsO, it is expected that PK will be similar between adult PsA and JPsA. The PK bridge thus supports the extrapolation of established efficacy of etanercept in adult PsA population to JPsA population.

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[1] Schanberg LE, Mulugeta L, Akinlade B, et al. Therapeutic Development in Polyarticular Course Juvenile Idiopathic Arthritis: Extrapolation, Dose Selection, and Clinical Trial Design. *Arthritis and Rheumatology* 2023, p.1-11. DOI 10, 1002/art.42534.

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

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Pediatric psoriatic arthritis, 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), as defined by the International League of Associations for Rheumatology (ILAR) criteria.[3] Clinical manifestations of JPsA are similar to adult PsA with peripheral and axial arthritis, enthesitis, dactylitis, psoriasis, and nail changes. It has been estimated that JPsA comprises between 2-11% of children with JIA, with a calculated annual incidence of approximately 3 per million children.[4,5] Standard of care therapy for JPsA is comprised of nonsteroidal anti-inflammatory agents (NSAIDs), corticosteroids (intra-articular and systemic), nonbiologic disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. There are three biologic DMARDs (golimumab, secukinumab, and ustekinumab) currently approved for the treatment of JPsA in the United States (U.S.). However, an unmet medical need exists for additional therapeutic options for pediatric patients with JPsA since not all patients respond to these approved treatments which can result in significant and permanent disability.

Etanercept (Enbrel) is a fusion protein that blocks the binding of tumor necrosis factor (TNF) α and β to their respective cell surface receptor sites. The product was first approved in the U.S. in 1998 for the treatment of rheumatoid arthritis (RA). It has been subsequently approved for the treatment of the following autoimmune disorders: polyarticular juvenile rheumatoid arthritis (now known as polyarticular JIA) in pediatric patients 4 years of age and older in 1999 that was extended down to 2 years of age in 2006, adults with psoriatic arthritis (PsA) in 2002, adults with ankylosing spondylitis (AS) in 2003, adult plaque psoriasis (PsO) in 2004, and pediatric patients ages 4 to 17 years old with PsO who are candidates for systemic therapy or phototherapy in 2016.

At the time of approval for adult PsA in 2002, the Pediatric Research Equity Act (PREA) had not been enacted yet, so an agreement to conduct a postmarketing pediatric assessment in JPsA was not sought as a requirement for the approval of that adult indication. In October 2019, the Agency, in collaboration with the University of Maryland Center for Regulatory Science and Innovation (FDA/M-CERSI), held a public workshop

[3] Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* (2004) 31:390-2.
[4] Ravelli A and Martini A. Juvenile idiopathic arthritis. *Lancet* 2007;369(9563):767-78.
[5] Stoll ML and Punaro M. Psoriatic juvenile idiopathic arthritis: a tale of two subgroups. Curr Opin Rheumatol 2011;23(5):437-443.

entitled "Accelerating Drug Development for pJIA."[6] Based on the discussions held at this public workshop, the need for treatments for JPsA, and the approach to pediatric assessments for PsA, the Agency reconsidered its approach to the pediatric assessment of PsA.

As stated in an Advice letter to the Applicant on November 20, 2020, the Agency considered the high degree of similarity between adults with PsA and pediatric patients with JPsA 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 JPsA based on matching of the pharmacokinetic (PK) exposures between the two populations. However, safety and immunogenicity, if relevant, in pediatric patients cannot be leveraged from the studies in adults and would need to be supported by a reasonable safety database in pediatric patients with JPsA or, with appropriate justification, a relevant pediatric population. To support this approach to extrapolation of efficacy of etanercept from adults with PsA to children with PsA, the Applicant provided a justification supported by the following: (1) information supporting disease similarity between adult and pediatric patients with psoriatic arthritis; (2) establishment of PK bridging (comparable exposures) between adult and pediatric patients; (3) justification and relevant information to support the extrapolation of efficacy in pediatric patients with JPsA from adult subjects with PsA; and (4) justification of the relevance of the safety data from children with PsO and polyarticular juvenile idiopathic arthritis (pJIA), and adults with PsA.

No clinical trials or dedicated pharmacokinetic studies were conducted in pediatric patients with JPsA in support of this application. Efficacy in pediatric patients with JPsA was extrapolated from adults with PsA where efficacy had been demonstrated in adequate and well controlled clinical trials with the expectation that children with JPsA should respond to treatment similarly to adults with PsA based on the shared manifestations and pathogenesis of psoriatic arthritis in adults and children. To support the PK bridge between adults with PsA and children with JPsA, PK data for etanercept was compared in pediatric subjects across the approved indications for pediatric PsO and polyarticular JIA; in adults across the approved indications for RA, PsO, and PsA; in adults with PsO and pediatric subjects with PsO; and finally, between adults with PsA and pediatric subjects with PsO. Using the available PK data, the clinical pharmacology review team were able to establish a PK bridge based on the similarities of serum concentrations of etanercept between adults with PsA and pediatric subjects with PsO at the proposed JPsA dose of 0.8 mg/kg. Given the disease similarities between PsA and JPsA, the establishment of a PK bridge provided a scientific justification to extrapolate the efficacy of etanercept established in adults with PsA to pediatric patients with JPsA. Since the PK bridging process also established that the serum concentration of etanercept were similar in pediatric subjects with PsO and JIA, and JPsA is a subtype of JIA, it is also expected that the approved weight-based doing regimen would result in similar PK exposures of etanercept in these pediatric populations thus

[6] Schanberg LE, Mulugeta L, Akinlade B, et al. Therapeutic Development in Polyarticular Course Juvenile Idiopathic Arthritis: Extrapolation, Dose Selection, and Clinical Trial Design. *Arthritis and Rheumatology* 2023, p.1-11. DOI 10, 1002/art.42534.

permitting the leverage of safety data from adequate and well controlled clinical studies conducted in pediatric subjects with polyarticular JIA and PsO. Additional support of safety was provided from a retrospective analysis of 191 pediatric patients with JPsA treated with etanercept followed in the CARRA Registry (study 20210089). No new safety or unexpected safety signals were identified on review of these data or the nearly 24-years of cumulative, spontaneous postmarketing safety data in children less than 18 years of age exposed to etanercept collected by the Applicant submitted in support of this application. Additional support for safety was provided by a postmarketing safety update conducted by internal consultants in OSE's DPV-1 that also did raise any new safety concerns associated with administration of etanercept to pediatric patients. Based on the available safety data, the expectation is that the postmarketing safety experience for pediatric patients 2 years of age and older with JPsA will be similar to the experience of pediatric patients with JIA and PsO as well as adults with PsA.

In summary, pediatric JPsA is a rare and serious disorder with an unmet need for new therapies. The Applicant has provided adequate data and information to inform the benefit-risk assessment of etanercept for the treatment of pediatric patients with active JPsA in patients 2 years of age and older. Approval of etanercept will provide an additional treatment option for pediatric patients given the limited number of approved treatments for this disease in the U.S. Therefore, the review team recommends approval of supplement 5595. The Division signatory agrees with this assessment and recommendation.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Juvenile idiopathic arthritis (JIA), formerly known as juvenile rheumatoid arthritis (JRA), is a broad term used to describe a heterogeneous group of inflammatory disorders characterized by arthritis of one or more joints of unknown etiology persisting for 6 or more weeks in a child younger than 16 years of age<br>• Psoriatic JIA, also referred as juvenile psoriatic arthritis (JPsA), is a subtype of JIA and comprises between 2 to 11% of children with JIA<br>• Clinical manifestations of JPsA are similar to adult PsA with peripheral and axial arthritis, enthesitis, dactylitis, plaque psoriasis, and nail changes | • JPsA is a serious and potentially disabling form of JIA with significant impact on quality of life for patients and families. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Current Treatment Options | • There are three currently approved treatments (golimumab, secukinumab, and ustekinumab) for pediatric patients with JPsA<br>• Recommendations for treatment are based on Expert Consensus Treatment Guidelines. Determination of treatment is based on active disease manifestations<br>• Standard of care treatment for patients with oligoarticular JPsA is similar to treatment of adults with PsA: initial treatment with NSAIDs and intra-articular glucocorticoids, that can be escalated to include a non-biologic DMARD, and/or biologic DMARD, in face of persistent or increasing disease activity. Pediatric patients with axial disease are treated initially with an NSAID as well as a biologic DMARD | • There is an unmet need for safe and efficacious therapies for pediatric patients with JPsA since not all respond to currently approved treatments. |
| Benefit | • The efficacy etanercept has been previously demonstrated in adult patients with PsA. Two phase 3 studies (20130207 and 20021630) supported the approval of etanercept for the treatment of PsA in adult patients<br>• The efficacy of etanercept has been demonstrated in adult PsO and pediatric PsO studies<br>  ○ Studies 20021639 and 20021642 were phase 3 studies that led to the approval of etanercept for the treatment of adults with plaque psoriasis<br>  ○ Study 20030211 was a phase 3 study conducted in pediatric patients that lead to the approval of etanercept for the treatment of children 4 to 17 years old with PsO who are candidates for systemic therapy or phototherapy<br>• The efficacy of etanercept has been previously demonstrated in adult RA patients. Study 20021636 was a phase 3 study that supported the approval of etanercept for the treatment of adults with RA<br>• The efficacy of etanercept has been previously demonstrated in | • The efficacy of etanercept in pediatric patients age 2 years and older with active JPsA is based on PK-exposure matching and extrapolation from the established efficacy of etanercept in adults with PsA in pivotal trials (20130207 and 20021630). This approach is justified based on similarities of disease manifestation and disease progression in adults and pediatric patients with PsA. Additional efficacy information is provided by the established efficacy of etanercept, at similar exposures, in the related indications of adult and pediatric PsO, pediatric JIA, and adult RA. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | pediatric patients with polyarticular JIA 2 years of age and older<br>○ Studies 20021616 and 20021618 were phase 2/3 and 3b studies, respectively, reviewed in support of the original approval for polyarticular JIA in children ages 4 years and older<br>○ Studies 20021628 was a phase 3 study and 20021626 was a phase 4 registry in pediatric patients with polyarticular JRA while study 20021631 was phase 3 study in children ≥2 years and older with systemic-onset JRA that were reviewed in support of lowering the age threshold for JRA down to children ages 2 years and older | |
| Risk and Risk Management | • The PK exposure is expected to be similar in pediatric patients with polyarticular JIA, PsO, and JPsA, supporting the relevance of safety data from polyarticular JIA and PsO pediatric populations to the expected safety in the JPsA population<br>• The safety database comprised of safety data from the pediatric studies reviewed in support of the pediatric polyarticular JIA and PsO indications as well as real time safety data from pediatric patients with JPsA treated with etanercept followed in the CARRA Registry and nearly 24-years of postmarketing pharmacovigilance safety data in pediatric patients exposed to etanercept is sufficient to provide a risk assessment for etanercept in the JPsA population | • Polyarticular JIA and JPsA are both subtypes of JIA. It is reasonable to leverage the safety data from pediatric studies previously reviewed in support of the indication for polyarticular juvenile rheumatoid arthritis (now known as juvenile inflammatory arthritis) in children 4 years of age and older and the subsequent lowering of the age threshold down to 2 years and older<br>• Approximately 40-60% of pediatric patients with JPsA have PsO. Therefore, it is also reasonable to leverage the safety data from the pediatric study previously reviewed in support of the pediatric indication of PsO in children ages 4 to 17 years old who are candidates for systemic therapy or phototherapy<br>• Based on the available safety data from |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | | children treated with etanercept in the CARRA Registry and long-term, cumulative postmarketing safety data, the postmarketing safety experience for pediatric patients 2 years of age and older with JPsA is expected to be similar to that of pediatric patients with JIA and PsO as well as adults with PsA |

# 2 Therapeutic Context

## 2.1. Analysis of Condition

Juvenile idiopathic arthritis, formerly known as JRA, is a broad term used to describe a heterogeneous group of inflammatory disorders characterized by arthritis of one or more joints of unknown etiology persisting for 6 or more weeks that begins before 16 years of age.[7] It has been estimated that the worldwide prevalence of JIA ranges from 3.8 to 400/100,000 with an incidence of 1.6 to 23 per 100,000.[8] The most commonly used classification criteria for JIA currently is the 2001 revised ILAR which subdivides JIA into 7 different subgroups that are described in Table 1**Error! Reference source not found.**[9]

**Table 1. ILAR Classification of JIA Subtypes*[10]**

| Category | Diagnostic Criteria |
|---|---|
| **Systemic Arthritis** | Fever of at least 2 weeks duration (daily for at least 3 days) and arthritis in ≥1 joint, plus one or more of the following:<br>1. Erythematous rash<br>2. Generalized lymphadenopathy<br>3. Hepatomegaly and/or splenomegaly<br>4. Serositis<br>Exclusions: a, b, c, d |
| **Oligoarthritis (persistent or extended)** | Arthritis affecting ≤4 joints during the first 6 months of disease<br>There are 2 subcategories:<br>1. Persistent: affecting no more than 4 joints throughout the disease course<br>2. Extended: affecting more than 4 joints after the first 6 months of disease<br>Exclusions: a, b, c, d, e |
| **Polyarthritis, Rheumatoid Factor (-)** | Arthritis affecting ≥5 joints during the first 6 months of disease; test for RF is negative<br>Exclusions: a, b, c, d, e |
| **Polyarthritis, Rheumatoid Factor (+)** | Arthritis affecting ≥5 joints during the first 6 months of disease; ≥ 2 tests for RF at least 3 months apart during the first 6 months of disease is positive<br>Exclusions: a, b, c, e |
| **Psoriatic arthritis** | Arthritis and psoriasis, or arthritis and at least 2 of the following: |

[7] Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* (2004) 31:390-2.
[8] Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. *Joint Bone Spine* 2014;81(2):112-117.
[9] Petty et al. *J Rheumatol* (2004) 31:390-2.
[10] Petty et al. *J Rheumatol* (2004) 31:390-2.

| | |
|---|---|
| | 1. Dactylitis<br>2. Nail pitting or onycholysis<br>3. Psoriasis in a first-degree relative<br>Exclusions: b, c, d, e |
| **Enthesitis related arthritis (ERA)** | Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:<br>1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain**<br>2. The presence of HLA-B27 antigen<br>3. Onset of arthritis in a male over 6 years of age<br>4. Acute (symptomatic) anterior uveitis<br>5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative<br>Exclusions: a, d, e |
| **Unclassified arthritis** | Arthritis that fulfills criteria in no category or in 2 or more of the above categories |

Exclusions: a) Psoriasis or a history of psoriasis in the patient or first-degree relative; b) Arthritis in an HLA-B27 positive male beginning after the sixth birthday; c) Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease or acute anterior uveitis or a history of one of these disorders in a first-degree relative; d) the presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart; and e) the presence of systemic JIA in the patient.
*JIA is arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks.
**Inflammatory lumbosacral pain is defined as lumbosacral pain at rest with morning stiffness that improves with movement.
Abbreviation: RF=rheumatoid factor

Pediatric or juvenile psoriatic arthritis is a rare subtype affecting approximately 2-11% of the JIA population, with a calculated annual incidence of approximately 3 per million children.[11,12] It is defined by the presence of inflammatory arthritis and psoriasis and at least two of the following: dactylitis, nail pitting, onycholysis or family history of psoriasis in a first-degree relative (Table 1).[13] The arthritis in JPsA tends to be asymmetrical involving the peripheral joints such as the small joints of the hands and feet, ankles, and knees, as well as the axial skeleton. It has a bimodal age of onset, with peaks occurring in children during the preschool years (predominantly in females) and again later during mid to late childhood.[14] In younger children who develop JPsA, the disease clinically resembles early-onset oligoarticular JIA, while older children and adolescents who present with this disease may also have enthesitis with or without spinal or sacroiliac disease similar to that seen in adults with PsA. Other than a difference in the timing of psoriasis and arthritis onset, JPsA and adult PsA share many of the same disease characteristics and clinical manifestations suggesting that they may be a spectrum of the same disease (Table 2).[15]

[11] Stoll ML, Mellins ED. Psoriatic arthritis in childhood. A commentary on the controversy. *Clin Immunol* 2020;2149(1): 108395.
[12] Ravelli A and Martini A. Juvenile idiopathic arthritis. *Lancet* 2007;369(9563):767-78.
[13] Petty et al. *J Rheumatol* (2004) 31:390-2.
[14] Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, and Nigrovic P. Patients with juvenile psoriatic arthritis comprise two distinict populations. *Arthritis and Rheumatism* 2006;(54):3564-3372.
[15] Brunello F, Tirelli F, Pegoraro L, Dell'Apa F, Alfisi A, Calzamatta G, Folisi C, and Zulian F. New insights on juvenile psoriatic arthritis. *Front Pediatr* 10:884727. Doi: 10.3389/fped.2022.884727

**Table 2. Similarities and Differences Between PsA in Adults and JPsA in Children[16]**

| Clinical Feature | Adult PsA | JPsA |
|---|---|---|
| **Timing of psoriasis and arthritis onset** | Psoriasis prior to arthritis | Arthritis prior to psoriasis |
| **Peripheral arthritis** | | |
| **Oligoarticular** | 20-55% | 45-55% |
| **Polyarticular** | 20-60% | 35-55% |
| **Oligo-extended** | 7-40% | 15-38% |
| **Axial arthritis** | 7-40% | 10-30% |
| **Radiological damage** | 47% | 25% |
| **Enthesitis** | 30-50% | 12-45% |
| **Dactylitis** | 40-50% | 17-37% |
| **Nail involvement** | 41-93% | 37-57% |
| **Uveitis** | 8% | 8-13% |
| **HLA-B27 positive** | 40-50% | 10-25% |
| **ANA positive** | 16% | 40-46% |

There is also data suggesting that the pathogenesis of JPsA and PsA are similar based on elevated levels of the pro-inflammatory cytokines IL-17, IL-23, and tumor necrosis factor observed in patients with these diseases.[17] This has resulted in the clinical development of therapeutic biologic agents such as secukinumab, ustekinumab and golimumab that target these inflammatory cytokine pathways and are effective treatments of both PsA and JPsA. However, as discussed at the 2019 public workshop, "Accelerating Drug Development for pJIA," held at the University of Maryland Center for Regulatory Science and Intervention, an unmet medical need for additional therapeutic options exists for pediatric patients with JPsA since not all patients respond to these approved treatments which can result in significant and permanent disability.[18]

## 2.2. Analysis of Current Treatment Options

Table 3 lists the three currently approved biological DMARDs for JPsA (golimumab, secukinumab, and ustekinumab) as well as other biological and non-biologic DMARDs that are approved for the treatment of JIA which are used as off-label treatments for JPsA. In addition, several NSAIDs (celecoxib, naproxen, ibuprofen, rofecoxib, meloxicam, and tolectin), as well as glucocorticoids, are approved for the treatment of JIA and JRA, and are used as off-label treatments for JPsA.

[16] Brunello F, et al. *Front Pediatr* 10:884727. Doi: 10.3389/fped.2022.884727
[17] Carvalho AL, Hedrich CM. The molecular pathophysiology of psoriatic arthritis-the complexity interplay between genetic predisposition , epigenetic factors, and the microbiome. *Front Mol Biosci.* 2021;8:662047. Doi:10.3389/molb.2021.662047
[18] Schanberg LE, et al. *Arthritis and Rheumatology* 2023, p.1-11. DOI 10, 1002/art.42534.

## Table 3. Summary of Treatment Armamentarium Relevant to Proposed Indication

| Product Name | Relevant Indication | Year of Approval | Dosing/ Administration | Efficacy Information | Important Safety and Tolerability Issues |
|---|---|---|---|---|---|
| **FDA Approved Treatments for JPsA** | | | | | |
| Ustekinumab | Pediatric patients with JPsA | 2009/2022 | SC formulation:<br>< 60 kg dose is 0.75 mg at Wks 0 and 4 and then q12w thereafter<br><br>≥ 60 mg dose is 45 mg at Wks 0 and 4 and then q12w thereafter<br><br>> 100 kg with co-existent moderate-to-severe plaque psoriasis 90 mg at Wks 0 and 4 and then q12w thereafter | PK-extrapolation using data from adult PsA | Similar to safety profile in adults |
| Secukinumab | Pediatric patients with JPsA | 2016/2021 | Children ≥ 2 years:<br>≥ 15 kg to <50 kg dose is 75 mg SC at Wks 0, 1, 2, 3, and 4 and then q4w thereafter<br><br>≥ 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 JPsA | 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 pJIA study | Similar to safety profile in adults |
| **FDA Approve Treatments for JIA** | | | | | |
| Tofacitinib | Polyarticular Course JIA* | 2012/2020 | Children ≥ 2 years:<br>10 to <20 kg: 3.2 mg (3.2mL oral solution) BID;<br>20 to <40 kg: 4 mg (4 mL oral solution) BID<br><br>≥ 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 | Children (b) (4) years: IV formulation<br><75 kg 10 mg/kg at wks 0, 2, and 4, then q4w<br>≥75 kg 750 mg at wks 0, 2, and 4, then q 4w | RW study with fewer flares (IV); OL PK-extrapolation (SC) | Similar to safety profile in adults |

| Product Name | Relevant Indication | Year of Approval | Dosing/ Administration | Efficacy Information | Important Safety and Tolerability Issues |
|---|---|---|---|---|---|
| | | | Children ≥2 years: SC formulation<br>10 kg to <25 kg: 50 mg qw<br>25 kg to <50 kg: 87.5 mg qw<br>≥50 kg: 125 mg qw | | |
| Adalimumab | pJIA | 2002/2008 | Children ≥2years:<br>10 to <15 kg: 10 mg SC q2w<br><br>15 to <30 kg:20 mg SC q2w<br><br>≥30 kg: 40 mg SC q2w | RW study with fewer flares vs PBO | Infections, hypersensitivity, and ↑CPK |
| Etanercept | pJIA | 1998/1999 | Children ≥2 years:<br><63 kg: 0.8 mg/kg SC qw<br><br>≥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:<br>initial therapy: 40-60 mg/kg/day, divided into 3 to 6 doses<br><br>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; 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

JPsA patients are generally managed via expert, consensus-driven, treatment regimens recommended for JIA that were updated in 2019 by the American College of Rheumatology/Arthritis Foundation.[19] Initial treatment regimens are based on a patient's level of disease activity (amount of peripheral joint involvement and the presence/absence of axial skeletal involvement and/or systemic manifestations) and are similar to those used to treat adults with PsA. Patients with oligoarthritis without axial or systemic involvement or who have low disease activity are typically treated with NSAIDs and intra-articular injections of glucocorticoids that can be escalated to include a nonbiologic DMARD (methotrexate, sulfasalazine) as second-line treatment for persistent disease activity. Initiation of treatment

[19] Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guidelines for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. *Arthritis Care &Res* 2019. 71:717-734.

with a biological DMARD is generally reserved for patients who are intolerant or who are considered conventional DMARD failures as a result of persistent or progressing underlying disease activity. Short courses of oral glucocorticoids may be used in such cases as bridging therapy until non-biologic or biologic DMARD therapy becomes effective. Children who have dactylitis that fails to respond to local glucocorticoid injection, or who have sacroiliac and/or axial involvement are typically treated with a biologic DMARD along with an NSAID for symptomatic relief. Physical therapy to maintain range of motion, prevent deformities, and to minimize loss of function of affected joints is an integral component of the treatment and management of children with JPsA.

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

The following regulatory summary discusses only INDs pertinent to etanercept's approved indications. IND's 4571 and 5088 were initially submitted to the Agency's Center for Biologics Evaluation and Research (CBER) in December 1992 to study the indication of RA by Immunex, a subsidiary of Amgen, Inc. IND 4571 served as the repository for non-clinical information supporting all INDs under which various clinical development programs for etanercept were being conducted. Clinical studies in RA, pJIA and AS were conducted under IND 5088. The lyophilized formulation of etanercept was first approved as a treatment for RA in 1998 under BLA 103795/S-0000 which was subsequently followed by the approval of the pJIA indication with biweekly weight based dosing in 1999 under sBLA 103795/S-1001. In January 2000, IND 8806 was submitted by Immunex to study etanercept as a treatment of adults with PsA and PsO, and children with PsO. The indications for the treatment of PsA in adults and active AS were added to etanercept's label with the approvals of efficacy supplements S-5034 in 2002, and S-5123 in 2003, respectively. Etanercept's 50 mg once weekly dosing regimen for RA, PsA, and AS, as well as the once weekly weight-based dosing for pJIA were also approved in 2003 (sBLA 103795/S-5110). In 2004, the treatment of adult patients with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy was approved under sBLA 103795/S-5149. The PsO indication was expanded to include children ages 4 to 17 years old in 2016 by the Division of Dermatology and Dentistry under sBLA 103795/S-5552. Etanercept's remaining presentations were approved via various supplements under BLA 103795 as follows: the 50 mg/mL liquid formulation supplied in a single dose pre-filled syringe (PFS) in 2004 (S-5184); the SureClick Autoinjector (AI) in 2006 (S-5286); the Enbrel Mini for use with the AutoTouch AI in 2017 (S-5556), and the 25 mg/0.5 ml single dose vial in 2020 (S-5577).

## 3.2. Summary of Presubmission/Submission Regulatory Activity

Since the Pediatric Research Equity Act (PREA) was not enacted until 2003, a postmarketing requirement to conduct pediatric studies of etanercept in children with JPsA was not sought as a condition for approval of etanercept as a treatment for adults with PsA in 2002. In October

2019, the Agency in collaboration with the University of Maryland Center for Regulatory Science and Innovation (FDA/M-CERSI), held a public workshop titled "Accelerating Drug Development for pJIA" that brought together academia, industry, regulators and patients to discuss the cumulative experience with drug development for pJIA.[20] Based on the discussions held at this public workshop, the need for treatments for JPsA, and the approach to pediatric assessments for PsA, the Agency subsequently reconsidered its approach to the pediatric assessment of PsA and waivers previously issued to applicants for studies in JPsA.

On November 20, 2020, the Agency issued an Advice informing Amgen, Inc. that they considered the high degree of similarity between adults with PsA and pediatric patients with JPsA 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 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 JPsA or, with appropriate justification, a relevant pediatric population.

On July 1, 2021, the Applicant requested a Type C meeting with the Agency to obtain advice on an efficacy supplement for the proposed indication of etanercept for the treatment of PsA in children 2 years of age and older. In lieu of a face-to-face meeting, written responses were provided to the Applicant's questions on September 14, 2021, as follows:

- Feedback was provided regarding the adequacy of the proposed data to support submission of an efficacy supplement to expand the current PsA indication to include pediatric patients. The Applicant was informed their future submission needed to include (1) a justification that adult PsA and JPsA are similar; (2) PK matching between the adult RA, PsO, and PsA populations to the pediatric PsO and JIA populations to support PK-based efficacy extrapolation for JPsA; and (3) safety data from relevant pediatric populations (i.e., JIA and pediatric PsO). The Applicant was also informed (1) that inclusion of data from the CLIPPER and CLIPPER 2 studies in JIA and real-world data from the CARRA registry would be considered supplemental evidence and may not be necessary for regulatory decision-making but was at the Applicant's discretion to submit; and (2) that they should try to clarify how many patients enrolled in the pediatric PsO and JIA studies had JPsA which could be utilized as supplemental evidence for efficacy, safety, and PK. (3) It was essential to have PK data from adult patients with PsA to support the efficacy extrapolation for JPsA.
- The Applicant's proposed pediatric dosing regimen of 0.8 mg/kg weekly via subcutaneous (SC) injection for pediatric patient weighing <63 kg or 50 mg weekly

[20] Schanberg LE, et al. *Arthritis and Rheumatology* 2023, p.1-11. DOI 10, 1002/art.42534.

via SC injection for pediatric patients weighing ≥63 kg appeared reasonable but pediatric dosing for a JPsA indication would be informed by the PK data submitted, and therefore would be a review issue.

On September 28, 2022, the Agency issued clarifying comments regarding the written responses dated September 14, 2021, in which the Applicant was informed that their proposed PK analysis in adults with PsA may be sufficient to support the PK-based extrapolation of efficacy to JPsA, but the suitability of the data to support approval would be a review issue. The Applicant was also informed that their proposed overall data package appeared to be reasonable, but they would need to include pertinent information on the safety analysis conducted to ensure the quality of the PK samples were not adversely impacted by storage as well as including a comparative analysis of PK data from adults with PsA with the PK data from adults with other indications (RA and PsO) including all relevant data sets as part of their sBLA package.

On December 20, 2022, the Applicant submitted sBLA 103795/S5595 to add the indication to etanercept's label as a treatment of active JPsA in patients 2 years of age and older, which is the subject of this review.

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

## 4.1. Office of Scientific Investigations (OSI)

This section is not applicable as no clinical data from a study conducted by the Applicant with etanercept in pediatric subjects with active JPsA was 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 JPsA. The information provided is adequate from product quality perspective.

## 4.3. Clinical Microbiology

This section is not applicable as no changes to the manufacture of the commercial product were included in this submission.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

No new nonclinical studies were submitted or required to support this efficacy supplement.

# 6 Clinical Pharmacology

## 6.1. Executive Summary

In this application, the Applicant has submitted an sBLA seeking to expand etanercept's marketing approval to include the treatment of pediatric patients age 2 years and older with active JPsA. The extrapolation of established efficacy of etanercept from adult PsA population is based on PK-exposure matching between adult and JPsA patients.

No clinical trials or dedicated PK studies were conducted in patients with JPsA. As stated in an Advice Letter to etanercept IND 008806 on November 20, 2020, the Food and Drug Administration (FDA) considered the high degree of similarity between adult and pediatric patients with PsA to support a scientific rationale for extrapolation of efficacy from adults with PsA to the JPsA population. Pursuant to the Advice Letter from the FDA to explore an extrapolation of efficacy from adult PsA to JPsA, the Applicant has presented data in this submission to demonstrate that PK exposures are similar between the 2 populations. Etanercept PK was therefore compared in pediatric subjects across approved indications, in adults across approved indications, and between adults and pediatric subjects in approved indications.

The clinical pharmacology review is focused on the PK bridging to support the proposed extrapolation approach and the proposed dosing regimen of etanercept for the treatment of pediatric patients age 2 years and older with active JPsA.

### 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 103795/s-5595 and finds the application acceptable to support approval from a clinical pharmacology perspective. The Division Signatory agrees with this assessment and recommendations.

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

No PK information is available in patients with JPsA. The data from the pediatric subjects with psoriasis and JIA as well as data from adult patients with psoriasis, RA and PsA, along with the similarity of the pathophysiology of PsA and its clinical features between adults and children,

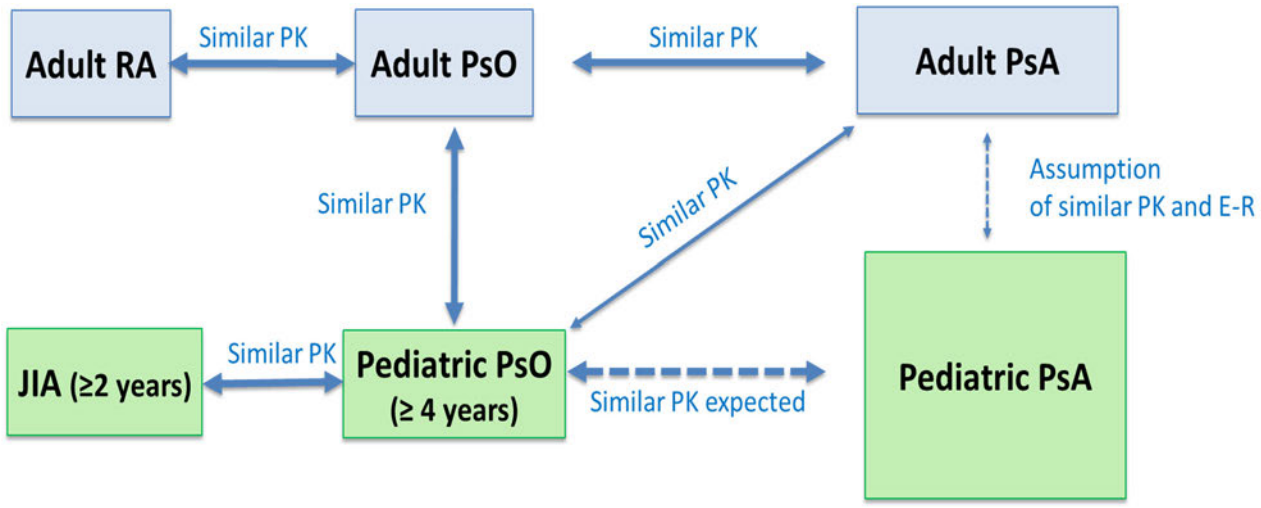
supports extrapolation of efficacy from adult PsA to JPsA, form the basis for the use of extrapolation for this application. Etanercept PK was therefore compared in pediatric subjects across approved indications, in adults across approved indications, and between adult and pediatric subjects in approved indications. In Written Responses issued on September 14, 2021, the FDA stated it was essential to have PK data from adult patients with PsA to support the efficacy extrapolation for JPsA. To address this requirement, the Applicant conducted a PK analysis of biomarker blood samples collected during the phase 3 study of etanercept in adult subjects with PsA, Study 20130207. In addition to exposure matching to support extrapolation of efficacy, etanercept PK was compared to support the proposed dose for patients with JPsA, to match the dosing regimens approved for the other pediatric indications of JIA and PsO.

The following PK analyses were performed to support the PK bridge between adult PsA and JPsA:

- Comparisons of etanercept PK exposure between pediatric psoriasis and JIA
- Comparisons of etanercept PK exposure between adult RA, adult psoriasis and adult PsA
- Comparisons of etanercept PK exposure between pediatric psoriasis and adult psoriasis and adult PsA

Figure 1 depicts the extrapolation approach for JPsA. PK is similar in adult patients with psoriasis and adult patients with RA; and between adult patients with psoriasis and adult patients with PsA; therefore, the disease is not expected to have a significant impact on PK. The PK in pediatric patients with psoriasis is similar to JIA, indicating that serum concentrations of etanercept are similar across indications within the pediatric age range. Therefore, PK in JPsA patients are expected to be similar to the other approved pediatric indications. To establish the PK bridge to pediatric patients with JPsA, 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 and JIA can be leveraged. For disease similarity and justification of the relevance of safety data from pediatric PsO and JIA, refer to Section 8.

**Figure 1. Extrapolation Approach to Support the Use of Etanercept in JPsA**




Source: Created by FDA Reviewer

Overall, the observed etanercept concentrations in subjects with JIA and pediatric PsO were within range of those observed for adult RA, PsA, and PsO after administration of etanercept. These analyses showed the similarity of etanercept PK across indications and ages when administered at a dose of 50 mg once weekly (QW) for adults or 0.8 mg/kg, up to 50 mg, QW for pediatric subjects. Therefore, PK exposure is expected to be comparable between adult PsA and JPsA. The PK bridge is established to support the extrapolation of the efficacy established in adults with PsA to pediatric patients with PsA. These results further support the use of the approved etanercept pediatric dosing regimen in JPsA:

- 0.8 mg/kg QW for pediatric patients < 63 kg (138 pounds)
- 50 mg QW for pediatric patients ≥ 63 kg (138 pounds)

### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

The recommended dosing for patients with JPsA is 0.8 mg/kg weekly, with a maximum of 50 mg per week.

**Therapeutic Individualization**

Therapeutic individualization is not recommended for patients with JPsA.

**Outstanding Issues**

None

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The following studies were used to compare the PK of etanercept between approved pediatric indications, between approved adult indications, and between approved adult and pediatric indications:

**Pediatric Studies**

- **Study 20030211:** a 3-part, phase 3 study with a 12-week, double-blind, placebo-controlled treatment period, a 24-week open-label treatment period, and a 12-week randomized double-blind withdrawal-retreatment period, in pediatric subjects 4 to 17 years of age with plaque PsO. Pharmacokinetic samples were collected on day, at the end of the double-blind period (week 12), at week 24 of the open-label period, and at the end-of-treatment, early-termination, or 30-day follow-up visit, as applicable.
- **Study 20021616:** a 2-part, phase 2/3, combination open-label and double-blind, randomized, multicenter study in pediatric subjects 4 to 17 years of age with polyarticular course JRA. Pharmacokinetic samples were collected on days 1 and 15, at the end of months 1, 2, and 3, and 30 days after discontinuation of study drug (or at the end of month 4 for subjects continuing into part 2 of the study).
- **Study 20021628:** a 2-part, phase 3, double-blind, multicenter study in pediatric subjects 2 to 18 years of age with polyarticular course JRA. Pharmacokinetic samples were collected on days 1, 30, 60, 90, and 120.
- **Study 20021631:** a 3-part, phase 3, combination open-label and double-blind, multicenter study in pediatric subjects 2 to 17 years of age with systemic onset JRA (JIA). Pharmacokinetic samples were collected on day 1 and at each monthly visit during parts 1A and 1B of the study.

**Adult Studies**

- **Study 20021636:** a phase 3 double-blind, randomized study with a 16-week blinded period in adult subjects with active RA. Subjects received etanercept 50 mg once weekly (QW) or 25 mg twice a week (BIW) SC for 16 weeks or placebo for 8 weeks followed by etanercept 25 mg BIW for the remaining 8 weeks. Pharmacokinetic samples were collected at multiple timepoints during weeks 1 and 8, as well as at weeks 4, 8, 12, and 16.
- **Study 20021639:** a phase 3, double-blind, randomized study with a 24-week blinded period followed by a withdrawal and retreatment period in adult subjects with PsO. Subjects received etanercept 25 mg QW, 25 mg BIW, 50 mg BIW SC, or placebo. Pharmacokinetic samples were collected on day 1 and at weeks 2, 4, 8, 12, and 24. Additional samples were collected during the withdrawal retreatment period and early termination visit.
- **Study 20021642:** a phase 3, double-blind, randomized study with a 12-week blinded period followed by up to 36 weeks of open-label therapy in adult subjects with PsO.

Subjects received etanercept 25 mg BIW, 50 mg BIW SC, or placebo. Pharmacokinetic samples were taken before study start and at weeks 2, 4, 8, and 12.

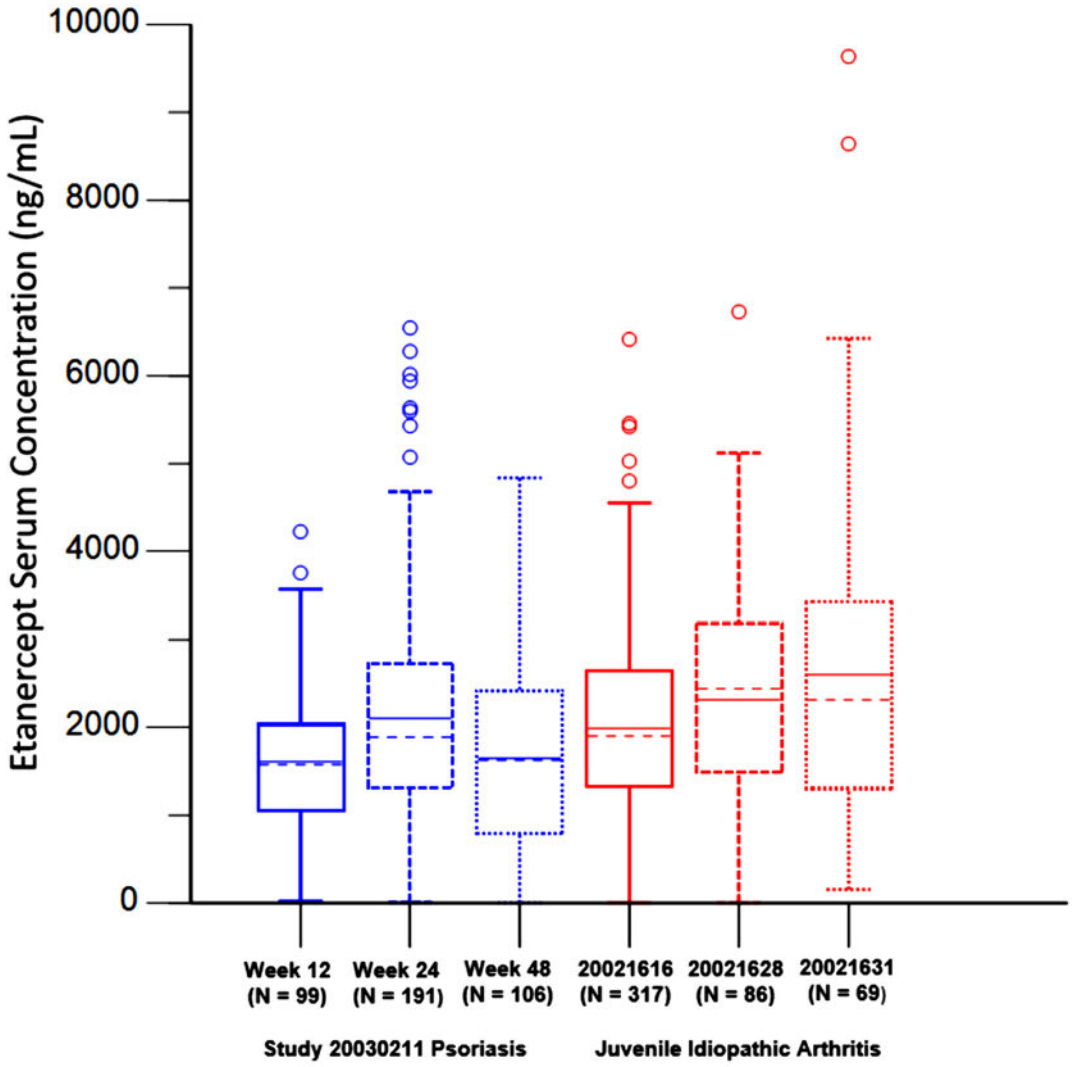
- **Study 20030115:** a phase 3, open-label, long-term extension study in adult subjects with PsO who participated in previous phase 3 etanercept PsO studies. Eligible subjects who had completed Studies 20021642 and 20021639 received etanercept 50 mg QW SC for at least 12 weeks. Pharmacokinetic samples were collected after subjects had received etanercept 50 mg QW for at least 4 weeks, at which point it was assumed that the etanercept concentration-time profiles would be close to steady-state. Blood samples were collected at multiple timepoints during a 1-week dosing interval and etanercept concentrations were summarized on day 7.
- **Study 20130207:** a phase 3, multicenter double-blind, randomized controlled study of etanercept and methotrexate (MTX) in combination or as monotherapy in subjects with PsA. Etanercept serum concentrations were quantified from biomarker samples collected on day 1 and at weeks 24 and 48.

There were no planned PK endpoints for Study 20130207. In Written Responses issued on 14 September 14, 2021, the FDA stated it was essential to have PK data from adult patients with PsA to support the efficacy extrapolation for JPsA. To address this requirement, Amgen conducted a PK analysis of biomarker blood samples collected during the phase 3 study of etanercept in adult subjects with PsA, Study 20130207. The Applicant identified samples from the subset of subjects who received etanercept 50 mg SC QW plus oral placebo in Study 20130207 and who had consented to additional sample analysis beyond what was listed in the protocol. Samples from this subset of subjects that still met stability requirements were included in the PK analysis.

***Similar PK Exposure Across Approved Pediatric Indications***

The steady-state etanercept concentrations in pediatric subjects with psoriasis from Study 20030211 were compared with concentrations in subjects with JIA from Studies 20021616, 20021628, and 20021631. The results showed that etanercept serum concentrations were similar in pediatric subjects with psoriasis and JIA, indicating that serum concentrations of etanercept are similar across indications within the pediatric age range (Figure 2).

**Figure 2. Comparison of Etanercept Serum Drug Concentrations Between Pediatric Subjects With Psoriasis (0.8 mg/kg up to 50 mg, QW) and JIA**




JIA = juvenile idiopathic arthritis; PsO = psoraisis; QW = once weekly
Boxes show mean (solid lines), median (dashed lines), 25th (bottom), and 75th (top) percentiles. Whiskers represent the lowest and highest values still within 1.5 times the respective interquratile range; data values that do not fall within 1.5 times the respective interquartile range are plotted as outliers.

Source: Figure 2 in Summary of Clinical Pharmacology Studies

***Similar PK Exposure Across Approved Adult Indications***

Etanercept steady-state concentrations in adult subjects with RA in Study 20021636 were compared with etanercept steady-state concentrations in adult subjects with psoriasis from Studies 20021639 and 20021642. The results showed that etanercept serum concentrations were similar in adult subjects with RA and psoriasis (Table 4).

**Table 4. Serum Etanercept Concentrations (ng/mL) at Week 8 Following Administration of Etanercept in Adult Subjects With Rheumatoid Arthritis (25 mg SC BIW or 50 mg SC QW) and Psoriasis (25 mg SC BIW)**

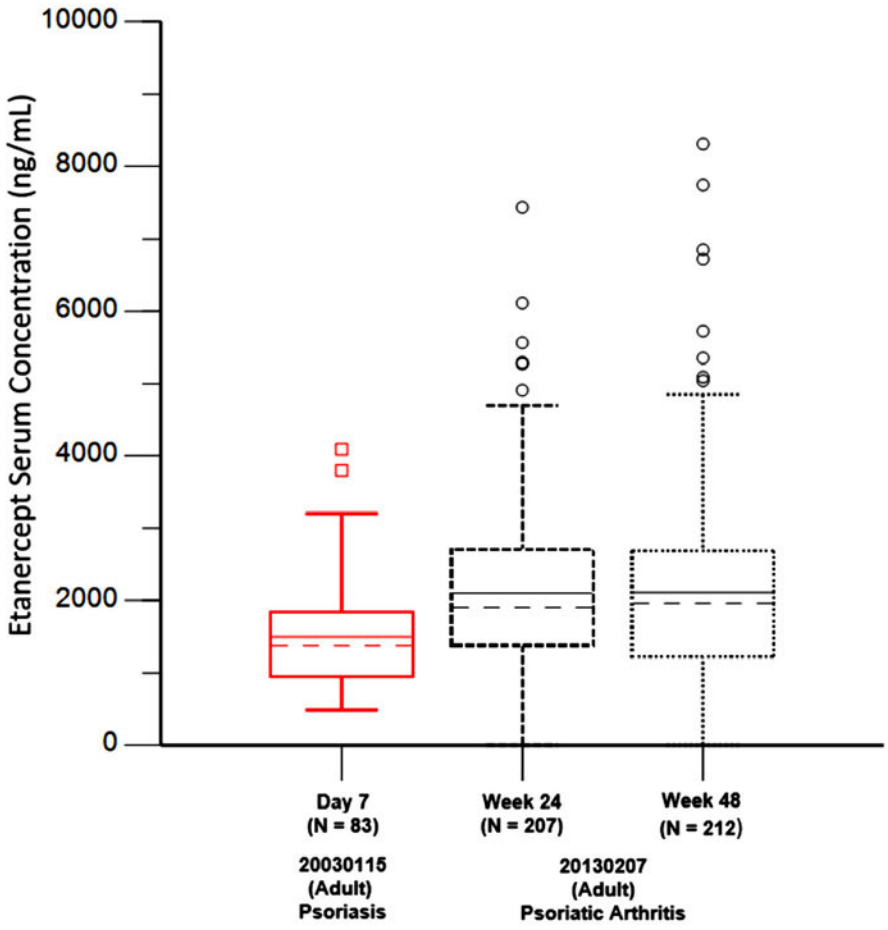
| | Rheumatoid Arthritis | | Psoriasis | |
|---|---|---|---|---|
| Week 8 | Study 20021636 | | Study 20021639 | Study 20021642 |
| Etanercept dose | 25 mg BIW | 50 mg QW | 25 mg BIW | 25 mg BIW |
| Number of subjects | 16 | 21 | 143 | 184 |
| Concentration (SD) | 1420 (730) | 1210 (694) | 1710 (974) | 1790 (1200) |

BIW = twice a week; CSR = clinical study report; QW = once weekly; SC = subcutaneous

Source: Table 3 in Summary of Clinical Pharmacology Studies

Eligible subjects who completed psoriasis Studies 20021639 and 20021642 could enroll in the long-term extension Study 20030115, in which they received etanercept 50 mg QW. The PK of etanercept across adult indications was investigated further using the data from psoriasis Study 20030115 and the PsA Study 20130207. The steady-state etanercept concentrations in adults with psoriasis who had received etanercept 50 mg QW for at least 4 weeks in Study 20030115 were compared with concentrations in adults with PsA from Study 20130207 at week 24 and week 48 (Figure 3. Comparison of Etanercept Serum Drug Concentrations Between Adult Subjects with Psoriasis and PsA (50 mg QW SC) PK). The results showed that etanercept serum concentrations were similar in adult subjects with psoriasis and PsA, indicating that serum concentrations of etanercept are similar across indications.

**Figure 3. Comparison of Etanercept Serum Drug Concentrations Between Adult Subjects with Psoriasis and PsA (50 mg QW SC) PK**




PK = pharmacokinetic; PsA = psoriatic arthritis; PsO = psoriasis; QW = once weekly; SC = subcutaneous
In the box plot the dashed line is the median and the solid line is the arithmetic mean. The ends of the box are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 interquartile range (IQR) of the lower quartile, and the highest value still within 1.5 IQR of the upper quartile, where IQR is the difference between the third and first quartiles, the middle 50%. Data values that do not fall between the whiskers are plotted as outliers outside of the whiskers.
In Study 20030115, PK samples were collected after subjects had been on the 50 mg QW dosing regimen for at least 4 weeks. The box plot shows data from day 7 of the PK assessment week.

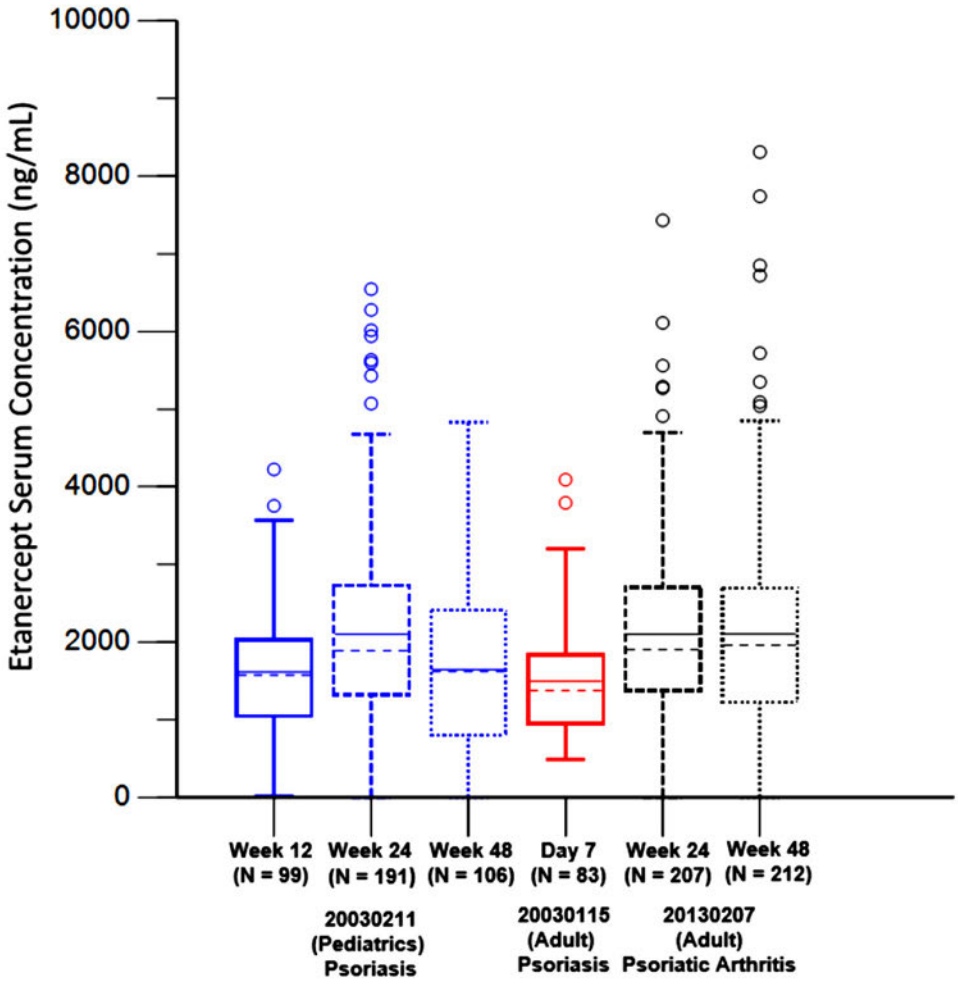
Source: Figure 3 in Summary of Clinical Pharmacology Studies

***Similar PK Exposure in Pediatric and Adult Subjects***

Etanercept steady-state concentrations in pediatric subjects 4 to 17 years of age with psoriasis in Study 20030211 were compared with the steady-state etanercept concentration in adult subjects with psoriasis from Study 20030115. The comparison demonstrated similar PK between adults (50 mg QW SC) and pediatric subjects 4 to 17 years of age (0.8 mg/kg, up to 50 mg, QW SC) with psoriasis. Furthermore, etanercept steady-state serum concentrations in adult and pediatric subjects with PsO were comparable to steady-state concentrations in adult subjects with PsA

from Study 20130207 (Figure 4). This comparison further confirms the similarity in etanercept PK across indications and age groups.

**Figure 4. Comparison of Etanercept Serum Drug Concentrations Between Pediatric Subjects (0.8 mg/kg up to 50 mg, QW SC) With Psoriasis and Adult Subjects (50 mg QW SC) With Psoriasis or PsA**




PK = pharmacokinetic; PsA = psoriatic arthritis; PsO = psoriasis; QW = once weekly; SC = subcutaneous
In the box plot the dashed line is the median and the solid line is the arithmetic mean. The ends of the box are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 interquartile range (IQR) of the lower quartile, and the highest value still within 1.5 IQR of the upper quartile, where IQR is the difference between the third and first quartiles, the middle 50%. Data values that do not fall between the whiskers are plotted as outliers outside of the whiskers.
In Study 20030115, PK samples were collected after subjects had been on the 50 mg QW dosing regimen for at least 4 weeks. The box plot shows data from day 7 of the PK assessment week.

Source: Figure 4 in Summary of Clinical Pharmacology Studies

### 6.3.2. Clinical Pharmacology Questions

**Does the clinical pharmacology program provide supportive evidence of effectiveness?**

Yes. The PK bridge is established to support the extrapolation of the efficacy established in adults with PsA to pediatric patients with JPsA. Overall, based on (1) the disease similarity of JPsA and adult PsA (2) the similarity in PK of etanercept across pediatric and across adult indications, as well as (3) the similarity in PK of etanercept between adults with PsA/psoriasis and pediatric psoriasis, it is expected that PK will be similar between adult PsA and JPsA. The PK bridge would support the extrapolation of established efficacy of etanercept in adult PsA population to JPsA population.

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

Yes. The proposed etanercept dosing regimen for the treatment of JPsA is 0.8 mg/kg QW administered SC, up to a maximum of 50 mg per week. This dose recommendation is based on the use of exposure matching for PK to support extrapolation of efficacy from adult PsA to JPsA. The proposed dosing regimen for patients with JPsA is the same as that approved for pediatric psoriasis and JIA.

The rationale that dose selection for etanercept in JPsA should be based on similar PK is supported by the following:

- Similar clinical features and pathophysiology in PsA between adults and pediatric subjects
- Efficacy of etanercept was demonstrated with these PK exposures in adult subjects with PsA
- Consistency of etanercept PK across indications and age groups:
    - Lack of differences in etanercept PK across indications in adult and pediatric subjects as demonstrated for pediatric psoriasis and JIA, and further shown by similar PK between adult PsA and adult psoriasis
- Similar etanercept observed concentrations between adults with PsA and pediatric subjects with psoriasis at the proposed JPsA dose
- The availability of direct safety experience with this dosing regimen in JIA and pediatric psoriasis patients. Based on the exposure matching for extrapolation from JIA and pediatric psoriasis and safety information in these patient populations, the safety profile of etanercept in JPsA is expected to be consistent with the safety profile of etanercept in JIA and pediatric PsO

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

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

An alternative dosing regimen for subpopulations based on intrinsic patient factors is not necessary based on the Enbrel USPI.

**Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

Etanercept is recombinant human TNF receptor fragment crystallizable (huTNFR:Fc), a fully human dimer of 2 molecules of the extracellular portion of p75 tumor necrosis factor receptor (TNFR) fused to the Fc portion of a type 1 human immunoglobulin (Ig) G (IgG1) and therefore food-drug or drug-drug interactions are not expected.

# 7 Sources of Clinical Data and Review Strategy

## 7.1.Table of Clinical Studies

In support of adding to etanercept's indications the treatment of JPsA in children 2 years and older, the Applicant submitted the results from a matched PK/pharmacodynamic (PD) exposure analysis for etanercept as well as efficacy and safety data from clinical studies conducted in adults with PsA, PsO, and RA, and in children with polyarticular JRA and PsO treated with etanercept. PK/PD and efficacy data were primarily provided from the phase 3 study 20130207 conducted in adults with PsA treated with etanercept and MTX in combination or as monotherapy alone, and the phase 3 study 20021630 conducted in adults with active PsA and PsO treated with etanercept. Evidence of safety and additional PK/PD data were provided from the phase 2/3 study 20021616 conducted in children ages ≤4 to ≤18 years of age with active polyarticular JRA refractory to MTX treated with etanercept, and from studies 20030211 and 20050111 which were phase 3 studies conducted in children ages 4 to ≤18 years old with PsO treated with etanercept. Efficacy, safety, and PK/PD data from these studies were previously reviewed in support of the marketing approval for etanercept's indications as a treatment for adults with PsA and children with JRA and PsO. Additional support of etanercept's safety as a treatment for JPsA was provided by an uncontrolled, retrospective analysis of safety and efficacy data from a subgroup of children ages ≥2 and <18 years old with JPsA followed in the CARRA Registry (study 20210089). Other supportive evidence of efficacy and safety as well as PK/PD data comes from various phase 3 and 4 etanercept studies conducted in children with JRA (studies 20021626, 20021618, 20021628) and systemic-onset JRA (study 20021631), and adults with PsO (studies 20021639 and 20021642) and RA (studies 2002618 and 2021642) that have also been previously reviewed in support of these etanercept indications.

The key design features of these clinical trials and registries are summarized in Table 5 below.

**Table 5. Key Design Features of Controlled and Uncontrolled Studies in Adults with PsA, PsO, and RA; and Children with JIA, JPsA, PsO, and SOJA**

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | ***Controlled Studies to Support Efficacy and Safety*** | | | | | | |
| 20130207 | NCT01623752 | P3, MC, DB, R, PC, parallel group, efficacy, safety, and PK study | ETN 50 mg SC QW + MTX 20 mg QW;<br>ETN 50 SC mg QW + oral PBO;<br>SC PBO QW + MTX 20 mg QW | **1º endpoint:** ACR 20 response at Wk 24<br><br>**2º endpoints:** MDA response at WK 24; individual components of the ACR response, PsA disease activity, physical function, and QOL | 48 weeks | N=851 | Adults with PsA who were naïve to ETN and other biologics | 124 centers in Europe, Latin America, North America, and South Africa |
| 20021630 | NCT00317499 | P3, DB, R, PC, parallel group, efficacy and safety study with OL extension | 24-week, double-blind period: ETN 25 mg SC BIW vs PBO SQ QIW;<br>52-week, OLE: ETN 25mg SC BIW | **1º endpoint:** ACR 20 response rate at Wk 12<br><br>**2º endpoints:** ACR20/50/70 at various time points; individual components of the ACR response rate; modified Total Sharp Score; PASI 50/75; HAQ-DI and SF-36 | 106 weeks | N=205 | Adults 18-70 yo with active PsA ($\geq$ 3 swollen joints and $\geq$ 3 tender joints) in $\geq$ 1 of the following forms: 1) DIP involvement, 2) polyarticular arthritis, 3) arthritis mutilans, 4) asymmetric PsA, or 5) AS-like; with target PsO lesion $\geq$ 2 cm and an inadequate response to MTX therapy | 17 centers in US |

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | ***Studies to Support Safety*** | | | | | | |
| 20021616 | NCT03780959 | P2/3, MC, 2-part, efficacy, safety, population PK study conducted in 2-parts (OL period followed by DB efficacy period) | Part 1 (3-month OL): ETN 0.4 mg/kg up to 25 mg SC BIW; Part 2: Responders in Part 1 were randomized to continue receiving treatment with ETN vs PBO for 4 months or until disease flare occurred, whichever was earlier | **1º endpoint:** JRA Definition of Improvement (DOI)<br><br>**2º endpoints:** Number of subjects with disease flare; time to flare; individual components of the JRA DOI; articular severity score; Pain VAS; CRP; and morning stiffness | 7 months | Part 1: N=69; Part 2: N=51 | Children ages 4 ≤ to ≤ 18 yo with moderately to severely active polyarticular JRA with a variety of JIA onset types refractory or intolerant to MTX on concomitant NSAIDs and/or prednisone (≤ 0.2 mg/kg/day or 10 mg/d maximum) | Approximately 9 centers in the US and Canada |
| 20030211 | NCT00078819 | P3, MC, R, efficacy, safety and PK study conducted in 3 parts | Part 1 (12-week, DB, PC portion): ETN 0.8 mg/kg up to 50 mg SC QW vs PBO SC QW; Part 2 (24-week, OL portion): ETN 0.8 mg/kg up to 50 mg SC QW; Part 3 (12-weeK, R, DB, withdrawal -retreatment portion): Subjects who achieved PASI 75 were re-randomized to ETN 0.8 mg/kg up to 50 mg SC QW or PBO SC | **1º endpoint:** PASI 75 response at Week 12<br><br>**2º endpoints:** PASI 50 response, sPGA, CDLQI, and PASI 90 response at Wk 12 | 48 weeks | N=211 | Children ages 4 ≤ to ≤ 18 yo with PsO currently or previously treated with phototherapy or systemic therapy, or poorly controlled with topical treatment | 42 centers in US and Canada |

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| 20050111 | NCT00141921 | P3, OLE, safety and efficacy study | ETN 0.8 mg/kg up to 50 mg SC QW | **1º endpoint:** incidence of AEs, SAE, and AESI<br><br>**2º endpoints:** PASI 50/75/90;percent improvement in PASI score from baseline; sPGA; CDLQI; improvement in articular pain from baseline | 264 weeks | N=182 | Children ages 4 ≤ to ≤ 18 yo with PsO who completed 20030211 or achieved PASI 50 at Wk 12 | 38 centers in US and Canada |
| 20210089 | NA | Retrospective study utilizing existing safety and efficacy data collected within the CARRA Registry | ETN 0.8mg/kg up to 50 mg SC QW | **Safety:** AESI, SAEs, and malignancies<br><br>**Efficacy:** ACR30/50/70/90/100; cJADAS-10; and ACR provisional criteria for inactive disease at 6 and 12 months from baseline use of ETN | N/A | N=191 | Children ages ≥ 2 and <18 yo with JPsA treated with ETN | 70 clinical sites in the US and Canada |
| | | ***Other studies pertinent to the review of efficacy or safety*** | | | | | | |
| 20021626 | NCT00078793 | P4, OLE, safety registry [Pediatric Rheumatology Collaborative Study Group (PRVSG)] | ETN 0.8mg/kg up to 50mg QW alone, vs ETN 0.8 mg/kg up to 50m g QW + MTX; vs NTX alone | **Safety:** AEs, growth data, occurrence of any new AI diseases; cancer rates; Child Behavior Checklist (subscales and total scores)<br><br>**Efficacy:** improvement in number of active arthritic joints; PGA | 36 months | N=594 | Children ages ≥ 2 and <18 yo with JRA or polyarticular JRA who had not received treatment with other biologic therapy within 6 months or any previous anti-TNF therapy, and did not have a significant concurrent medical condition | 26 clinical sites in US and Canada |

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| 20021618 | NCT00357903 | P3b, OLE, efficacy, safety, and QOL study | ETN 50 mg SC QW for adult subjects; 0.8 mg/kg up to 50 mg QW for pediatric subjects | **Efficacy: Adults** – ACR20/50 /70; DAS28; morning stiffness; SDAI; CDAI; change in ACR components; pain VAS; and HAQ-DI<br><br>**Efficacy: Peds**- JRA-DOI 30/50/70 and subcomponents; LOM; joint counts; pain VAS; articular severity score, morning stiffness, and complete joint response<br><br>**Safety:** SAEs; deaths; AESI; exposure to ETN; and safety-related discontinuations | Up to 10 years | N=714 adults and 69 pediatric subjects | Subjects with DMARD-refractory RA and JRA (diagnosed at ≤ 16 years of age) who have been enrolled in study 20021618 | 38 sites in US and Canada |
| 20021628 | NTC03781375 | P3, MC, DB, PC, efficacy, and safety study | ETN 0.8 mg/kg up to 25 mg BIW + MTX PO or SC QW; vs PBO + MTX PO or SC QW | **1º endpoint**: JRA DOI at 6 Months<br><br>**2º endpoints:** JRA DOI 505/70%; TEAEs, VS; and lab tests | 13 Months | N=25 | Children ages ≥ 2 and <18 yo with polyarticular JRA taking concomitant stable doses of MTX between 0.3 to 1 mg/kg/wk | 7 sites in US<br><br>(Discontinued due to poor enrollment) |

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| 20021631 | NCT00078806 | P3, 3-part combination OL and DB, efficacy, safety, and population PK study | Part 1A (OL): ETN 0.4 mg/kg BIW<br>Part 1B (OL): ETN 0.8 mg/kg BIW<br>Part 2 (DB): ETN 0.4 mg/kg or 0.8 mg/kg BIW;<br>Part 3 (OL): ETN 0.4 mg/kg or 0.8 mg/kg BIW; | **Efficacy:** comparison of responders defined by a 50% reduction in prednisone dose and no increase in systemic or articular disease activity over the 1 month between 2 consecutive visits after reduction; response with improvement defined as response with respect to 50% prednisone reduction and improvement in at least 1 of the baseline systemic features<br><br>**Safety:** TEAEs; infections; ISR; anti-ETN antibodies; VS; and labs | 13 Months | N=19 | Children ages ≥ 2 and <18 yo with active SOJRA on stable doses of prednisone | 11 sites in US and Canada<br><br>(Discontinued due to poor enrollment) |

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| 20021639 | NA | P3, MC, R 2-part, 24-Wk DB and 48-Wk withdrawal and retreatment period, efficacy, safety, and PK study | ETN 25 mg SC QW, 25 mg SC BIW, or 50 mg SC BIW vs PBO SC | **1º endpoint**: PASI 75 at Wk 12<br><br>**2º endpoints:** PASI 50/75/90 at Wk 24; subject and physician's global assessments of clear/almost clear; DLQI; EQ-5D-FTl; portion who discounted due to LOE; PK, safety and immunogenicity | 72 Weeks | N=652 | Adults ≥ 18 yo with PsO involving ≥ 10% BSA and minimum PASI score of 10 at screening | 47 sites in US |
| 20021642 | NA | P3, MC, R, 2-part, 12-Wk DB and 36-Wk OL, efficacy, safety, and PK study | ETN 25 mg SC BIW or 50 mg SC BIW vs PBO SC | **1º endpoint:** PASI 75 at Wk 12<br><br>**2º endpoints**: PASI 50/90 at Wk 12; percent improvement from baseline in PASI score; subject and physician's global assessments of clear/ almost clear; DLQI; SF-36; PK, safety and immunogenicity | 48 Weeks | Part 1 N= 583; Part 2 N=557 | Adults ≥ 18 yo with PsO involving ≥ 10% of BSA and minimum PASI score of 10 at screening | 50 sites in US, Canada, and Europe |

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| 20021636 | NA | P3, MC, R, DB, PC, efficacy, safety, and PK study | ETN 50 mg SC QW or 25 mg SC BIW vs PBO SC | **1º endpoint:** ACR20 at WK8<br><br>**2º endpoints**: safety, ACR20/50 at Wk 16, improvement in individual components of ACR criteria at Wk 8 and 16; and PK | 16 Weeks | N=420 | Adults ≥ 18 yo with active RA naïve to ETN and other TNF antagonists | 48 sites in US |

ACR20/50/70= American College of Rheumatology20%, 50%, 70% response; AE=adverse events; AESI=adverse events of special interest; AS=ankylosing spondylitis; BIW= biweekly; CARRA=Childhood Arthritis and Rheumatology Research Alliance; CRP=C-reactive protein; DB=double blind; DOI= definition of improvement; ETN=etanercept; HAQ-DI=Health Assessment Questionnaire Disability Index; ISR=injection site reactions; LOE=loss of efficacy; MC=multicenter; MDA=minimal disease activity; MTX=methotrexate; OL=open-label; OLE=open label extension; PBO=placebo; PC=placebo controlled; PGA=Physician Global Assessment; PK=pharmacokinetics; PO=by oral route; PsA=psoriatic arthritis; P3=phase 3; QOL=quality of life; QW=once weekly; R=randomized; RA= rheumatoid arthritis; SAE=serious adverse events; SC=subcutaneous; SF-36=36-Item Short Form Health Survey; SOJRA=systemic onset juvenile rheumatoid arthritis; TEAE=treatment emergent adverse events; TNF=tumor necrosis factor; US=United States; VAS-visual analog scale; VS=vital signs; vs=versus; WK=week; yo=years old;

### 7.2. Review Strategy

There were no randomized, placebo-controlled, efficacy studies of etanercept conducted in children with active JPsA submitted in support of this application. As permitted under 21 CFR 314.55 and per written interactions with the Applicant, an assessment of etanercept treatment in children aged 2 to less than 18 years old with active JPsA was conducted via a full extrapolation approach from existing efficacy, safety and PK/PD data in adults with PsA and children with polyarticular JRA and PsO treated with etanercept (efficacy) as well as children and adults with polyarticular JRA, PsO, PsA and RA treated with etanercept (safety). As the efficacy data from the phase 3, multicenter, randomized, double-blind, placebo-controlled studies 20130207 and 20021630 conducted in adults with PsA were previously reviewed by the Agency in support of the marketing approvals for these indications, they will not be re-presented here. Since the efficacy analysis for the retrospective study 20210089 of pediatric JPsA patients enrolled in the CARRA Registry was uncontrolled, and there were missing clinical assessments for some of the pediatric subjects (n=32) included in this analysis, the efficacy was not reviewed in support of this application.[21]

## 8 Statistical and Clinical and Evaluation

### 8.1. Review of Relevant Individual Trials Used to Support Efficacy

Because efficacy in JPsA is extrapolated from efficacy established in adult patients with PsA, as detailed elsewhere in this review, no new efficacy studies in JPsA were required/submitted with this application.

### 8.2. Review of Safety

#### 8.2.1. Safety Review Approach

While no dedicated clinical trials have been conducted/required in pediatric patients with JPsA, the safety in that population is supported by the safety experience with etanercept in pediatric patients with JIA and PsO as well as an adequate justification provided by the Applicant of the relevance of these safety data to JPsA.

In support of the safety profile of etanercept in children with JPsA, the Applicant submitted summaries of safety data from the following clinical trials:

- Study 20030211 was a 3-part, phase 3, 12-week, double-blind, placebo-controlled

[21] Correll CK, Stryker S, Collier D, et al. Occurrence of adverse events and change in disease activity after initiation of etanercept in paediatric patients with juvenile psoriatic arthritis in the CARRA Registry. *RMD Open* 2023;9:e002943. doi:10.1136/rmdopen-2022-002943

treatment period, with a 24-week open-label treatment period, and a 12-week, randomized, double-blind, withdrawal period in 211 pediatric subjects ages 4 to 17 years with PsO

- Study 20050111 was an open-label, 264-week extension of 182 pediatric subjects with PsO who had participated in study 20030211
- Study 20021616 was a 2-part, phase 2/3, combination open-label and double-blind randomized, multicenter study in 69 pediatric subjects ages 4 to 17 years with polyarticular course JRA
- Study 20021618 was a phase 3b, open-label extension study in 69 pediatric subjects with polyarticular course JRA who completed study 20021616
- Study 20021626 was a multicenter, open-label registry study in 594 pediatric subjects ages 1 to 18 years with JRA
- Study 20021628 was a 2-part, phase 3, combination open-label and double-blind, multicenter study in 25 pediatric subjects ages 2 to 17 years with JRA
- Study 20021631 was a 3-part, phase 3, combination open-label and double-blind, multicenter study in 19 pediatric subjects ages 2 to 17 years with JRA

Since the safety data from these seven studies were previously reviewed in support of etanercept's marketing approval as a treatment for pediatric patients ages 4 years old and older with PsO (studies 20030211 and 20050111; sBLA 103795/S-5552), polyarticular course JRA (studies 20021616 and 20021618; sBLA 103795/S-1001), and to lower the polyarticular course JRA age threshold to include children ≥2-4 years of age (studies 20021626, 20021628, and 20021631; sBLA103795/S-5256), these data will not be re-presented here as the safety of etanercept as a treatment for children with PsO or polyarticular course JRA has been previously established. (See the clinical review for sBLA 103795/S-5552 dated September 27, 2016, by the Division of Dermatology and Dental products, and the clinical reviews for sBLA 103795/S-1001 and S-5256 dated May 3, 1999, and April 26, 2006, respectively.)

Additionally, the Applicant included the following supportive safety data:

- Study 20210089 which is a multicenter registry of pediatric patients between the ages 2 and 17 years with JPsA (CARRA Registry)
- A summarized safety analysis of adverse events associated with the administration of etanercept in children less than 18 years of age from the Applicant's postmarketing Amgen Global Safety Database (AGSD) during the 23-year time period from November 2, 1998 (international birthdate) to February 2, 2022, as well as an updated summary of this safety analysis for the 7-month time period from February 3, 2022, to September 1, 2022
- An updated safety analysis of pediatric postmarketing adverse event reports from the AGSD for the time period from September 2, 2022, to February 2, 2023, contained in the 120-day safety update submitted as an addendum to this supplemental BLA on April 18, 2023

These sources of safety data which have not been previously reviewed by the Agency are the

focus of this safety review and are included in pertinent sections of the following discussion, and were examined by this clinical reviewer for any new or unexpected safety signals associated with the administration of etanercept in pediatric patients.

### 8.2.2. Review of the Safety Database

**Overall Exposure**

Not applicable since this application did not contain any safety from clinical trials in pediatric patients with JPsA treated with etanercept.

**Adequacy of the safety database**

The pediatric safety profile of etanercept which has been previously established based on safety data from approximately 918 pediatric study subjects between the ages 1 to 18 years old with polyarticular JIA or PsO exposed to etanercept while participating in either clinical studies or registries in addition to supportive safety data from real time use of etanercept by a safety cohort of 191 pediatric subjects with JPsA followed in the CARRA registry is adequate to provide sufficient basis for extrapolation of etanercept's safety to the subpopulation of pediatric patients with JPsA. (Note: For purposes of this safety analysis, pediatric subjects who completed the randomized, controlled studies and went on to participate in the open-label extension (OLE) studies for these trials were only counted once in this tally.)

### 8.2.3. Safety Results

Refer to Sections 8.2 through 8.2.5 for details.

### 8.2.4. Specific Safety Studies/Clinical Trials

In support of the safety profile of etanercept in pediatric patients, this application also contained the results of a retrospective safety analysis of a subcohort of pediatric subjects with JPsA participating in the CARRA Registry (study 20210089). The latter is a convenience cohort containing data from over 10,000 children with JIA collected from approximately 70 clinical sites in North America. A total of 191 CARRA Registry patients ages 2 to <18 years JPsA and with any observed exposure to etanercept during the time period from June 30, 2015 to the analysis cut-off date of August 2, 2012, were identified and included in this retrospective safety analysis of real time use. Safety outcomes were expressed as incidence rates of follow-up for all serious events, all targeted events (i.e., pre-specified events of special interest), and malignancies with follow-up time at risk based on the earliest date of death, registry discontinuation date, or latest data collection date. For the purposes of this analysis, follow-up started at initiation of use of etanercept or at registry enrollment for patients already receiving treatment with etanercept, but was censored or stopped 91 days after starting another biologic DMARD or 91 days after stopping etanercept unless it was restarted within those 91 days for the nonmalignancy safety events; whereas patient follow-up was not stopped because of stopping etanercept or starting another biologic therapy for malignancy safety events.

Demographically, the majority of the JPsA patients in this safety subcohort were female (66%) and white (81%), with a mean age of 11.7 years and a mean disease duration of 3.5 years. Additionally, 56% of the JPsA patients in this retrospective safety analysis were taking etanercept at the time they enrolled in the CARRA Registry, while 59% were taking concomitant non-biologic DMARDs at the start of follow-up that included MTX (56%), sulfasalazine (3%), and leflunomide (2%). There was one report of a serious adverse event (SAE) of new onset neuropathy (tingling sensation of the foot) that started approximately four months after treatment with etanercept was initiated. According to information in the registry report, this SAE was not thought to be consistent with demyelination since it resolved and treatment with etanercept was subsequently continued. Based on this one SAE, the observed rate of SAEs was calculated to be 0.18 (0.03 to 1.29) per 100 person-years. There was a total of 4 adverse events of special interest reported: 3 cases of new onset uveitis and 1 case of malignancy. The three new-onset cases of uveitis were reportedly consistent with JIA-associated uveitis and responded to treatment with topical corticosteroid ophthalmic drops. Based on the occurrence of these three cases, the observed incidence rate of new-onset uveitis was calculated to be 0.55 (0.18 to 1.69) per 100 person-years. The one case of malignancy involved a 9 year-old female patient who presented with an abdominal mass diagnosed as liver sarcoma on tumor resection. This patient had initiated treatment with etanercept 30 months prior to presenting with the malignancy, and had been previously treated with adalimumab and MTX. Based on this single case, the observed incident rate of malignancy was calculated to be 0.13 (0.02 to 0.90) per 100 person-years.

### 8.2.5. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

Since etanercept's initial marketing approval, routine pharmacovigilance of the product's postmarketing safety profile has resulted in the addition of new safety information to the product's label. These safety updates include boxed warnings for the development of serious infections including tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis), and opportunistic infections; and malignancies including lymphomas, particularly in children and adolescents. New drug class warnings were also added under Section 5 Warnings and Precautions of etanercept's label for the occurrence of neurological reactions (demyelinating disorders), leukemias, other malignancies (including melanoma, non-melanoma skin cancer, and Merkel cell carcinoma), worsening or new onset congestive heart failure, hematological reactions (pancytopenias and aplastic anemia), reactivation of hepatitis B infection, and the development of lupus-like syndrome or autoimmune hepatitis. Section 6.3 Postmarketing Experience has also been updated to include the occurrence of adverse events such as (b) (4), uveitis, inflammatory bowel disease, macrophage activation syndrome, systemic vasculitis, psoriatic-like skin lesions, and headache associated with the use of etanercept. Section 7 Drug Interactions was updated as well to include the potential occurrence of neutropenias as a drug-drug reaction when etanercept is co-administered with sulfasalazine.

Review of postmarketing data contained in the most recent etanercept Periodic Benefit-Risk Evaluation/Periodic Safety Update Report (PBRE/PSUR) covering the time period from February 3, 2020 to February 2, 2023, submitted on May 3, 2023, did not identify any new or unexpected serious adverse events that needed to be included in etanercept's current label. According to information contained in this PBRE/PSUR, worldwide cumulative exposure to etanercept for pediatric subjects ages 2 to 16 years old was 179,506 patient-years and 70,003 patient-years for PsO/PsA and JIA, respectively. [Note: Calculation of worldwide cumulative exposure for etanercept was based on data collected from the drug's international birthdate to the end of the reporting period (February 2, 2023) for the PBRE/PSUR.]

This application also contained a summary of postmarketing safety reports derived from spontaneous, solicited, and non-interventional study sources associated with the administration of etanercept in children less than 18 years of age identified via query of the Applicant's AGSD during the 23-year time period from November 2, 1998 (etanercept's internal birth date) to February 2, 2022. A total of 24,231 cases comprised of 52,568 adverse events were identified, out of which 7,853 adverse events were classified as SAEs while the remaining 44,715 adverse events were nonserious in nature. Demographically, 69% of the subjects who made up this postmarketing pediatric cohort were female with a mean age of approximately 12-years old. The most frequently reported SAEs (>500 events) by MedDRA high-level group terms (HLGTs) were joint disorders (N=803), infections - pathogens unspecified (N=791), and general system disorders not elsewhere classified (NEC) (N= 571). According to the Applicant, review of the 803 case reports of SAE joint disorders revealed that these events were disease-related to the indicated pediatric populations. Further review of the 791 case reports of SAEs infections – pathogens unspecified, showed pneumonia (127 events) was the most frequently reported infectious event associated with the pediatric administration of etanercept while constitutional symptoms (i.e., MedDRA preferred terms condition aggravated, pain, malaise, and gait inability) were the most commonly reported events for the general system disorders NEC HLGT. Of the 44,715 nonserious AEs identified in this query, the most frequently reported nonserious AEs (>3000 events) were administration site reactions (N=11670), general system disorder NEC (N=3794), and medication errors and other product use errors and issues (N=3645). Administration site reactions, which included injection site reactions, were seen across all pediatric disease populations and age subgroups while the pattern of distribution of constitutional symptom reports captured under nonserious general system disorder NEC was reportedly similar to that observed for the postmarketing cases classified as SAEs. The preferred terms of product usage process (N=646), product dose omission issue (N-506), and incorrect dose administered (N=342) made up the majority of the nonserious AE reports under the medication errors and other product use errors and issues HLGT.

Further examination of this pediatric postmarketing data by pediatric disease indication revealed that approximately 54% of the pediatric postmarketing AE cases were reported to have occurred in pediatric patients with JIA followed by unknown indication (17%), PsO (12%), RA (7%), ankylosing spondylitis (AS) (4%), and PsA (3%). Overall, the pattern of HLGT SAE events was comparable across the pediatric indications with the exception of pediatric PsO and AS where there were higher incidences of cases of the HLGTs epidermal and dermal conditions

(N=27) and neurological disorders NEC (N=11), respectively, which is not unexpected given that PsO affects the skin and neurological disorders are not uncommon events in patients with AS.

For completeness, the Applicant also included in this application an updated summary of a 7-month search of the AGSD for the time period from February 3, 2022 to September 1, 2022, in which an additional 647 cases comprising a total of 1390 pediatric postmarketing AEs were identified. The majority of the subjects in this postmarketing cohort were also female (64%) with a mean age of approximately 12 years old. The majority of these postmarketing AEs (1186 cases; 85%) were nonserious in nature. Of the remaining 204 cases that were classified as SAEs, the overall pattern of distribution of these cases by HLGT and by pediatric indication was similar to what was previously observed in the 23-year, pediatric postmarketing safety review for the time period from November 2, 1998 to February 2, 2022.

The 120-day safety update submitted on April 18, 2023, contained a second, updated search of the AGSD for the 5-month time period from September 2, 2022 to February 2, 2023 in which an additionally 488 cases comprising a total of 1,020 pediatric postmarketing AEs were identified. The demographic characteristics of this pediatric postmarketing cohort were consistent with that of the prior postmarketing analyses, with 66% of the subjects female with a mean age of approximately 12-years old. Of the 1,020 pediatric postmarketing AEs identified, the majority (847; 83%) were also nonserious. Of the remaining 173 AEs that were classified as SAE, the most frequently reported HLGTs were joint disorders (N=28); followed by gastrointestinal inflammatory conditions (N=22), and general system disorders NEC (N=10). Further examination of these data revealed that 18 of the 22 cases of gastrointestinal inflammatory conditions were originally reported from a 2015 publication that was then re-reported to the AGSD in 2016. In view of this data entry error, the Applicant states the overall safety profile of etanercept remains unchanged. Two cases of malignancy were also identified in this 120-day safety update involving a 13 year-old male with B27-postive axial juvenile spondylarthritis who developed Epstein-Barr virus negative Hodgins's lymphoma, and a 24-year old male with rheumatoid spondylitis who developed classical Hodgkin's lymphoma. Overall, the patterns of distribution of SAEs by pediatric indication were similar to those observed in the 23-year and 7-month pediatric postmarketing reviews. Since lymphoma is already listed as a SAE under the boxed warning for malignancies, the reported pediatric events observed during this 5-month, pediatric postmarketing 120-day safety update as well as in the original 23-year analysis and the prior 7-month safety update are consistent with etanercept's known safety profile.

Postmarketing safety consultants in DPV-1 located in the Agency's OSE previously completed a Pediatric Postmarketing Pharmacovigilance Review for etanercept on April 8, 2021, in which they had reviewed 476 U.S. serious pediatric reports received in the FAERS database with etanercept from November 4, 2015 through September 30, 2020. DPV-1 identified 11 pediatric cases with a non-fatal outcome that contained serious, unlabeled adverse events such as necrotizing pancreatitis (1), immune reconstitution inflammatory syndrome (1), metabolic syndrome (1), facial paralysis (2), tics (1), mood swing and emotional disorder (2), and suicidal ideation (3). Based on their review, DPV-1 did not identify any new pediatric safety signals for etanercept and recommended no regulatory safety action at that time. In support of this

extrapolated safety review, DPV-1 completed an updated review of an additional 693 spontaneous postmarketing adverse event reports associated with etanercept in patients less than 18 years of age collected in FAERs, the medical literature, and Applicant-submitted period safety reports from October 1, 2020 to February 23, 2023 and identified one case of suicidal ideation and mood disorder with etanercept that occurred in a 16-year-old patient as well as two literature case reports of chronic inflammatory demyelinating polyneuropathy (CIDP) that occurred post discontinuation of etanercept in pediatric patients with JIA. Due to the small number of reports of CIDP and the existing Warning in the etanercept label for peripheral demyelinating neuropathies, DPV-1 did not recommend adding CIDP to the product's labeling at this time, but will continue routine pharmacovigilance of CIDP with etanercept.

**Expectations on Safety in the Postmarket Setting**

The Applicant's postmarketing pediatric safety updates suggest that the safety profile of etanercept in the pediatric PsA population age 2 years and older will be similar to the experience of pediatric patients with JIA and PsO. This is supported by the lack of new postmarketing pediatric safety findings associated with the administration of etanercept in pediatric patients on a review by internal postmarketing safety consultants in OSE's DPV-1. No strengthening of the current Warnings and Precautions statements in the product's USPI is therefore indicated.

There are currently no pending postmarketing safety commitments or required studies for etanercept. Postmarketing safety data for this product will continue to be assessed through routine pharmacovigilance by OSE's DPV-1.

### 8.2.6. Integrated Assessment of Safety

No new or unexpected safety signals were identified on review of the retrospective safety analysis of the 191 pediatric patients with JPsA followed in the CARRA Registry (study 20210089) or the nearly 24-years of cumulative, spontaneous postmarketing safety data in children 1 to less than 18 years of age exposed to etanercept collected by the Applicant submitted in support of this application. This is supported by the postmarketing safety update conducted by internal consultants in OSE's DPV-1. Based on the available safety data, the expectation is that the postmarketing safety experience for pediatric patients 2 years of age and older with JPsA will be similar to the experience of pediatric patients with JIA and PsO as well as adults with PsA.

## 8.3. Statistical Issues

Not applicable as no new efficacy or safety data from randomized, controlled trials were included in this application.

## 8.4. Conclusions and Recommendations

The Applicant proposed a full extrapolation of efficacy established in adults with PsA with leveraging of safety established in children with polyarticular JIA and PsO in support of adding the new pediatric indication of treatment of JPsA for etanercept. Additional supportive safety data comes from a retrospective analysis of a cohort of children with JPsA followed in the CARRA Registry, and a cumulative review of nearly 24-years of postmarketing pharmacovigilance safety data from pediatric patients exposed to etanercept.

The efficacy of etanercept is based on PK matching of systemic exposure and extrapolation of established efficacy of etanercept in PsA. As discussed in Section 6, the clinical pharmacology review team were able to establish a PK bridge based on the similarities of serum concentrations of etanercept between adults with PsA and pediatric subjects with PsO at the proposed JPsA dose of 0.8 mg/kg. Given the significant similarities between PsA and JPsA, the establishment of a PK bridge provided a scientific justification to extrapolate the efficacy of etanercept established in adults with PsA to pediatric patients with JPsA based on data from adequate and well controlled clinical trials conducted with etanercept in adults with PsA. Since the PK bridging process also established that the serum concentrations of etanercept were similar in pediatric subjects with PsO and polyarticular JIA, and JPsA and polyarticular JIA are subtypes of JIA, it is also expected that the approved weight-based doing regimen would result in similar PK exposures of etanercept in these pediatric populations thus permitting the extrapolation of safety from adequate and well controlled clinical studies conducted in pediatric subjects with polyarticular JIA and PsO that were previously reviewed in support of these indications.

Additional support of safety was provided from a retrospective analysis of 191 pediatric patients with JPsA treated with etanercept followed in the CARRA Registry (study 20210089) and nearly 24-years of cumulative, spontaneous, postmarketing safety data in children 1 to less than 18 years of age exposed to etanercept collected by the Applicant submitted in support of this application. The safety data from the CARRA Registry coupled with the Applicant's postmarketing pediatric safety update, suggest that the safety profile of etanercept in the pediatric PsA population age 2 years and older will be similar to the experience of pediatric patients with polyarticular JIA and PsO. This is supported by the lack of new postmarketing pediatric safety findings associated with the administration of etanercept in pediatric patients on a review by internal postmarketing safety consultants in OSE's DPV-1. No strengthening of the current Warnings and Precautions statements in the product's USPI is therefore indicated.

The Applicant has provided adequate data and information to inform the benefit-risk assessment of etanercept for the treatment of pediatric patients with active JPsA in patients 2 years of age and older. Overall, the efficacy and safety evidence provided in this submission supports a favorable benefit/risk profile of etanercept for the treatment of JPsA in patients 2 years and older at the proposed dosing regimen of 0.8 mg/kg administered weekly via subcutaneous injection in children weighing <63 kg, or 50 mg administered weekly via subcutaneous injection in children weighing >63 kg. Approval of etanercept will provide an additional treatment option for pediatric patients given the limited number of approved treatments for this disease in the U.S. Therefore, the review team recommends approval of

etanercept for the treatment of children age 2 years and older with JPsA using the currently approved weight-based dosing regimen.

# 9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held for this pediatric efficacy supplement. No issues were identified warranting advisory committee input.

# 10 Pediatrics

Since PREA was not enacted until 2003, a postmarketing requirement to conduct pediatric studies of etanercept in children with JPsA was not sought as a condition for approval of etanercept as a treatment for adults with PsA in 2002. This pediatric efficacy application was in response to an Advice letter dated November 20, 2020, from the Agency to the Applicant soliciting an application to expand the adult indication for PsA to the pediatric age groups based on extrapolation of existing efficacy and safety data supported by matched PK/PD exposure. The results and review findings for this pediatric efficacy supplement were presented and discussed at the September 19, 2023, meeting of the pediatric review committee (PeRC) who concurred with the review team's recommendation to add the treatment of active JPsA in pediatric patients 2 years and older to etanercept's other indications based on the data reviewed in this application.

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

The following is a high-level summary for the product label changes based on review of the data submitted in support of this application as well as major editorial changes to update the content and format of the Enbrel label as per current labeling guidelines:

1) Under Highlights
    a. Added under Recent Major Changes information and dates regarding updates to the Indications and Usage, Juvenile Psoriatic Arthritis and Dosage and Administration sections and removal of prior updates to the Dosage and Administration, Preparation of Enbrel and Warnings and Precautions, Allergic Reactions.
    b. Added under Indications and Usage, subsection Pediatric patients, subbulleted new indication for "Juvenile Psoriatic Arthritis, 2 years of age or older (JPsA)". Revised for consistency existing subbulleted indication to read "Polyarticular Juvenile Idiopathic Arthritis (pJIA), 2 years of age or older".
    c. Changed Patient Population in box summary under Dosage and Administration to read "pJIA, Pediatric PsO and JPsA".
    d. Edited Contraindications to align with section 4 Contraindications of the Full Prescribing Information to read "Enbrel is contraindicated in patients with sepsis".
    e. Under Drug Interactions changed the first bullet to read "Live vaccines – Avoid concurrent administration with Enbrel," and the fourth bullet to read "Cyclophosphamide – Not recommended for use with Enbrel".
    f. Under Full Prescribing Information: Contents; under Section 1 Indications and Usage added "1.6 Juvenile Psoriatic Arthritis".

g. Under Full Prescribing Information, boxed Warning for Serious Infections, changed to “Test patients for latent tuberculosis…” from “Patients should be tested…”; “Initiate treatment for latent infection…” from “Treatment for latent infection should be initiated…”; “Consider empiric anti-fungal therapy…” from “Empiric anti-fungal therapy should be considered…”; “Monitor patients closely…” from “Patients should be…”

2) Under Section 1 Indications and Usage
   a. Under subsection 1.2 Polyarticular Juvenile Idiopathic Arthritis, have corrected the sentence to read “Enbrel is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 years of age and older.”
   b. Under subsection 1.3 Psoriatic Arthritis added the word “adult” to clarify the population “ …and improving physical function in adult patients with psoriatic arthritis (PsA).
   c. Added subsection 1.6 Juvenile Psoriatic Arthritis and the following statement “Enbrel is indicated for the treatment of active juvenile psoriatic arthritis (JPsA) in pediatric patients 2 years of age and older.” The review team agrees with inclusion of JPsA in 1.6 as a separate indication of "treatment of active juvenile PsA in pediatric patients 2 years of age and older" for consistency with current labeling practice for treatment of overall indication rather than listing of specific claims as in Section 1.3 PsA.
3) Under Section 2 Dosage and Administration
   a. Added the following new subheader 2.1 Testing and Procedures Prior to Treatment Initiation with the following text: “Perform the following evaluations and procedures prior to initiating treatment with Enbrel:
      - Prior to initiating Enbrel and periodically during therapy, evaluate patients for active tuberculosis and test for latent infection *[see Warnings and Precautions (5.1)].*
      - Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with Enbrel *[see Warnings and Precautions (5.8)].*
   b. Created the following new subheader 2.2 Important Administration Instructions for the existing text.
   c. Updated subheader 2.3 title to read “Recommended Dosage in Adult Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis” and changed the name of Table 1 located under this subheader to “Recommended Dosage for Adult Patients with RA, AS, PsA and PsO” and changed the second column header in the table to “Recommended Dosage”
   d. Under newly re-ordered subheader 2.4
      - Updated its title to read “Recommended Dosage for Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis, Plaque Psoriasis, and Juvenile Psoriatic Arthritis”
      - Added the following sentence: “The recommended weight-based dosage for pediatric patients is administered by subcutaneous injection (Table

2)."
- Deleted the existing sentence: "Enbrel is administered by subcutaneous injection."
- Updated the title of Table 2 to read "Recommended Dosage for Pediatric Patients with pJIA, PsO and JPsA" and changed the column headers to "Body Weight" and "Recommended Dosage".
- For clarity changed "Doses…" to "Dosages…" at the beginning of the second sentence under Table 2.
- For consistency "Doses" was replaced by "Dosages" in the statement "Dosages of Enbrel higher than those described in Table 2 have not been studied in pediatric patients."

e. Changed the title of newly re-ordered subheader 2.5 to "Preparation Instructions of Enbrel".
f. Deleted the old subheader 2.4 Monitoring to Assess Safety and the text under it since which has been move up as the first bullet under the new subsection 2.1.

4) Under Section 4 Contraindications changed the text to read "Enbrel is contraindicated in patients with sepsis."
5) Under Section 5 Warnings and Precautions
   a. Changed the title to subheader 5.4 to "New Onset or Worsening of Heart Failure".
   b. Under subheader 5.7 Allergic Reactions, the text of the last sentence has been updated to read "If an anaphylactic reaction or other serious allergic reaction occurs, discontinue administration of Enbrel and initiate appropriate therapy immediately."
   c. Under subheader 5.8 Immunizations the text has been updated to read: "Avoid concurrent administration of live vaccines with Enbrel. It is recommended that patients, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating Enbrel therapy "*[see Drug Interactions (7.1) and Use in Specific Populations (8.4)]*."
   d. Under subheader 5.9 Autoimmunity the text of the last sentence has been updated to read "If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with Enbrel, discontinue treatment and evaluate the patient."
   e. The title of subheader 5.11 has been changed to: "Not Recommended for Use in Patients with Granulomatosis (b) (4) Polyangiitis (b) (4) Immunosuppressants."
   f. The title of subheader 5.12 has been changed to: "Not Recommended for Use with Anakinra or Abatacept."
   g. The title of subheader 5.13 has been changed to: "Increased Mortality in Patients with Moderate to Severe Alcoholic Hepatitis."
6) Under Section 8 Use in Specific Populations
   a. The text under subheader 8.4 Pediatric Use has been re-written with the addition of the new indication as follows:

"Polyarticular Juvenile Idiopathic Arthritis
The safety and effectiveness of Enbrel have been established in pediatric patients (b) (4) 2 years of age and older with pJIA. Enbrel has been studied in 69 children with moderately to severely active polyarticular JIA 2 to 17 years of age.

The safety and effectiveness of Enbrel in pediatric patients less than 2 years of age with pJIA have not been established.

Juvenile Psoriatic Arthritis
The safety and effectiveness of Enbrel have been established in pediatric patients 2 years to 17 years old with JPsA. Use of Enbrel in JPsA is supported by evidence from adequate and well controlled studies of Enbrel in adults with PsA; pharmacokinetic data from adult patients with PsA, RA, and PsO; and pharmacokinetic data from pediatric patients with active JIA and PsO. Safety of Enbrel in JPsA is supported by a clinical study in 69 pediatric patients with moderately to severely active JIA aged 2 to 17 years; a clinical study in 211 pediatric patients with moderate to severe PsO aged 4 to 17 years; and an open-label extension study in 182 pediatric patients with moderate to severe PsO aged 4 to 17 years.

The observed pre-dose (trough) concentrations are generally comparable between adults with RA and PsA and pediatric patients with active JIA, as well as adults with PsO and pediatric patients with PsO. The PK exposure is expected to be comparable between adult PsA and pediatric patients with JPsA *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1, 14.2, 14.3, 14.5, 14.6)]*.

The safety and effectiveness in pediatric patients below the age of 2 years have not been established in JPsA.

Plaque Psoriasis
The safety and effectiveness of Enbrel for plaque psoriasis have been established in pediatric patients 4 years of age and older. Enbrel has been studied in 211 pediatric patients with moderate to severe PsO aged 4 to 17 years.

The safety and effectiveness of Enbrel in pediatric patients below the age of 4 years with PsO have not been established."

b. The title to subheader 8.6 had been changed to "Use in Patients with Diabetes."

7) Under Section 12 Clinical Pharmacology
   a. Under subheader 12.3 Pharmacokinetics
      - A new fourth paragraph has been added as follows: "The mean (± SD) serum steady-state trough concentrations for 50 mg QW dosing in adult PsA subjects were 2.1 ± 1.2 mcg/mL and 2.1 ± 1.4 mcg/mL at weeks 24 and 48, respectively."
      - A new sixth paragraph has been added as follows: "Overall, the observed

etanercept concentrations in patients with JIA and pediatric PsO were within the range of those observed for adult RA, PsA and PsO after administration of Enbrel."

8) After Section 17 Patient Counseling Information
    a. The Applicant updated the image "Amgen" to the JPEG version in compliance with current labeling guidance

# 12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary for this pediatric efficacy supplement to add to etanercept's indications the treatment of active JPsA in patients 2 years and older since no new safety signals were identified on review of the data contained in this submission.

# 13 Postmarketing Requirements and Commitment

There are no new safety or efficacy issues identified in this review that warrant a postmarketing requirement (PMR) or postmarketing commitment (PMC).

# 14 DRTM Division Director/Signatory Comments

The Deputy Division Director (Signatory for this application) agrees with the team's review, assessment, and conclusions, as detailed in this document.

The action for this sBLA is Approval. No post-marketing required studies or commitments are warranted based on this submission.

# 15 Appendices

## 15.1. References

1. Brunello F, Tirelli F, Pegoraro L, Dell'Apa F, Alfisi A, Calzamatta G, Folisi C, and Zulian F. New insights on juvenile psoriatic arthritis. *Front Pediatr* 10:884727. Doi: 10.3389/fped.2022.884727
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## 15.2. Financial Disclosure

This section is not applicable as no new clinical trial data were submitted.

## 15.3. OCP Appendices (Technical documents supporting OCP recommendations)

**Bioanalytical Method used to measure serum concentrations of etanercept (Study 20130207):**

Serum concentrations for etanercept were measured using a validated enzyme-linked immunosorbent assay. The assay range was from 10.0 ng/mL (lower limit of quantification [LLOQ]) to 400 ng/mL (upper limit of quantification). In this indirect sandwich assay procedure, standards, quality controls, blank, and human serum study samples were diluted in an assay buffer with a minimal required dilution of 1:10 and then added to a plate that had been passively coated with a mouse monoclonal antibody against etanercept. After capture of etanercept to the immobilized antibody, unbound materials were removed by a wash step. A polyclonal antibody against recombinant human TNFR:Fc was added to bind to the captured etanercept. After another wash step, horseradish peroxidase conjugated donkey anti-goat IgG antibody was added for detection of the captured complex from the step before. After another wash step, a tetramethylbenzidine peroxide substrate solution was added to produce colorimetric signal, which was proportional to the amount of etanercept bound by the capture reagent.

Etanercept serum concentration at predose on day 1, week 24, and week 48 were reported. Nominal times (weeks post first dose) were used to present PK data in a box plot and tables. Concentrations below the LLOQ (10.0 ng/mL) were set to zero before data analysis.

The PK analysis dataset was comprised of 610 serum samples from 212 subjects. The maximum duration of the sample storage date was 2675 days. Twenty-five samples exceeded the validated long-term stability of 2437 days and were reported as not Reportable.

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