Primary Review, Cross-Discipline Team Leader Review, and Division Directory Summary

Date	See electronic stamp date
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Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	sBLA 125504 – Supplement 97 (AxJSpA) sBLA 125504 – Supplement 98 (JAS)
Applicant	Novartis
Date of Submission	October 17, 2025, for sBLA 125504 – Supplement 97 (AxJSpA) October 20, 2025, for sBLA 125504 – Supplement 98 (JAS)
PDUFA Goal Date	April 17, 2026
Proprietary Name	Cosentyx
Established or Proper Name	Secukinumab
Dosage Form(s)	Subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	• For JAS – treatment of active ankylosing spondylitis (AS) in adults and pediatric patients 12 years of age and older • For AxJSpA – no indication is being sought
Applicant Proposed Dosing Regimen(s)	For patients weighing < 50 kg – secukinumab 75 mg SC at Weeks 0, 1, 2, 3, and 4, followed by every 4 weeks thereafter. For patients weighting ≥ 50 kg – secukinumab 150 mg SC at Weeks 0, 1, 2, 3, and 4, followed by every 4 weeks thereafter.
Recommendation on Regulatory Action	Approval of Supplements 97 and 98
Recommended Indication(s)/Population(s)	• For JAS – treatment of active ankylosing spondylitis (AS) in adults and pediatric patients 12 years of age and older • For AxJSpA – no indication is being sought; Addition of new descriptive information on pediatric subjects with axial symptoms to the Pediatric Use section (Section 8.4) for Axial Juvenile Spondyloarthritis (AxJSpA) without establishing a new treatment indication
Recommended Dosing Regimen(s)	For patients weighing < 50 kg – secukinumab 75 mg SC at Weeks 0, 1, 2, 3, and 4, followed by every 4 weeks thereafter. For patients weighting ≥ 50 kg – secukinumab 150 mg SC at Weeks 0, 1, 2, 3, and 4, followed by every 4 weeks thereafter.

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Juvenile Ankylosing Spondylitis (JAS)

Juvenile ankylosing spondylitis (JAS) is a serious inflammatory condition characterized by inflammatory back pain, morning stiffness, and progressive axial skeleton involvement. Currently, there are no FDA-approved therapies for JAS. The benefit of secukinumab for active ankylosing spondylitis in patients 12 years of age and older is supported by a 4-way extrapolation strategy. This strategy leverages efficacy data from adult ankylosing spondylitis (AS) trials, pharmacokinetic (PK) data demonstrating that the proposed weight-based dosing regimen (75 mg SC for patients <50 kg; 150 mg SC for patients ≥50 kg) results in exposures comparable to those in adult AS patients and in pediatric patients with related inflammatory conditions (psoriasis [PsO], juvenile psoriatic arthritis [JPsA], and enthesitis-related arthritis [ERA]) receiving the same dosing regimen, identical ASAS classification criteria reflecting similarity in disease pathophysiology between adult AS and JAS, and safety data from pediatric PsO and ERA/JPsA trials using the identical dosing regimen. The safety profile of secukinumab is well-characterized across multiple pediatric indications receiving the same weight-based dosing regimen. Based on PK matching, data from the closely related approved pediatric JPsA and ERA indications indicate that the safety of the proposed dosing regimen would align with the established safety profile of secukinumab in other pediatric indications. This alignment supports leveraging of safety data from the approved adult regimen, without the need for new clinical studies.

The Division recommends approval of sBLA 125504 Supplement 98 to expand the ankylosing spondylitis indication to include pediatric patients 12 years of age and older, as the expected efficacy based on adult AS data, PK data demonstrating comparable drug exposures, and scientific justification provided by identical ASAS classification criteria, combined with the well-characterized safety profile in pediatric populations receiving the identical dosing regimen, outweighs the safety risks, and addresses an unmet medical need in this pediatric population.

Axial Juvenile Spondyloarthritis (AxJSpA)

Axial juvenile spondyloarthritis (AxJSpA) is a serious inflammatory condition representing the clinical presentation of non-radiographic axial spondyloarthritis before age 16. AxJSpA is characterized by inflammatory back pain and morning stiffness similar to JAS but without definitive radiographic evidence of sacroiliitis. The available evidence for secukinumab in AxJSpA consists of a retrospective analysis of six pediatric subjects from trials F2304 and F2304E1 with axial symptoms, of whom four (66.67%) demonstrated improvement in disease activity measures, though significant uncertainties preclude establishing effectiveness including

the limited sample size, uncertainty regarding unvalidated Applicant-defined criteria for AxJSpA, inconsistent response patterns with two subjects (33.3%) withdrawn due to inadequate response, and variable back pain responses.

The Division recommends approval of sBLA 125504 Supplement 97 to add descriptive information about pediatric patients with axial symptoms to Section 8.4 Pediatric Use of the label without establishing a new treatment indication. Due to the limited number of pediatric patients with axial symptoms enrolled in the study for JPsA and ERA (NCT03031782) and the uncertainty in identifying subjects with AxJSpA, the effectiveness and safety of secukinumab in AxJSpA have not been established. However, safety findings were generally comparable to those observed in pediatric patients treated for JPsA and ERA.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Juvenile ankylosing spondylitis (JAS) is a descriptive term for the clinical presentation of ankylosing spondylitis (AS) before 16 years of age. JAS is classified using the established criteria for AS in adults, the Assessment of Spondyloarthritis International Society (ASAS) criteria. The condition is characterized by inflammatory back pain with insidious onset, nocturnal pain that improves upon rising, pain that improves with exercise, and morning stiffness lasting 15 minutes or more. The use of identical classification criteria for adult AS and JAS reflects the fundamental similarity in disease pathophysiology and clinical presentation between these age groups, with both conditions sharing pathophysiologic mechanisms involving IL-17A-mediated inflammation and progressive inflammatory processes affecting the axial skeleton. The true incidence of JAS is unknown; however, it is estimated that 10-20% of patients diagnosed with AS present before 16 years of age, and that most of these cases occur in patients who are at least 8 years of age. The overall prevalence of JAS is estimated to be fewer than 1 per 1000 children. JAS is extremely rare in children below 12 years of age because the characteristic inflammatory processes and structural changes require time to develop, making the adolescent population (12 to < 18 years) the primary pediatric demographic affected by this condition. Axial juvenile spondyloarthritis (AxJSpA) appears to be a pediatric entity	JAS and AxJSpA are serious inflammatory conditions affecting the pediatric population with significant impact on quality of life. JAS shares classification criteria and disease characteristics with adult AS, supporting extrapolation of efficacy data through a 4-way extrapolation strategy that bridges data across four distinct populations and disease states: (1) Adult PsO ↔ Pediatric PsO (PK Matching), (2) Adult PsO → Adult AS (Similar PK), (3) Pediatric PsO → Juvenile AS (Safety), and (4) Adult AS → Juvenile AS (Efficacy + Expected Similar PK). This approach leverages adult AS efficacy data, pediatric safety data primarily from pediatric PsO trials (with additional support from ERA and JPsA studies), and pharmacokinetic data to ensure appropriate drug exposure across related populations and age groups. AxJSpA represents a recently defined clinical entity with limited available data; the retrospective analysis of six subjects provides limited evidence of safety and potential efficacy but is insufficient to establish a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	that closely approximates non-radiographic axial spondyloarthritis (nr-axSpA) in adults. The condition shares similar clinical manifestations with JAS and nr-axSpA, including inflammatory back pain with insidious onset, nocturnal pain that improves upon rising, morning stiffness lasting 15 minutes or more, and tenderness in the cervical, thoracic, or lumbar spine or sacroiliac joints. Like JAS, AxJSpA is mediated by IL-17A-driven inflammation and shares pathophysiologic features with other spondyloarthropathies. Unlike AS or JAS as defined here, AxJSpA does not rely on conventional radiographic imaging (X-ray) for diagnosis. One set of classification criteria known as the Weiss criteria published in December 2024[1], consists of seven weighted domains with a total maximum score of 100 points. To meet the classification threshold for AxJSpA, individuals must achieve a score of 55 points or higher. The imaging domains carry the highest weights (active inflammation on imaging worth up to 23 points and structural lesions on imaging worth up to 23 points), while clinical domains include pain chronicity (maximum 9 points), pain pattern (maximum 13 points), pain location (maximum 12 points), morning stiffness (maximum 9 points), and genetics (maximum 11 points). Importantly, while imaging evidence typical of sacroiliitis is required for classification, it alone is not sufficient, as individuals must also meet additional clinical criteria to surpass the threshold. AxJSpA may be associated with other pediatric inflammatory arthritis conditions such as enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA), which may also feature axial involvement and share overlapping clinical manifestations including enthesitis, peripheral arthritis, and inflammatory back pain.	new treatment indication. The proposed labeling appropriately reflects these differences, with expansion of the AS indication to include patients 12 years of age and older for JAS, while providing descriptive information in the pediatric use section on pediatric patients with axial symptoms who show signs and symptoms of AxJSpA.

[1] Weiss PF, et al. Classification Criteria for Axial Juvenile Spondyloarthritis. Arthritis Rheumatol. 2024. These criteria were used in this submission to identify patients in the retrospective analysis. Use of these criteria for this review does not constitute FDA endorsement of these criteria as the classification standard.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Currently, there are no FDA-approved therapies for either JAS or AxJSpA, representing an unmet medical need in the pediatric population. In clinical practice, adolescent patients with JAS are typically managed off-label with non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and biologic DMARDs (bDMARDs). Multiple biologic treatment options are approved for adult AS, including TNF inhibitors, IL-23 inhibitors, and IL-17 inhibitors such as secukinumab, but these lack pediatric approval for JAS. For AxJSpA, the treatment landscape is more complex. Pediatric patients with axial spondyloarthritis features who meet diagnostic criteria for ERA or JPsA have access to FDA-approved biologic therapies for those indications, including secukinumab which is approved for both ERA and JPsA. Additionally, the literature suggests that biologic therapies demonstrate efficacy for treating axial disease manifestations in pediatric patients with ERA and JPsA, with studies documenting improvements in back pain, spinal mobility, and inflammatory markers in patients with axial involvement. For pediatric patients with axial spondyloarthritis features who do not meet criteria for ERA or JPsA, off-label treatments similar to those used for JAS are used, including NSAIDs and bDMARDs.	There is an unmet need for safe and effective therapies for pediatric patients with JAS and AxJSpA, as there are no FDA-approved therapies available for either condition.
Benefit	The efficacy of secukinumab in JAS is supported by a 4-way extrapolation strategy leveraging adult AS data. The extrapolation is justified by identical ASAS classification criteria for adult AS and JAS, similar IL-17A-mediated disease pathophysiology, and PK data demonstrating that weight-based dosing (75 mg for <50 kg; 150 mg for ≥50 kg) results in exposures comparable to effective adult doses and exposures observed in pediatric patients with related inflammatory conditions. Safety is supported by data from pediatric populations (PsO, ERA, and JPsA) receiving the identical weight-based dosing regimen. The primary uncertainty is the absence of dedicated clinical trials in adolescent JAS patients. The evidence for secukinumab in AxJSpA consists of a retrospective analysis of 6 pediatric subjects from trials F2304 and F2304E1, of whom 4	The benefit of secukinumab for active AS in patients 12 years of age and older is supported by the 4-way extrapolation strategy that leverages efficacy from adult AS trials, PK data demonstrating comparable drug exposures across populations, and identical ASAS classification criteria. The proposed indication addresses an unmet need where no therapies are currently FDA-approved for JAS. The benefit-risk profile is favorable, as the expected efficacy based on robust adult data and PK data outweighs the well-characterized safety risks across multiple approved indications, supporting expansion of the AS indication to include

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(66.67%) demonstrated improvement in JADAS scores. The uncertainties include the limited sample size insufficient to draw definitive conclusions, and the fact that only 1 subject met published classification criteria (Weiss et al., 2024). A retrospective analysis was necessary as the original trials did not prospectively enroll subjects with AxJSpA, and there were no classification criteria to identify the pediatric equivalent of nr-AxSpA.	patients 12 years of age and older. The available evidence for secukinumab in AxJSpA is insufficient to establish effectiveness and does not support approval of a new treatment indication due to the limited sample. However, the available evidence for pediatric patients with axial symptoms has been added to the label in Section 8.4 for Pediatric Use to provide limited information on patients with signs and symptoms of AxJSpA.
Risk and Risk Management	The safety profile of secukinumab is well-established across multiple indications in both adult and pediatric populations. The most common adverse reactions observed across clinical trials include nasopharyngitis, diarrhea, and upper respiratory tract infections. The primary safety concerns associated with secukinumab relate to its mechanism of action as an IL-17A antagonist, which may increase the risk of infections, including serious bacterial, viral, and fungal opportunistic infections. In clinical trials, higher rates of infections were observed in secukinumab-treated subjects compared to placebo. Serious infections have been reported in postmarketing surveillance, including some fatal infections, cases of hepatitis B virus reactivation, and tuberculosis reactivation in patients with a history of latent TB. To mitigate infection risk, the FDA-approved label recommends evaluating patients for active or latent tuberculosis prior to treatment initiation, completing all age-appropriate vaccinations before starting therapy, and exercising caution when considering use in patients with chronic or recurrent infections. If a serious infection develops, secukinumab should be discontinued until the infection is resolved. Additional safety concerns include hypersensitivity reactions, with cases of anaphylaxis, angioedema, and urticaria reported both in clinical trials and postmarketing settings. The label contraindicates secukinumab use in	For the proposed JAS indication, the safety profile is supported by pediatric safety data from related conditions including enthesitis-related arthritis, juvenile psoriatic arthritis, and pediatric psoriasis using the same weight-based dosing regimen. Adult AS trials established efficacy at specific exposure levels, and PK data demonstrate that the proposed JAS dosing regimen results in these efficacious exposure levels. These exposure levels have been demonstrated to be safe in pediatric populations receiving the identical dosing regimen. While the lack of dedicated clinical trials in JAS patients introduces some uncertainty regarding the exact safety profile in this specific population, the large safety database across related pediatric inflammatory conditions, combined with the well-characterized efficacy data from adult AS patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients with previous serious hypersensitivity reactions to secukinumab or any excipients. Inflammatory bowel disease represents another important risk, with exacerbations and new-onset cases of Crohn's disease and ulcerative colitis observed across clinical programs. The label advises caution when prescribing secukinumab to patients with inflammatory bowel disease and recommends monitoring for signs and symptoms of IBD during treatment. Postmarketing reports have identified severe eczematous eruptions, including atopic dermatitis-like eruptions, dyshidrotic eczema, and erythroderma, with some cases requiring hospitalization and treatment discontinuation. Neutropenia has also been observed in clinical trials. Risk management strategies incorporated into the secukinumab label include warnings and precautions sections addressing infections, hypersensitivity reactions, tuberculosis screening, inflammatory bowel disease monitoring, eczematous eruptions, and immunization considerations. The label recommends avoiding live vaccines during treatment and instructs patients to seek medical advice if signs or symptoms of infection occur.	establishing efficacious exposure levels and the demonstration of comparable drug exposures, supports a favorable benefit-risk profile for secukinumab in the treatment of juvenile ankylosing spondylitis in patients 12 years of age and older.

2. Background

Product Introduction

Secukinumab is a monoclonal IgG1 antibody that binds to and neutralizes interleukin-17A, thereby inhibiting the release of proinflammatory cytokines and mediators of tissue damage. The original BLA 125504 was approved on January 21, 2015, for moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Following this initial approval, secukinumab received subsequent approvals for multiple indications and is currently approved for the treatment of moderate to severe plaque psoriasis (PsO) in patients 6 years and older who are candidates for systemic therapy or phototherapy, active psoriatic arthritis (PsA) in patients 2 years of age and older, active ankylosing spondylitis (AS) in adults, active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation in adults, active enthesitis-related arthritis (ERA) in pediatric patients 4 years of age and older, and moderate to severe hidradenitis suppurativa in adults.

Analysis of Condition

Juvenile Ankylosing Spondylitis

Juvenile ankylosing spondylitis (JAS) is a descriptive term for the clinical presentation of ankylosing spondylitis (AS) before 16 years of age. The condition is characterized by inflammatory back pain with insidious onset, nocturnal pain that improves upon rising, pain that improves with exercise, and morning stiffness lasting 15 minutes or more. Extraspinal features may include peripheral arthritis, enthesitis, dactylitis, and uveitis.

JAS is classified using the established criteria for AS in adults, the Assessment of Spondyloarthritis International Society (ASAS) criteria[2]. The use of identical classification criteria for adult AS and JAS reflects the similarity in disease pathophysiology and clinical presentation between these age groups, with both conditions sharing pathophysiologic mechanisms involving IL-17A-mediated inflammation and progressive inflammatory processes affecting the axial skeleton. This similarity in disease pathophysiology and classification supports efficacy extrapolation from adult AS to JAS based on achievement of comparable exposure levels, while safety is established through data from pediatric populations with related inflammatory conditions receiving the identical dosing regimen.

The true incidence of JAS is unknown; however, it is estimated that 10-20% of patients diagnosed with AS present before 16 years of age, and that most of these cases occur in

[2] Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, Dougados M, Hermann KG, Landewé R, Maksymowych W, van der Heijde D. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009 Jun;68 Suppl 2:ii1-44. doi: 10.1136/ard.2008.104018. PMID: 19433414.

patients who are at least 8 years of age[3]. The overall prevalence of JAS is estimated to be fewer than 1 per 1000 children. JAS is extremely rare in children below 12 years of age because the characteristic inflammatory processes and structural changes require time to develop, making the adolescent population (12 to < 18 years) the primary pediatric demographic affected by this condition.

Axial Juvenile Spondyloarthritis

Axial juvenile spondyloarthritis (AxJSpA) is a pediatric entity that closely approximates non-radiographic axial spondyloarthritis (nr-axSpA) in adults. The condition shares similar clinical manifestations with nr-axSpA, including inflammatory back pain with insidious onset, nocturnal pain that improves upon rising, and prolonged morning stiffness. Like nr-axSpA, AxJSpA is mediated by IL-17A-driven inflammation and shares pathophysiologic features with other spondyloarthropathies.

One set of classification criteria for AxJSpA known as the Weiss criteria published in December 2024, consists of seven weighted domains with a total maximum score of 100 points[4,5]. To meet the classification threshold for AxJSpA, individuals must achieve a score of 55 points or higher. The two imaging domains carry the highest weights (active inflammation on imaging worth up to 23 points and structural lesions on imaging worth up to 23 points), while clinical domains include pain chronicity (maximum 9 points), pain pattern (maximum 13 points), pain location (maximum 12 points), morning stiffness (maximum 9 points), and genetics (maximum 11 points). Importantly, while imaging evidence typical of sacroiliitis is required for classification, it alone is not sufficient, as individuals must also meet additional clinical criteria to surpass the threshold.

AxJSpA overlaps with other pediatric inflammatory arthritis conditions such as enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA), which also feature axial involvement and share overlapping clinical manifestations including enthesitis, peripheral arthritis, and inflammatory back pain. This overlap in clinical presentation reflects the shared IL-17A-mediated inflammatory pathways across these conditions.

Analysis of Current Treatment Options

[3] Burgos-Vargas R, Vazquez-Mellado J. The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. Arthritis & Rheumatism. 1995 June;38(6):835-844
[4] Weiss PF, Brandon TG, Aggarwal A, Burgos-Vargas R, Colbert RA, Horneff G, Laxer RM, Minden K, Ravelli A, Ruperto N, Smith JA, Stoll ML, Tse SM, Van den Bosch F, Maksymowych WP, Lambert RG, Biko DM, Chauvin NA, Francavilla ML, Jaremko JL, Herregods N, Kasapcopur O, Yildiz M, Srinivasalu H, Lovell DJ, Nigrovic PA, Foeldvari I, Klein-Gitelman MS, Ozen S, Naden R, Hendry AM, Joos R. Classification Criteria for Axial Disease in Youth with Juvenile Spondyloarthritis. Arthritis & Rheumatology. 2024;76(12):1797-1808.
[5] The classification criteria published by Weiss et al were used in this submission to identify patients in the retrospective analysis. Use of these criteria for this review does not constitute FDA endorsement of these criteria as the classification standard.

Currently, there are no FDA-approved therapies for either JAS or AxJSpA, representing an unmet medical need in the pediatric population. In clinical practice, adolescent patients with JAS are typically managed off-label with non-steroidal anti-inflammatory drugs (NSAIDs) and biologic DMARDs (bDMARDs). Multiple biologic treatment options are approved for adult AS, including TNF inhibitors, IL-23 inhibitors, and IL-17 inhibitors such as secukinumab, but these lack pediatric approval for JAS. For AxJSpA, the treatment landscape is more complex. Pediatric patients with axial spondyloarthritis features who meet diagnostic criteria for ERA or JPsA have access to FDA-approved biologic therapies for those indications, including secukinumab which is approved for both ERA and JPsA. Additionally, the literature demonstrates that biologic therapies show efficacy for treating axial disease manifestations in pediatric patients with ERA and JPsA, with studies documenting improvements in back pain, spinal mobility, and inflammatory markers in patients with axial involvement. For pediatric patients with axial spondyloarthritis features who do not meet criteria for ERA or JPsA, off-label treatments similar to those used for JAS are employed, including NSAIDs and bDMARDs.

Regulatory Background

The original BLA 125504 for secukinumab was approved on January 21, 2015, for moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Following this initial approval, secukinumab received subsequent approvals for multiple indications and is currently approved for the treatment of moderate to severe plaque psoriasis (PsO) in patients 6 years and older who are candidates for systemic therapy or phototherapy, active psoriatic arthritis (PsA) in patients 2 years of age and older, active ankylosing spondylitis (AS) in adults, active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation in adults, active enthesitis-related arthritis (ERA) in pediatric patients 4 years of age and older, and moderate to severe hidradenitis suppurativa in adults.

FDA issued a Written Request for pediatric studies addressing JAS and AxJSpA. For JAS, the Written Request specified that the efficacy of secukinumab in patients aged 12 to < 18 years could be wholly extrapolated from efficacy data in adults with AS because the classification criteria are identical, with no new clinical studies required. However, for AxJSpA, the Written Request required a retrospective analysis of data from a completed phase 3 trial and its extension trial in subjects with ERA and JPsA to evaluate efficacy and safety in the subset of pediatric subjects who fulfill agreed upon criteria for AxJSpA. A retrospective analysis was necessary as the original trials did not prospectively enroll subjects with AxJSpA, and there were no classification criteria available to identify the pediatric equivalent of nr-AxSpA.

In response to the Written Request, the Applicant submitted two parallel, supplemental Biological License Applications (sBLAs) for Cosentyx® (secukinumab). These sBLAs address both AxJSpA and JAS. The sBLA for AxJSpA (sBLA 125504 – Supplement 97) provides clinical data in pediatric subjects with axial symptoms without seeking a new indication, whereas the sBLA for JAS (sBLA 125504 – Supplement 98) seeks to expand the current

indication of active ankylosing spondylitis in adults to "active ankylosing spondylitis in adults and pediatric patients 12 years of age and older."

3. Product Quality

No new product quality information was provided.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical information was provided.

5. Clinical Pharmacology

5.1 Executive Summary

The Applicant, Novartis Pharmaceuticals Corporation, is seeking the approval of Cosentyx® [non-proprietary name: secukinumab (AIN457)] for the treatment of juvenile ankylosing spondylitis (JAS) for pediatric patients aged 12 to < 18 years of age. The proposed subcutaneous (SC) dosing regimen is 75 mg (< 50 kg) or 150 mg (≥ 50 kg) at Weeks 0, 1, 2, 3, 4 and every 4 weeks (Q4W) thereafter.

Secukinumab is approved in adults with active ankylosing spondylitis (AS) and adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation. The recommended dosing regimen for AS and nr-axSpA is 150 mg SC at Weeks 0, 1, 2, 3, 4 and Q4W thereafter. If a patient continues to have active AS, consider a dosage of 300 mg Q4W.

No clinical trials were conducted in pediatric patients with active JAS in support of BLA 125504/S-098. BLA 125504/S-098 was submitted in response to the FDA's Written Request. The Written Request specified that the efficacy of secukinumab in patients aged 12 to < 18 years could be wholly extrapolated from adults with AS because the classification criteria are identical to those used for adult AS (Assessment of Spondyloarthritis International Society [ASAS] criteria), and the same enrollment criteria would be expected to yield similar efficacy results between adult AS and JAS populations. Safety for JAS population can be leveraged from pediatric patients with enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (JPsA), and psoriasis (PsO).

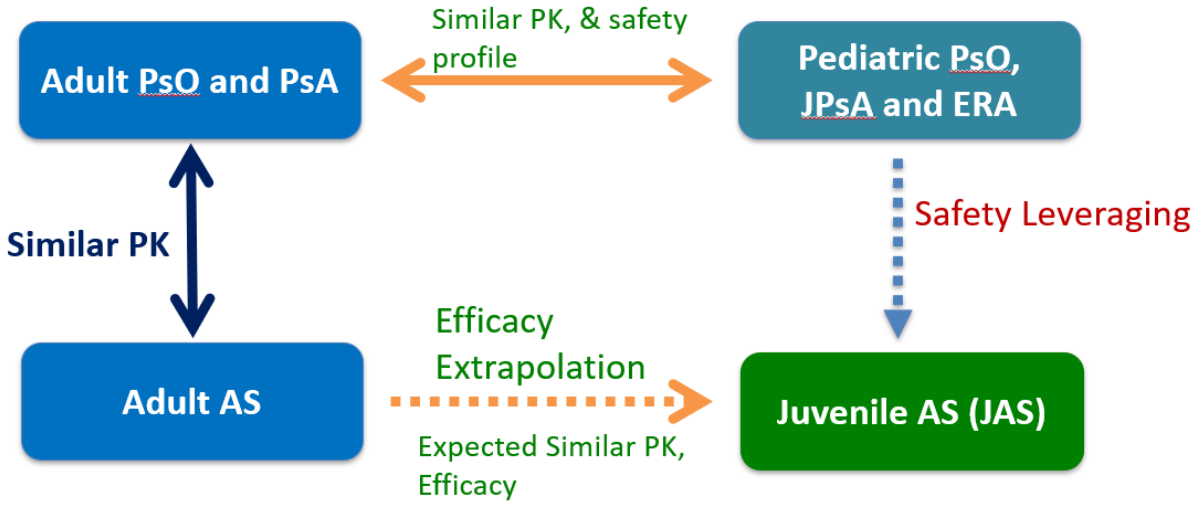
To support the approval of SC dosing regimen of secukinumab in JAS, a pharmacokinetics (PK) based considerations in support of a SC regimen that approximates the exposure levels of the approved 150 or 300 mg SC Q4W regimen in adult AS patients was proposed by the Applicant. However, a 4-way extrapolation strategy (Figure 1) was considered by the Agency and was communicated to the Applicant asking for the required data through multiple information requests during this review cycle.

The efficacy in JAS was demonstrated through a 4-way extrapolation strategy (Figure 1) that bridges PK and efficacy and leverages safety across four patient populations:

(1) Disease similarity between adult AS and pediatric patients with JAS
(2) Adult PsO/PsA ↔ Adult AS (similar PK),
(3) Pediatric PsO/ERA/JPsA → Juvenile AS (PK and safety), and
(4) Adult AS → Juvenile AS (efficacy).

This approach leverages adult AS efficacy data, pediatric safety data primarily from pediatric PsO trials (with additional support from ERA and JPsA studies).

Figure 1: Four Way Extrapolation from Clinical Studies in Adult AS and Related Pediatric Populations



Source: FDA Primary Reviewer's Analysis

The PK comparison between adult AS and adult PsO/PsA supported the lack of disease impact on secukinumab PK. Therefore, PK were bridged from pediatric populations, including pediatric PsO, JPsA, and ERA to pediatrics with JAS.

Given the identical diagnostic criteria and ASAS classification criteria for adult AS and JAS, similar IL-17A-mediated disease pathophysiology, efficacy as demonstrated in adult AS can be extrapolated to pediatric patients with JAS based on PK matching. See clinical review in section 2 for more details.

Based on PK comparison, secukinumab concentrations in pediatric patients (12 years of age and older) with JAS who received the recommended pediatric dosing regimen were predicted to be comparable to those exposures observed in adult patients with AS. Therefore, efficacy established in adult AS was extrapolated to pediatric patients with JAS.

Similarly, based on the comparable exposures, safety profiles in adult AS population and pediatric patients with PsO, PsA, and ERA were leveraged to support the safety assessment of secukinumab in pediatric patients with JAS following the proposed dosing regimen.

Overall, the 4-way extrapolation supports the establishment of safety and efficacy of the proposed dosing regimen in JAS patient population.

Recommendations

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under sBLA 125504/S098 and finds the sBLA approvable for 12 years of age and older with JAS.

5.2 Summary of Clinical Pharmacology Assessment

5.2.1 Pharmacology and Clinical Pharmacokinetics

The following are the major clinical pharmacology findings of the current review:

Overall, the PK are generally comparable between adults with AS, PsO, and PsA and pediatric patients with PsO, JPsA, and ERA.

Based on PK comparison, secukinumab concentrations in pediatric patients (12 years of age and older) with JAS who received the recommended pediatric dosing regimen were predicted to be comparable to exposures observed in adults with AS.

5.2.2 General Dosing and Therapeutic Individualization

General Dosing

The recommended dose of secukinumab for JAS is the same secukinumab dosing regimen that is approved for other pediatric indications (JPsA, ERA, and PsO), namely, SC injections at Weeks 0, 1, 2, 3, and 4 and every 4 weeks (Q4W) thereafter:
• For adolescent patients < 50 kg, the dose is 75 mg SC
• For adolescent patients ≥ 50 kg, the dose is 150 mg SC

Therapeutic Individualization

None.

Outstanding Issues

None.

5.3 Comprehensive Clinical Pharmacology Review

5.3.1 General Pharmacology and Pharmacokinetic Characteristics

The observed pharmacokinetics (PK) of secukinumab administered subcutaneously in adult patients with PsO, PsA, AS and nr-axSpA were similar. The secukinumab PK is also similar in pediatric patients with JPsA, ERA, and PsO for the same weight tiered dosing regimen.

Absorption

Following a single subcutaneous dose of either 150 mg or 300 mg (administered as two injections of 150 mg) of COSENTYX in PsO subjects, secukinumab reached peak mean (± SD) serum concentrations (Cmax) of 13.7 ± 4.8 mcg/mL and 27.3 ± 9.5 mcg/mL, respectively, by approximately 6 days post dose.

Following multiple subcutaneous doses of COSENTYX (administered as one or two injections of 150 mg), the mean (± SD) serum trough concentrations of secukinumab ranged from 22.8 ± 10.2 mcg/mL (150 mg) to 45.4 ± 21.2 mcg/mL (300 mg) at Week 12. At the 300 mg dose at Week 4 and Week 12, the mean trough concentrations resulted from the Sensoready pen were approximately 30% higher than those from the prefilled syringe. Following multiple subcutaneous doses of 300 mg administered via the 300 mg/2 mL UnoReady pen, the mean serum trough concentrations of secukinumab were generally consistent with those in the previous Sensoready pen study used to deliver 300 mg.

Steady-state concentrations of secukinumab were achieved by Week 24 following the every 4-week dosing regimen. The mean (± SD) steady-state trough concentrations ranged from 16.7 ± 8.2 mcg/mL (150 mg) to 34.4 ± 16.6 mcg/mL (300 mg administered as two injections of 150 mg).

In healthy subjects and subjects with PsO, secukinumab bioavailability ranged from 55% to 77% following subcutaneous COSENTYX dose of 150 mg or 300 mg (administered as two injections of 150 mg).

Following subcutaneous administrations of 300 mg of COSENTYX at Weeks 0, 1, 2, 3, and 4 and then every 4 weeks thereafter, steady-state concentrations of secukinumab were achieved by Week 24 in both HS trials. The mean (± SD) steady-state trough concentrations were 25.7 ± 15.7 mcg/mL and 26.0 ± 13.9 mcg/mL in HS Trial 1 and HS Trial 2, respectively.

Following subcutaneous administrations of 300 mg of COSENTYX at Weeks 0, 1, 2, 3, and 4 and then every 2 weeks thereafter, steady-state concentrations of secukinumab were achieved by Week 16 in both HS trials. The mean (± SD) steady-state trough concentrations were 55.0 ± 26.1 mcg/mL and 58.1 ± 30.1 mcg/mL in HS Trial 1 and HS Trial 2, respectively.

Distribution

The mean volume of distribution during the terminal phase (Vz) following a single intravenous administration ranged from 7.10 to 8.60 L in PsO subjects.

Secukinumab concentrations in interstitial fluid in lesional and non-lesional skin of PsO subjects ranged from 27% to 40% of those in serum at 1 and 2 weeks after a single subcutaneous dose of COSENTYX 300 mg (administered as two injections of 150 mg).

Elimination

Metabolism

The metabolic pathway of secukinumab has not been characterized. As a human IgG1κ monoclonal antibody secukinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Excretion
The mean systemic clearance (CL) ranged from 0.14 L/day to 0.22 L/day and the mean half-life ranged from 22 to 31 days in PsO subjects following intravenous and subcutaneous administration across all PsO trials.

Dose Linearity
Secukinumab exhibited dose-proportional PK in subjects with PsO over a dose range from 25 mg (approximately 0.083 times the recommended dose) to 300 mg following subcutaneous administrations.

Weight
Secukinumab clearance and volume of distribution increase as body weight increases.

Specific Populations

Geriatric Patients
Population PK analysis indicated that the clearance of secukinumab was not significantly influenced by age in adult subjects with PsO, PsA and AS. Subjects who are 65 years and older had apparent clearance of secukinumab similar to subjects less than 65 years old.

Pediatric Patients
In a pool of the two pediatric trials, subjects with moderate to severe PsO (6 years of age and older) were administered subcutaneous secukinumab at the recommended pediatric dosing regimen. At Week 24, secukinumab steady state mean ± SD serum trough concentrations were 32.6 ± 10.8 mcg/mL (n = 8), 19.8 ± 6.96 mcg/mL (n = 24), and 27.3 ± 10.1 mcg/mL (n = 36), in subjects who weighed less than 25 kg and received 75 mg of subcutaneous secukinumab, subjects who weighed at least 25 kg and less than 50 kg and received 75 mg of subcutaneous secukinumab, and subjects who weighed at least 50 kg and received 150 mg of subcutaneous secukinumab, respectively.

In a pediatric trial, JPsA and ERA patients (2 to less than 18 years of age) were administered subcutaneous secukinumab at the recommended pediatric dosing regimen. At Week 24, patients who weighed at least 15 kg and less than 50 kg, and patients who weighed at least 50 kg had a mean ± SD steady-state trough concentration of 25.2 ± 5.45 mcg/mL (n = 10) and 27.9 ± 9.57 mcg/mL (n = 19), respectively.

5.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. This sBLA for JAS is supported by 4-way extrapolation approach which includes a PK matching based efficacy extrapolation and leverage of safety data from previously approved pediatric indications (PsO, JPsA, and ERA). This supplement S098 is relying on the following considerations in an extrapolation approach for JAS:

- The disease similarity between adult patients with AS and pediatric patients with JAS
- The similar systemic exposure of secukinumab between adults with PsO/PsA and adults with AS
- PK bridging of secukinumab in pediatric patients with PsO, JPsA, and ERA to pediatric patients with JAS
- Efficacy extrapolation from adult patients with AS to pediatric patients with JAS
- Justification of relevance of safety data from other pediatric indications including pediatric PsO, JPsA, and ERA

Adult AS and JAS share numerous features, including genetic risk factors, family history, pathogenic mechanism, and clinical and radiologic manifestations. The symptoms and comorbidities of JAS can significantly impair health-related quality of life. JAS and adult AS alike, exhibit involvement of both peripheral and axial joints. Peripheral arthritis, which affects joints outside of the spine such as the hips, knees, or ankles, can be seen in both forms of the disease, although it is often more prominent in JAS. Axial arthritis, characterized by inflammation of the sacroiliac joints and joints of the spine, is a hallmark in both JAS and adult AS. This overlapping pattern of joint involvement further supports the concept that JAS and adult AS share core features and are part of the same disease spectrum. Extra-articular disease manifestations such as acute anterior uveitis, iritis, and inflammatory bowel disease occur in both juvenile and adult forms. Extra-articular manifestations occurred with similar frequency in juvenile and adult AS patients. These similarities provide the basis to extrapolate efficacy and leverage safety data from adult AS to JAS. Refer to Section 2 for more details on clinical similarity between JAS and adult AS patients.

A cross-study comparison of secukinumab serum exposure across patient populations is shown in Table 1 below. The comparison included PK data from: JPsA and ERA patients in Study F2304 (who received the same regimen proposed for adolescent AS patients), pediatric PsO patients in Study A2310, adult PsO patients in Study A2302, and adult AS patients in Study F2310.

Table 1. Observed arithmetic mean (± SD) secukinumab concentrations ($C_{min,4w}$ and $C_{min,ss}$) in JPsA and ERA, pediatric PsO and adult AS, PsO and PsA.

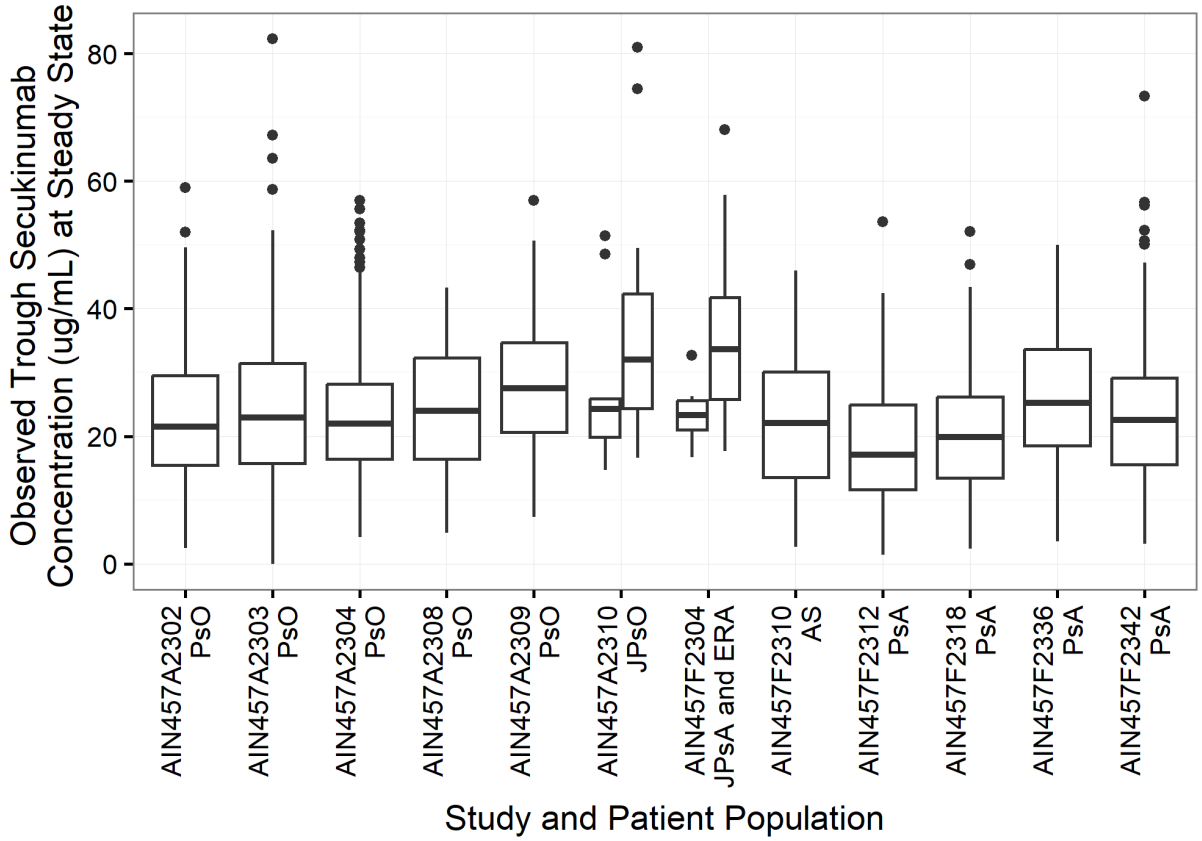
Time (weeks)	75 mg									
	JPsA and ERA (F2304) (<50 kg)		PsO (A2310) (<25 kg)		PsO (A2310) (25-<50 kg)					
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)				
4	12	50.7±9.95	4	105±16.9	14	52.0±10.7				
24	10	25.2±5.45	2	29.4±7.42	14	20.4±7.44				
52	10	21.7±5.04	1	22.2	14	18.7±8.18				
104	7	22.2±5.29	-	-	-	-				
Time (weeks)	150 mg									
	Adult AS (F2310)		JPsA and ERA (F2304) (≥50 kg)		PsO (A2310) (≥50 kg)		Adult PsO (A2302)		Adult PsA (F2312)	
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)

4	62	54.0±17.4	32	61.6±17.3	4	77.2±18.7	231	44.9±14.6	81	47.6±13.1
24	63	20.5±9.75	19	27.9±9.57	7	24.7±8.04	206	17.7±9.43	85	19.3±9.61
52	59	20.5±9.03	20	26.6±7.84	8	26.1±8.87	171	16.7±8.19	82	18.7±9.48
104	57	19.5±9.63	20	22.4±6.37	-	-	-		77	18.9±9.08

Note: Cmin at Week 4 and Cmin,ss at Weeks 24, 52, and 104
Source: Response to FDA Information Request for JAS, dated March 20th, 2026, Table 3-1, page 6-7.

A comparison of the observed trough concentration at steady state ($C_{min,ss}$) following the approved 150 mg Q4W dosing regimen (with or without loading dose) in adults with PsO, PsA, and AS and pediatric patients with PsO, JPsA, and ERA following the approved 75/150 mg Q4W dosing regimen was given in Figure 2.

Figure 2 Comparison of Observed $C_{min,ss}$ in pediatric patients with PsO, JPsA, and ERA patients, and adult patients with PsO, PsA, AS treated with the approved regimens.



Note: The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range (IQR) beyond the box or the more extreme values whichever is closer to the box. Dots are the individual observed/predicted Cmin concentration data. The observed Cmin concentration data are from the following studies: AIN457A2302, AIN457A2303, AIN457A2304, AIN457A2308, AIN457A2309 for PsO adults; AIN457F2310, AIN457F2320 for AS adult; AIN457F2312, AIN457F2318, AIN457F2336, AIN457F2342 for PsA adults. For Pediatric studies (PsO, JPsA and ERA) 75 mg and 150 mg are staggered in separate boxes,
Source: FDA Reviewer's Analysis.

Based on the Applicant's analysis in Table 1, typical pre-dose concentrations at steady-state ($C_{min,ss}$) from 24 weeks onwards were in the range between 19.5 and 20.5 µg/mL at 150 mg SC Q4W in adults AS patients. Similarly, $C_{min,ss}$ in adults with PsO ranged from 16.7 to 17.7 µg/mL

at 150 mg SC Q4w, and 19.7 to 19.3 μg/mL in adults with PsA. In general, the serum secukinumab concentrations in adults with active AS were in the same range as adult patients with PsO and PsA. This comparison suggested that diseases (PsA, PsO, and AS) have no impact on secukinumab PK. Therefore, the PK data observed in pediatric patients with PsO, JPsA, and ERA are relevant to pediatric patients with active JAS.

Comparable, albeit slightly higher, values were observed in pediatric PsO, JPsA, and ERA patients for both body weight subgroups when compared with adults with AS. This suggested that exposures of the proposed regimen for pediatric patients with JAS are expected to match the exposures in adults with AS following the approved dosing regimen of 150 mg Q4W. Similarly, Figure 2 also suggested that JAS patients treated with the approved 75/150 mg SC Q4W regimen should achieve exposure levels in the range of those achieved in adult AS treated with the approved 150 mg SC Q4W regimen. Therefore, the comparable exposures supported the extrapolation of efficacy in adults with AS to pediatrics with JAS from a clinical pharmacology perspective.

Does the available safety data in pediatric subjects support the recommended dosing regimen in JAS patients 12 years of age and older?

Yes. In this submission, the safety data are leveraged from the known secukinumab safety profiles across various indications in both adult AS and other relevant pediatric populations. The proposed JAS dosing regimen is expected to result in exposures that are comparable to adult patients with AS, and support the leverage of safety profiles in adults with AS to JAS. In addition, the comparable systemic exposure between JAS and pediatric PsO, JPsA, and ERA populations support the leverage of established safety profile in PsO, JPsA, and ERA to JAS. Therefore, the safety profiles in JAS are expected to be similar to adults with AS, pediatric patients with PsO, JPsA, and ERA.

In addition, significant overlap in the underlying comorbidities and treatments in JAS with ERA/JPsA and pediatric PsO patients with similar safety profile seen e.g. with anti-TNF treatments. This supports the leveraging of safety experience with secukinumab in ERA/JPsA and pediatric PsO patient populations to support application in JAS patients.

Refer to Section 7 for more details on clinical safety in these clinical trials in adult AS, pediatric PsO, JPsA, and ERA.

Overall, the 4-way extrapolation supports the establishment of safety and efficacy of the proposed dosing regimen in JAS patient population, and the proposed dosing regimen is appropriate from a clinical pharmacology perspective.

What was the Impact of Immunogenicity on Secukinumab Exposure?

Treatment-emergent ADA in adults with AS was below 1% in Phase 3 studies conducted in adults with AS, F2305, F2310 and F2314, over a 52-week period. In the 2 AS patients with transient ADA in Study F2305 and the 1 AS patient with transient ADA in Study F2314, the

ADA were not associated with AEs, loss of efficacy, or alteration of PK. It should be acknowledged that these results from the descriptive analyses must be interpreted with caution due to the small sample size of ADA-positive subjects.

Are the bioanalytical methods properly validated to measure PK and PD in plasma samples?

There was no new PK data information since the previous submission has been collected or analyzed hence no Summary of Biopharmaceutics Studies and associated bioanalytical reports were submitted in this sBLA. The bioanalytical method which was recently used (in study P12301) for the measurement of secukinumab serum concentrations has been reviewed earlier in 2023. (see unireview in DARRTS dated 10/06/2023, Reference ID: 5256774).

6. Clinical/Statistical- Efficacy

Review Strategy

For JAS, efficacy was extrapolated from adult AS. As noted in the FDA Written Request, the identical ASAS classification criteria for adult AS and JAS provide scientific justification for efficacy extrapolation, as the same enrollment criteria would be expected to yield similar efficacy results between adult and juvenile AS populations. Additionally, the Applicant's PK data demonstrate that the proposed weight-based dosing regimen (75 mg SC for patients <50 kg; 150 mg SC for patients ≥50 kg) results in steady-state drug exposures comparable to those that produced efficacy in adult patients with AS and comparable to exposures in pediatric patients with related inflammatory conditions receiving the same dosing regimen.

For AxJSpA, efficacy was assessed through a retrospective analysis of data from a completed phase 3, randomized, double-blind, placebo-controlled, treatment withdrawal trial (F2304) and its associated extension trial (F2304E1). These trials enrolled subjects with ERA and JPsA. For this assessment, an AxJSpA analysis cohort was retrospectively identified from the trial population. This cohort consists of subjects who met either published classification criteria for AxJSpA (Weiss et al., 2024) or a set of Applicant-defined criteria designed to identify individuals with signs and symptoms suggestive of AxJSpA. This retrospective approach was necessary as the original trials did not prospectively enroll subjects with AxJSpA as criteria to identify the pediatric equivalent of nr-axSpA did not exist.

Review of Efficacy

Juvenile Ankylosing Spondylitis (JAS)

Efficacy Extrapolation from Adult AS

The efficacy of secukinumab was assessed in 816 adult subjects with active AS in 3 randomized, double-blind, placebo-controlled trials (F2305, F2310, and F2314). Subjects had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 despite

non-steroidal anti-inflammatory drug (NSAID), corticosteroid, or disease modifying anti-rheumatic drug (DMARD) therapy.

Trial F2305 evaluated 371 subjects who were treated with secukinumab 10 mg/kg IV at Weeks 0, 2, and 4 (for both treatment arms) or placebo, followed by either secukinumab 75 mg SC or 150 mg SC every 4 weeks or placebo. The primary endpoint was the percentage of subjects who achieved an ASAS20 response at Week 16. Subjects treated with secukinumab 10 mg/kg IV/75 mg SC, and 10 mg/kg IV/150 mg SC demonstrated greater improvements in ASAS20 compared to placebo at Week 16 (60.8% in the secukinumab 10 mg/kg IV/150 mg SC group vs 59.7% in the secukinumab 10 mg/kg IV/75 mg SC group vs 28.7% in placebo; both $p<0.0001$).

Trial F2310 evaluated 219 subjects who were treated with secukinumab 75 mg SC, 150 mg SC, or placebo at Weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks. The primary endpoint was the percentage of subjects who achieved an ASAS20 response at Week 16. Subjects treated with 150 mg of secukinumab demonstrated statistically significant improvements in ASAS20 response compared to placebo at Week 16 (61.1% in the secukinumab 150 mg group vs 28.4% in placebo; $p=0.0001$). ASAS40 response was 36.1% in the 150 mg group compared to 10.8% in placebo ($p=0.0008$). Subjects treated with 150 mg of secukinumab also demonstrated greater improvements in all ASAS20 components in addition to other measures of disease activity including BASDAI score, BASMI, and hsCRP.

Trial F2314 evaluated 226 subjects who were treated with secukinumab 10 mg/kg IV at Weeks 0, 2, and 4 (for both treatment arms) or placebo, followed by either secukinumab 150 mg SC or 300 mg SC every 4 weeks or placebo. The primary endpoint was the percentage of subjects who achieved an ASAS20 response at Week 16. Subjects treated with SC secukinumab (150 mg and 300 mg) demonstrated improved signs and symptoms, and had comparable efficacy responses, regardless of dose, that were superior to placebo at Week 16 for the primary and most secondary endpoints. At Week 16, the ASAS20 response rates were 58.1% for the secukinumab 150 mg SC group ($p=0.0102$, adjusted) and 60.5% for the 300 mg SC group ($p=0.0075$, adjusted) compared to 36.8% for placebo. Both secukinumab doses were also superior to placebo on the hierarchically tested secondary endpoints of ASAS40, hsCRP, ASAS 5/6, and total BASDAI.

Conclusions re: JAS Efficacy

The benefit of secukinumab for active ankylosing spondylitis in patients 12 years of age and older is supported by a 4-way extrapolation strategy that leverages efficacy from adult AS trials, and PK data demonstrating comparable drug exposures across populations.

The proposed indication addresses an unmet medical need where no therapies are currently FDA-approved for JAS, and the extrapolation strategy provides support that secukinumab will be effective in adolescent patients. The benefit-risk profile appears favorable, as the expected efficacy based on adult AS data and PK data combined with the well-characterized safety profile in pediatric populations receiving the identical dosing regimen outweighs the safety risks, supporting expansion of the AS indication to include patients 12 years of age and older (See Section 5, Clinical Pharmacology).

Axial Juvenile Spondyloarthritis (AxJSpA)

The submission for AxJSpA was based on a retrospective analysis of data from a completed phase 3, randomized, double-blind, placebo-controlled, treatment withdrawal trial (F2304) and its associated extension trial (F2304E1). These trials originally enrolled subjects with ERA and JPsA. For this submission, a subgroup of subjects (the AxJSpA analysis cohort) was retrospectively identified from the trial population using two methods: published classification criteria for AxJSpA (Weiss et al., 2024) or a set of Applicant-defined criteria for signs and symptoms suggestive of AxJSpA.

Core Trial F2304 Design and Enrollment

Trial F2304 was a 2-year, phase 3, randomized, double-blind, placebo-controlled, event-driven, treatment-withdrawal trial to evaluate the safety and efficacy of SC secukinumab compared with placebo in pediatric subjects with active ERA or JPsA. The trial enrolled 86 subjects (52 with ERA and 34 with JPsA).

This trial had three periods. Treatment Period 1 (TP1) was an open-label period lasting up to 12 weeks in which all enrolled subjects received secukinumab (75/150 mg SC based on weight < 50 or ≥ 50 kg) administered weekly for the first 4 weeks, then every 4 weeks thereafter. Subjects who achieved a JIA ACR30 response at week 12 were then eligible to enter Treatment Period 2 (TP2). TP2 was a randomized withdrawal phase, in which responders were randomized 1:1 to either continue secukinumab or switch to placebo every 4 weeks for up to 100 weeks or until disease flare occurred. The trial was designed to continue until either 33 flare events occurred or randomized subjects completed 104 weeks. Subjects who experienced a disease flare during TP2 or completed TP2 without flaring entered Treatment Period 3 (TP3), an open-label extension in which subjects received secukinumab every 4 weeks up to week 100. The primary endpoint was time to JIA flare in TP2.

Extension Trial F2304E1 Design and Enrollment

Trial F2304E1 was an optional, 4-year, multicenter, open-label extension trial to evaluate the use of SC secukinumab in pediatric subjects (aged 2 to < 18 years at the time of screening for trial F2304) with active ERA or JPsA who completed the entire treatment period of the core trial F2304.

The extension trial treatment involved two groups: Group 1 received secukinumab 75 mg SC every 4 weeks for subjects weighing < 50 kg, and Group 2 received secukinumab 150 mg SC every 4 weeks for subjects weighing ≥ 50 kg. At Week 104E1 (start of the extension trial), all subjects received the same dose as in Week 100 of the core trial according to their weight. Starting at Week 108, dose escalation was allowed based on investigator discretion for subjects whose signs and symptoms were not adequately controlled. The trial enrolled 55 subjects (19 who received secukinumab 75 mg SC, and 36 who received secukinumab 150 mg SC). The primary endpoint was JIA ACR 30 response over time up to Week 312.

Identification of Subjects with Signs and Symptoms of AxJSpA

To identify a subset of subjects from trial F2304 who met the published classification criteria for AxJSpA at or before the baseline visit, the Applicant created a survey of trial sites that enrolled subjects. The investigators were asked to complete the survey for each subject enrolled into the trial from their respective sites (regardless of completion status). The survey consisted of information on MRI, X-ray, HLA-B27, and axial pain chronicity from available data. No new assessments were performed as part of this survey.

The Applicant was able to identify 1 subject who met the published AxJSpA classification criteria. The investigator reported this subject as having had a positive MRI showing unequivocal inflammatory and structural lesions consistent with AxJSpA. Specific MRI findings regarding the nature and extent of inflammatory changes (e.g., bone marrow edema, synovitis) and structural changes (e.g., erosions, sclerosis, fat metaplasia) were not detailed in the submitted materials. This subject also had morning stiffness and a positive FABER test at baseline according to the F2304 clinical trial database.

However, given that trial F2304 did not assess the SI-joint, X-rays, MRI, or HLA-B27 status as part of the enrollment criteria or trial procedures, the Applicant developed alternative criteria based on symptoms consistent with axial spondyloarthritis derived from the core dataset of trial F2304. Under the Applicant-defined AxJSpA criteria, a subject was categorized as having AxJSpA if they met 4 of the following 5 criteria at the time of trial entry: (1) tenderness reported in cervical, thoracic, lumbar spine or SI-Joint; (2) presence of morning stiffness ≥ 15 minutes; (3) positive FABER test for at least one SI-joint (pain in one SI joint); (4) presence of inflammatory back pain with a response of "Yes" to all of the following questions - does the pain have a slow (insidious) onset, does the pain occur at night and improve upon getting up, and does the pain improve with exercise; and (5) a score of ≥ 50 for nocturnal back pain on a VAS 0-100 scale. Using these criteria, the Applicant identified 5 additional subjects with signs and symptoms suggestive of AxJSpA beyond the single subject identified using the published classification criteria.

Of the 6 identified subjects comprising the AxJSpA analysis cohort, 4 entered the extension trial (the subject who met the published classification criteria, and 3 of the 5 subjects who met the Applicant-defined criteria for signs and symptoms suggestive of AxJSpA). The remaining 2 subjects did not enter the extension trial due to lack of efficacy (1 subject with “lack of efficacy” before Week 12; 1 subject was an ACR30 non-responder at Week 12).

Retrospective Analysis Objectives and Endpoints

The primary objectives of the retrospective analysis were to evaluate the safety and efficacy of secukinumab in a retrospectively identified AxJSpA analysis cohort using data from trial F2304, and to assess the long-term safety and tolerability of secukinumab in this cohort from trial F2304E1. This analysis cohort was composed of subjects from the original trial population who were identified as having AxJSpA based on one of two methods: either meeting the published classification criteria or meeting a set of Applicant-defined criteria designed to identify individuals with signs and symptoms suggestive of the condition. The endpoints for the primary objectives included the Juvenile Arthritis Disease Activity Score

(JADAS) at Week 12 in addition to safety related endpoints (e.g., adverse events, tolerability assessments, vital signs, and laboratory parameters).

The secondary objectives of the retrospective analysis were to evaluate the safety and efficacy of secukinumab in the AxJSpA analysis cohort using data from trial F2304, and to compare the long-term safety and tolerability of secukinumab between this subset and those who did not meet such criteria for AxJSpA. The secondary endpoints included JADAS during the randomized withdrawal period, Physician's Global Assessment of disease activity (VAS), Parent/Subject Global Assessment of overall wellbeing (VAS included within CHAQ), overall back pain (VAS), nocturnal back pain (VAS), modified Schober's test, Juvenile Spondyloarthritis Disease Activity (JSpADA) index, JIA ACR30/50/70/90/100, and safety related endpoints (e.g., adverse events, tolerability assessments, vital signs, and laboratory parameters).

Retrospective Analysis of Efficacy

Primary Efficacy Endpoint (JADAS at Week 12)

The JADAS (Juvenile Arthritis Disease Activity Score) is a composite disease activity measure developed to assess disease activity in children and adolescents with juvenile idiopathic arthritis (JIA). The JADAS typically includes 4 core components: physician global assessment of disease activity (measured on a visual analogue scale from 0-10), parent/patient global assessment of overall well-being (also on a 0-10 scale), active joint count, and an acute phase reactant, usually erythrocyte sedimentation rate (ESR) normalized to a 0-10 scale. Different versions of the JADAS exist based on the number of joints assessed. The JADAS-71 evaluates 71 joints, whereas the JADAS-27 assesses 27 joints (excluding the hips, ankles, and feet). The total JADAS score is calculated by summing these four components, with the maximum possible score varying depending on the version used (JADAS-71 can range from 0 to 101, while JADAS-27 ranges from 0 to 57). Higher scores indicate greater disease activity.

Table 2. JADAS-27 and JADAS-71 Score Over Time up to Week 12 for Subjects in the AxJSpA Analysis Cohort from Trial F2304 (Full Analysis Set)

Subject ID	Age/Sex	Visit	JADAS-27	JADAS-71
(b) (6)	15/M	Baseline	31.8	35.8
		Week 4	18.7	19.7
		Week 8	15.2	16.2
		Week 12	8.8	8.8
(b) (6)	16/M	Baseline	15.3	19.3
		Week 4	15.5	15.5
		Week 8	15.7	17.7
		Week 12	23.7	24.7

(b) (6) *	16/F	Baseline	16.9	16.9
		Week 4	12.3	13.3
		Week 8	11.9	11.9
		Week 12	NA	NA
(b) (6)	16/M	Baseline	14.8	14.8
		Week 4	15.1	15.1
		Week 8	13.4	14.4
		Week 12	9.4	9.4
(b) (6)	13/M	Baseline	25.2	30.2
		Week 4	12.633	12.633
		Week 8	17.133	17.133
		Week 12	12.0	13.0
(b) (6) #	16/M	Baseline	14.334	14.334
		Week 4	3.928	3.928
		Week 8	1.318	1.318
		Week 12	5.027	5.027

Source: Adapted by Clinical Reviewer from CAIN457F2304 – Listing 16.2.6-1.7
All subjects received secukinumab 150 mg SC during TP1 of the core trial
*Subject was discontinued due to "Lack of Efficacy" before Week 12
#Subject was identified by the Weiss criteria, 2024

Four of the 6 subjects (66.67%) in the AxJSpA analysis cohort demonstrated improvement in both JADAS-27 and JADAS-71 scores at Week 12 compared to baseline. These 4 responders subsequently entered the extension trial F2304E1 and, as shown in the table below, generally maintained or continued to have improvement in JADAS scores throughout the long-term follow-up period, though 2 of the 4 subjects experienced period of disease activity fluctuation or treatment discontinuation during the extension trial.

Table 3. JADAS-27 and JADAS-71 Scores Over Time During TP2 of Trial F2304 and Extension Trial F2304E1 for Subjects in the AxJSpA Analysis Cohort (Full Analysis Set)

Subject ID	Age/Sex	Treatment Period/Trial	Treatment	Visit	JADAS-27	JADAS-71
(b) (6)	15/M	Baseline	AIN457 150 mg	Baseline	31.8	35.8
		Randomized withdrawal period (TP2)	AIN457 150 mg	Week 16	6.4	6.4

Subject ID	Age/Sex	Treatment Period/Trial	Treatment	Visit	JADAS-27	JADAS-71
		Randomized withdrawal period (TP2)	AIN457 150 mg	Week 52	3	3
		Extension	AIN457 150 mg	Week 104	0.9	0.9
		Extension	AIN457 150 mg	Week 156	0.8	0.8
		Extension	AIN457 150 mg	Week 208	3.1	3.1
		Extension	AIN457 150 mg	Week 260	1.1	1.1
		Extension	AIN457 150 mg	Week 312	8.38	8.38
(b) (6)	16/M	Baseline	AIN457 150 mg	Baseline	14.8	14.8
		Randomized withdrawal period (TP2)	Placebo	Week 16	8.2	8.2
		Randomized withdrawal period (TP2)	Placebo	Week 100	2.3	2.3
		Extension	AIN457 150 mg	Week 104	0.9	0.9
		Extension	AIN457 150 mg	Week 156	1.3	1.3
		Extension	AIN457 300 mg	Week 208	1.2	1.2
		Extension	AIN457 300 mg	Week 260	1.2	1.2
		Extension	AIN457 300 mg	Week 312	1	1
(b) (6) *	13/M	Baseline	AIN457 150 mg	Baseline	25.2	30.2
		Randomized withdrawal period (TP2)	Placebo	Week 16	20.633	23.633
		TP3	AIN457 150 mg	Week 20	10.467	10.467
		TP3	AIN457 150 mg	Week 100	12.9	13.9

Subject ID	Age/Sex	Treatment Period/Trial	Treatment	Visit	JADAS-27	JADAS-71
		Extension	AIN457 150 mg	Week 104	14.6	15.6
		Extension	AIN457 300 mg	Week 156	8.5	8.5
		Extension	AIN457 300 mg	Week 208	18.35	18.35
		Extension	-	Week 260	NA	NA
		Extension	-	Week 312	NA	NA
(b) (6) #	16/M	Baseline	AIN457 150 mg	Baseline	14.334	14.334
		Randomized withdrawal period (TP2)	Placebo	Week 16	2	2
		Randomized withdrawal period (TP2)	Placebo	Week 84	15.2	15.2
		TP3	AIN457 150 mg	Week 88	2.242	2.242
		TP3	AIN457 150 mg	Week 100	1.436	1.436
		Extension	AIN457 150 mg	Week 104	0.4	0.4
		Extension	AIN457 150 mg	Week 156	0.3	0.3
		Extension	AIN457 150 mg	Week 208	0.952	0.952
		Extension	AIN457 150 mg	Week 260	0.3	0.3
		Extension	AIN457 150 mg	Week 312	0.4	0.4

Source: Adapted by Clinical Reviewer from CAIN457F2304-Listing 16.2.6-1.7, CAIN457F2304-Listing 16.2.5-1.1, CAIN457F2304E1-Listing 16.2.6-1.4, and CAIN457F2304E1-Listing 16.2.5-1.1
*Subject discontinued due to "Post study access to treatment"
#Subject was identified by the Weiss criteria, 2024

Secondary Efficacy Endpoints

JIA ACR Response

JIA ACR response criteria are standardized measures used to assess treatment response in pediatric subjects with juvenile idiopathic arthritis (JIA). These criteria were adapted from the American College of Rheumatology (ACR) response criteria used in adult subjects with rheumatoid arthritis. A JIA ACR response requires improvement in a specified percentage

(e.g., 30%, 50%, 70%, 90%, or 100%) in at least 3 of 6 core outcome variables, with no more than one of the remaining variables worsening by more than 30%. The 6 core outcome variables are: physician global assessment of disease activity, parent/patient global assessment of overall well-being, functional ability (typically measured by the Childhood Health Assessment Questionnaire or CHAQ), number of joints with active arthritis, number of joints with limited range of motion, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

Table 4 (below) presents JIA ACR response data during the core trial F2304 and extension trial F2304E1. Two subjects were withdrawn during the core trial and did not enter the extension trial (Subject (b) (6) due to lack of efficacy, and subject (b) (6) due to ACR 30 non-responder status at Week 12). Subject (b) (6) discontinued the trial due to "post study access to treatment" during the extension trial. Four of the 6 subjects (66.67%) were responders and entered the extension trial. Of these 4 subjects, 3 (75% of the responder subjects, or 50% of the total subjects who were in the AxJSpA analysis cohort) achieved JIA ACR 100 response at some timepoint during the extension trial. The remaining subject achieved a maximum level of JIA ACR 50 response.

Table *4*. JIA ACR 30/50/70/90/100 Response for Subjects in the AxJSpA Analysis Cohort from Trials F2304 and F2304E1 (Full Analysis Set)

Subject ID	Treatment Period	Treatment	Visit	JIA ACR 30	JIA ACR 50	JIA ACR 70	JIA ACR 90	JIA ACR 100
(b) (6)	TP1	AIN457 150 mg	Week 4	No	No	No	No	No
	TP1	AIN457 150 mg	Week 8	Yes	Yes	No	No	No
	TP1	AIN457 150 mg	Week 12	Yes	Yes	Yes	No	No
	TP2	AIN457 150 mg	Week 16	Yes	Yes	Yes	No	No
	TP2	AIN457 150 mg	Week 52	Yes	Yes	Yes	Yes	No
	Extension trial	AIN457 150 mg	Week 104	Yes	Yes	Yes	Yes	Yes
	Extension trial	AIN457 150 mg	Week 156	Yes	Yes	Yes	Yes	Yes
	Extension trial	AIN457 150 mg	Week 208	Yes	Yes	Yes	No	No
	Extension trial	AIN457 150 mg	Week 260	Yes	Yes	Yes	Yes	Yes
	Extension trial	AIN457 150 mg	Week 312	Yes	Yes	Yes	Yes	Yes

Subject ID	Treatment Period	Treatment	Visit	JIA ACR 30	JIA ACR 50	JIA ACR 70	JIA ACR 90	JIA ACR 100
(b) (6) **	TP1	AIN457 150 mg	Week 4	No	No	No	No	No
	TP1	AIN457 150 mg	Week 8	No	No	No	No	No
	TP1	AIN457 150 mg	Week 12	No	No	No	No	No
(b) (6) **	TP1	AIN457 150 mg	Week 4	Yes	Yes	No	No	No
	TP1	AIN457 150 mg	Week 8	Yes	Yes	Yes	No	No
	TP1	NA	Week 12	NA	NA	NA	NA	NA
(b) (6)	TP1	AIN457 150 mg	Week 4	No	No	No	No	No
	TP1	AIN457 150 mg	Week 8	No	No	No	No	No
	TP1	AIN457 150 mg	Week 12	Yes	Yes	Yes	No	No
	TP2	Placebo	Week 16	Yes	Yes	Yes	No	No
	TP2	Placebo	Week 100	Yes	Yes	Yes	Yes	No
	Extension trial	AIN457 150 mg	Week 104	Yes	Yes	Yes	Yes	No
	Extension trial	AIN457 150 mg	Week 156	Yes	Yes	Yes	Yes	No
	Extension trial	AIN457 300 mg	Week 208	Yes	Yes	Yes	Yes	Yes
	Extension trial	AIN457 300 mg	Week 260	Yes	Yes	Yes	Yes	Yes
	Extension trial	AIN457 300 mg	Week 312	Yes	Yes	Yes	Yes	Yes
(b) (6) $	TP1	AIN457 150 mg	Week 4	Yes	No	No	No	No
	TP1	AIN457 150 mg	Week 8	No	No	No	No	No
	TP1	AIN457 150 mg	Week 12	Yes	Yes	No	No	No

Subject ID	Treatment Period	Treatment	Visit	JIA ACR 30	JIA ACR 50	JIA ACR 70	JIA ACR 90	JIA ACR 100
	TP2	Placebo	Week 16	No	No	No	No	No
	TP3	AIN457 150 mg	Week 20	Yes	Yes	No	No	No
	TP3	AIN457 150 mg	Week 100	Yes	No	No	No	No
	Extension trial	AIN457 150 mg	Week 104	Yes	No	No	No	No
	Extension trial	AIN457 300 mg	Week 156	Yes	No	No	No	No
	Extension trial	AIN457 300 mg	Week 208	Yes	No	No	No	No
	Extension trial	NA	Week 260	NA	NA	NA	NA	NA
	Extension trial	NA	Week 312	NA	NA	NA	NA	NA
(b) (6) #	TP1	AIN457 150 mg	Week 4	Yes	Yes	No	No	No
	TP1	AIN457 150 mg	Week 8	Yes	Yes	Yes	Yes	No
	TP1	AIN457 150 mg	Week 12	Yes	Yes	Yes	No	No
	TP2	Placebo	Week 16	Yes	Yes	Yes	No	No
	TP2	Placebo	Week 84	Yes	Yes	No	No	No
	TP3	AIN457 150 mg	Week 88	Yes	Yes	Yes	No	No
	TP3	AIN457 150 mg	Week 100	Yes	Yes	Yes	Yes	No
	Extension trial	AIN457 150 mg	Week 104	Yes	Yes	Yes	Yes	No
	Extension trial	AIN457 150 mg	Week 156	Yes	Yes	Yes	Yes	Yes
	Extension trial	AIN457 150 mg	Week 208	Yes	Yes	Yes	Yes	Yes
	Extension trial	AIN457 150 mg	Week 260	Yes	Yes	Yes	Yes	Yes
	Extension trial	AIN457 150 mg	Week 312	Yes	Yes	Yes	Yes	Yes

NA = "Not available." JIA ACR criterion achieved in order of 30/50/70/90/100 represents ≥30%/50%/70%/90%/100% improvement in the ACR Juvenile Idiopathic Arthritis response criteria. In the core study, only the first and last visit corresponding to TP2 & TP3 were included. JIA ACR response achieved relative to baseline is indicated as Yes/No. **Subjects (b) (6) (due to 'Lack of Efficacy') and (b) (6) (ACR 30 non-responder at Week 12) were withdrawn during the core trial and did not enter TP2 and extension trial. $Subject (b) (6) discontinued the extension trial due to "Post study access to treatment." #Patient (b) (6) was identified by Weiss criteria, 2024, and discontinued the study (on Day 1400) due to "Post study access to treatment." The source data was adapted by the Clinical Reviewer from CAIN457F2304-Listing 16.2.6-1.7, CAIN457F2304-Listing 16.2.5-1.1, CAIN457F2304E1-Listing 16.2.6-1.4, and CAIN457F2304E1-Listing 16.2.5-1.1.

Global Assessments of Disease Activity

Table 5 (below) presents the physician global assessment (PGA VAS) and parent/subject global assessment VAS for subjects in the AxJSpA analysis cohort during trials F2304 and F2304E1.

All 6 subjects demonstrated improvement in Physician Global Assessment scores from baseline, including the 2 subjects who discontinued treatment during the core trial. However, the 2 subjects who discontinued treatment notably experienced worsening of their Parent/Subject Global Assessment of Overall Well-being scores from baseline. Throughout the trial, both global assessment measures showed some fluctuation for most subjects.

Table *5*. Physician Global Assessment of Disease Activity and Parent/Subject Global Assessment of Overall Well-being for Subjects in the AxJSpA Analysis Cohort in Trials F2304 and F2304E1 (Full Analysis Set)

Subject ID	Age/ Sex	Treatment Period	Treatment	Visit	Physician Global Assessment (VAS mm)	Parent/Subject Global Assessment (VAS mm)
(b) (6)	15/M	Baseline	-	Baseline	100	100
		TP1	AIN457 150 mg	Week 12	40	16
		TP2	AIN457 150 mg	Week 16	35	7
		TP2	AIN457 150 mg	Week 52	15	15
		Extension trial	AIN457 150 mg	Week 104	5	4
		Extension trial	AIN457 150 mg	Week 312	5	6
(b) (6) **	16/M	Baseline	-	Baseline	73	60

Subject ID	Age/ Sex	Treatment Period	Treatment	Visit	Physician Global Assessment (VAS mm)	Parent/Subject Global Assessment (VAS mm)
		TP1	AIN457 150 mg	Week 8	55	72
		TP1	AIN457 150 mg	Week 12	48	69
		TP2	NA	Week 52	NA	NA
(b) (6) **	16/F	Baseline	-	Baseline	77	82
		TP1	AIN457 150 mg	Week 8	30	89
		TP1	NA	Week 12	NA	NA
		TP2	NA	Week 52	NA	NA
(b) (6)	16/M	Baseline	-	Baseline	65	73
		TP1	AIN457 150 mg	Week 12	11	83
		TP2	Placebo	Week 16	8	74
		TP2	Placebo	Week 52	9	33
		Extension trial	AIN457 150 mg	Week 104	4	5
		Extension trial	AIN457 300 mg	Week 312	4	6
(b) (6) $	13/M	Baseline	-	Baseline	59	80
		TP1	AIN457 150 mg	Week 12	24	25
		TP2	Placebo	Week 16	45	70
		TP3	AIN457 150 mg	Week 20	9	42
				Week 52	2	45
		Extension trial	AIN457 150 mg	Week 104	5	51
		Extension trial	AIN457 300 mg	Week 208	19	57

Subject ID	Age/ Sex	Treatment Period	Treatment	Visit	Physician Global Assessment (VAS mm)	Parent/Subject Global Assessment (VAS mm)
			NA	Week 312	NA	NA
(b) (6) #	16/M	Baseline	-	Baseline	29	45
		TP1	AIN457 150 mg	Week 12	5	11
		TP2	Placebo	Week 16	5	5
			Placebo	Week 84	30	12
		TP3	AIN457 150 mg	Week 88	14	7
		Extension trial	AIN457 150 mg	Week 104	2	2
		Extension trial	AIN457 150 mg	Week 312	2	2

NA= Not available. Physician global assessment of disease activity (VAS mm) ranges from 0 (no disease activity) to 100 (very severe disease activity). Parent or subject global assessment of overall well-being (VAS mm) ranges from 0 (very well) to 100 (very poor). **Subjects ((b) (6) – due to 'Lack of Efficacy' and (b) (6) – due to ACR 30 non-responder status at Week 12) were withdrawn during the core trial and did not enter TP2 and extension trial. $ Subject (b) (6) discontinued the extension trial due to "Post study access to treatment". # Subject (b) (6) was identified by Weiss criteria, 2024, and discontinued the trial (on Day 1400) due to "Post study access to treatment". Source: Adapted by Clinical Reviewer from CAIN457F2304-Listing 16.2.6-1.1, CAIN457F2304-Listing 16.2.5-1.1, and CAIN457F2304E1-Listing 16.2.6-1.1

Overall Back Pain (VAS)

The table below presents the visual analogue scale (VAS) scores for back pain observed during the core trial F2304. This parameter was recorded only for subjects with ERA during the core trial. Among the 3 subjects who reported back pain at baseline, 1 subject (33.3%) experienced improvement while on active treatment with secukinumab. Notably, subject (b) (6) reported worsened back pain at Week 12 while on active treatment with secukinumab (VAS score increased from 70 mm to 80 mm at Week 12), but subsequently reported improvement while on placebo during TP2 (VAS score decreased to 33 mm at Week 52 and 13 mm at Week 104).

Table 6. Overall Back Pain Score for Subjects in the AxJSpA Analysis Cohort (ERA subjects) from Trial F2304 (Full Analysis Set)

Subject Identifier	Age/Sex	Treatment Period	Visit	Overall Back Pain Score (VAS mm)
(b) (6)	15/M	Baseline	Baseline	99

Subject Identifier	Age/Sex	Treatment Period	Visit	Overall Back Pain Score (VAS mm)
		TP1	Week 12	12
		TP2	Week 52	24
			Week 104	4
(b) (6) *	16/M	Baseline	Baseline	70
		TP1	Week 12	76
		TP2	Week 52	NA
			Week 104	NA
(b) (6) $	16/M	Baseline	Baseline	70
		TP1	Week 12	80
		TP2	Week 52	33
			Week 104	13
(b) (6) #$	16/M	Baseline	Baseline	0
		TP1	Week 12	0
		TP2	Week 52	7
		TP3	Week 104	2

Abbreviations: VAS = Visual analogue scale; NA = Not available; TP = Treatment Period; M = Male; AxJSpA = Axial Juvenile Spondyloarthritis; ERA = Enthesitis-Related Arthritis. Overall back pain score (VAS mm) ranges from 0 (no pain) to 100 (most severe pain). Subject (b) (6) * was withdrawn from the study after TP1. $ Subjects (b) (6) and (b) (6) were on 'Placebo' in TP2. # Subject (b) (6) was identified by Weiss criteria, 2024. Source: Adapted by Clinical Reviewer from CAIN457F2304-Listing 16.2.6-1.4

Nocturnal Back Pain (VAS)

The table below presents the VAS scores for nocturnal back pain observed during the core trial F2304. Similar to overall back pain, this parameter was recorded only for subjects with ERA during the core trial. Among the 3 subjects who reported nocturnal back pain at baseline, 2 subjects (66.67%) reported improvement while on active treatment with secukinumab.

Table *7*. Nocturnal Back Pain Score for Subjects in the AxJSpA Analysis Cohort (ERA subjects) from Trial F2304 (Full Analysis Set)

Subject Identifier	Age/Sex	Treatment Period	Visit	Nocturnal Back Pain (VAS mm)
(b) (6)	15/M	Baseline	Baseline	100
		TP1	Week 12	12
		TP2	Week 52	4
			Week 104	4

(b) (6) *	16/M	Baseline	Baseline	68
		TP1	Week 12	76
		TP2	Week 52	NA
			Week 104	NA
(b) (6) $	16/M	Baseline	Baseline	84
		TP1	Week 12	78
		TP2	Week 52	23
			Week 104	10
(b) (6) #$	16/M	Baseline	Baseline	0
		TP1	Week 12	0
		TP2	Week 52	0
		TP3	Week 104	2

Abbreviations: VAS = Visual analogue scale; NA = Not available; TP = Treatment Period; M = Male; AxJSpA = Axial Juvenile Spondyloarthritis; ERA = Enthesitis-Related Arthritis. Nocturnal back pain score (VAS mm) ranges from 0 (no pain) to 100 (most severe pain). Subject (b) (6) * was withdrawn from the study after TP1. $ Subjects (b) (6) and (b) (6) were on 'Placebo' in TP2. # Subject (b) (6) was identified by Weiss criteria, 2024. Source: Study CAIN457F2304-Listing 16.2.6-1.4

Modified Schober's Test

The modified Schober's test is a physical exam procedure used to measure lumbar spine flexion. During this assessment, the medical provider marks a point on the spine at the level of the posterior superior iliac spines, and measures 10 cm above and 5 cm below this marked point, creating a 15 cm gap. The subject then bends forward, and the distance between the two marks is measured again. A change of at least 5 cm indicates normal lumbar spine flexion, while a smaller increase suggests restricted movement.

The table below shows the modified Schober's test results during the core trial F2304. Notably, two subjects ((b) (6) and (b) (6) were withdrawn from the trial during this phase. Subject (b) (6) had a decline in lumbar flexion from 5.2 cm at baseline to 4 cm at Week 12, while subject (b) (6) did not have any tests performed beyond baseline. Among the remaining 4 subjects, all had improvements in lumbar flexion over time.

Table 8. Modified Schober's Test Results for Subjects in the AxJSpA Analysis Cohort from Trial F2304 (Full Analysis Set)

Subject Identifier	Age/Sex	Treatment Period	Visit	Modified Schober Test (Lumbar Flexion) (cm)
(b) (6)	15/M	Baseline	Baseline	2
		TP1	Week 12	3.3
		TP2	Week 52	4.6
			Week 104	4.8

Subject Identifier	Age/Sex	Treatment Period	Visit	Modified Schober Test (Lumbar Flexion) (cm)
(b) (6)	16/M	Baseline	Baseline	5.2
		TP1	Week 12	4
		TP2	Week 52	NA
			Week 104	NA
(b) (6)	16/F	Baseline	Baseline	4
		TP1	Week 12	NA
		TP2	Week 52	NA
			Week 104	NA
(b) (6) $	16/M	Baseline	Baseline	4
		TP1	Week 12	4
		TP2	Week 52	7
			Week 104	7
(b) (6) $	13/M	Baseline	Baseline	2
		TP1	Week 12	4.5
		TP3	Week 52	6
			Week 104	5.6
(b) (6) #$	16/M	Baseline	Baseline	3
		TP1	Week 12	5
		TP2	Week 52	5.5
		TP3	Week 104	5

Abbreviations: NA = Not available; TP = Treatment Period; M = Male; F = Female; AxJSpA = Axial Juvenile Spondyloarthritis. Modified Schober Test ranges from 0 upwards (higher values indicate more flexibility). $ Subjects (b) (6) (b) (6) and (b) (6) were on 'Placebo' in TP2. # Subject (b) (6) was identified by Weiss criteria, 2024. Source: Study CAIN457F2304-Listing 16.2.6-1.6

JSpADA Index

The JSpADA (Juvenile Spondyloarthritis Disease Activity) Index is a composite disease activity measure developed to assess disease activity in children and adolescents with juvenile spondyloarthritis. This index includes multiple domains that capture different aspects of disease activity, such as physician global assessment of disease activity, patient/parent global assessment of overall well-being, active joint count, enthesitis count, presence of sacroiliitis or inflammatory back pain, and acute phase reactants. The JSpADA provides a numerical score that reflects overall disease activity, with higher scores indicating more active disease with a maximum score of 8.

The table below presents the JSpADA score for the subjects in the AxJSpA analysis cohort in core trial F2304. Two subjects ((b) (6) and (b) (6) were withdrawn from the trial. Among the remaining 4 subjects, all experienced improvement in the JSpADA scores compared to baseline.

Table *9*. JSpADA Index Score for Subjects in the AxJSpA Analysis Cohort from Trial F2304 (Full Analysis Set)

Subject Identifier	Age/Sex	Treatment Period	Visit	JSpADA Index
(b) (6)	15/M	Baseline	Baseline	7
		TP1	Week 12	6
		TP2	Week 52	1.5
			Week 104	1
(b) (6)	16/M	Baseline	Baseline	4.5
		TP1	Week 12	5
		TP2	Week 52	NA
			Week 104	NA
(b) (6)	16/F	Baseline	Baseline	5.5
		TP1	Week 12	NA
		TP2	Week 52	NA
			Week 104	NA
(b) (6) $	16/M	Baseline	Baseline	5.5
		TP1	Week 12	4
		TP2	Week 52	1.5
			Week 104	0.5
(b) (6) $	13/M	Baseline	Baseline	7
		TP1	Week 12	5.5
		TP3	Week 52	4.5
			Week 104	4
(b) (6) #$	16/M	Baseline	Baseline	6
		TP1	Week 12	2
		TP2	Week 52	1
		TP3	Week 104	0

Abbreviations: JSpADA = Juvenile Spondyloarthritis Disease Activity Index; NA = Not available; TP = Treatment Period; M = Male; F = Female; AxJSpA = Axial Juvenile Spondyloarthritis. JSpADA Index ranges from 0 to 8 and higher scores indicate more disease activity. $ Subjects (b) (6) (b) (6) and (b) (6) were on 'Placebo' in TP2. # Subject (b) (6) was identified by Weiss criteria, 2024. Source: Study CAIN457F2304-Listing 16.2.6-1.7

Clinical Impression of Efficacy

Among the 6 subjects in the AxJSpA analysis cohort, 4 subjects (66.67%) demonstrated improvement across multiple disease activity measures during the initial 12-week treatment period, including JADAS-27, JADAS-71, and JSpADA scores. These 4 responders generally maintained or continued improving during long-term follow-up in the extension trial, though disease activity fluctuations occurred in some cases. Two of the 6 subjects (33.3%) were withdrawn during the core trial due to inadequate response.

Among those who continued treatment, response patterns were inconsistent across different outcome measures. For example, while all subjects showed improvement in physician global assessments, the two discontinued subjects experienced worsening parent/subject global assessments of well-being. Back pain responses were also variable, with only 1 of 3 subjects (33.3%) reporting baseline back pain showing improvement on active treatment, and 1 subject paradoxically improving after switching to placebo. The modified Schober's test results were more encouraging, with all 4 subjects who completed assessments demonstrating improved lumbar flexion over time.

Overall, the data suggest that secukinumab may provide benefit for a subset of pediatric subjects with axial symptoms. However, due to the limited number of subjects included in this retrospective analysis and uncertainty identifying subjects with AxJSpA, it is difficult to draw conclusions on the effectiveness of secukinumab in AxJSpA. It is appropriate to add a descriptive statement in Section 8.4 (Pediatric Use) about this population.

7. Safety

Pediatric Data Submitted to Support Safety for JAS

Safety information for JAS was leveraged from studies of pediatric subjects with related conditions (e.g., PsO, ERA, and JPsA). This approach is part of the 4-way extrapolation strategy (See Section 5, Clinical Pharmacology).

The safety profile of secukinumab in pediatric populations with PsO, ERA, and JPsA is relevant to the JAS population for several reasons. All four conditions share a common pathophysiological mechanism involving IL-17A-mediated inflammation, the therapeutic target of secukinumab, which means that the mechanism of action and safety concerns related to IL-17 inhibition would be expected to be similar across these conditions. In addition, the classification criteria for JAS are identical to those used for adult AS (Assessment of Spondyloarthritis International Society [ASAS] criteria), and the same enrollment criteria would be expected to yield similar efficacy results between adult and juvenile AS populations. Safety for this population can be leveraged from existing studies of pediatric patients with ERA, JPsA, and psoriasis (PsO).

Additionally, a comparison of observed secukinumab PK data incorporating subjects from adult PsO and PsA studies demonstrated that these diseases do not significantly affect secukinumab

pharmacokinetics, and the PK in pediatric PsO, ERA, and JPsA represent secukinumab PK in JAS, given that the proposed dosing regimen for JAS is identical to the approved weight-based dosing regimen for pediatric PsO, ERA, and JPsA.

Safety in Pediatric Psoriasis (PsO)

The safety of secukinumab was assessed in two phase 3 trials in pediatric subjects with PsO.

The first (PsO8) was a randomized, double-blind, placebo and active-controlled, 236-week trial that enrolled 162 pediatric subjects 6 years of age and older with severe PsO. Severe PsO was defined by a PASI score ≥ 20, an IGA modified 2011 score of 4, and involvement of ≥ 10% of the body surface area. All subjects were candidates for systemic therapy and were randomized to receive placebo, a biologic active control, or secukinumab. In the secukinumab groups, dosing was weight-based: subjects with body weight < 25 kg received 75 mg, subjects with body weight 25 kg to < 50 kg received either 75 mg or 150 mg, and subjects with body weight ≥ 50 kg received either 150 mg or 300 mg. All subjects were dosed at Weeks 0, 1, 2, 3, and 4, then every 4 weeks thereafter.

The second (PsO9; NCT03668613) was a randomized, open-label, 208-week trial of 84 pediatric subjects 6 years of age and older with moderate to severe PsO. Moderate to severe PsO was defined by a PASI score ≥ 12, IGA mod 2011 score of ≥ 3, and BSA involvement of ≥ 10% at randomization. Subjects were randomized into two secukinumab arms: Arm 1 received 75 mg for body weight < 50 kg or 150 mg for ≥ 50 kg, while Arm 2 received 75 mg for body weight < 25 kg, 150 mg for body weight ≥ 25 kg and < 50 kg, or 300 mg for body weight ≥ 50 kg. The dosing was identical to PsO8, with administration at Weeks 0, 1, 2, 3, and 4, then every 4 weeks thereafter.

One case of methicillin-resistant Staphylococcus aureus toxic shock syndrome was reported in a secukinumab-treated pediatric subject during the placebo-controlled period. In the pediatric safety pool, which includes all subjects who took at least one dose of secukinumab during the treatment periods (198 subjects representing 287 subject-years), 22 (11%) subjects reported ≥ Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 neutropenia (≥ 1,000 to < 1,500 cells/mm^3). Of these subjects, 57% were followed for 1 year or more and 30% were followed for 2 years or more. During the placebo-controlled period, which included 80 pediatric subjects treated with secukinumab and 41 subjects treated with placebo for up to 12 weeks, ≥ CTCAE Grade 2 neutropenia was reported in 3 (4%) of the secukinumab-treated subjects compared with no placebo-treated subjects. Importantly, no serious infections were associated with cases of neutropenia.

Overall, the safety profile of secukinumab in these pediatric PsO trials was consistent with the safety profile reported in adult PsO trials, and the benefit-risk ratio was found to be acceptable for approval in those 6 years and older with moderate to severe plaque PsO who are candidates for systemic therapy or phototherapy.

Safety in ERA and JPsA

The safety of secukinumab was evaluated in Trial F2304, a phase 3, randomized, double-blind, placebo-controlled, treatment-withdrawal trial in pediatric subjects with JIA subtypes of ERA and JPsA. Subjects had a confirmed diagnosis of either ERA or JPsA according to ILAR classification criteria, inadequate response to ≥ 1 NSAID (for ≥ 1 month) or DMARD (for ≥ 2 months), and active disease defined as ≥ 3 active joints (swollen or tender with limited range of motion) and ≥ 1 site of active enthesitis. A total of 86 subjects were randomized and received at least one dose of secukinumab.

This trial had a three-period design. The core phase of the trial began with Treatment Period 1 (TP1), an open-label phase lasting up to 12 weeks in which all enrolled subjects received secukinumab (75/150 mg SC based on weight < 50 or ≥ 50 kg) administered weekly for the first 4 weeks, then every 4 weeks thereafter. Subjects who achieved a JIA ACR30 response at week 12 were then eligible to enter Treatment Period 2 (TP2), the randomized withdrawal phase, in which responders were randomized 1:1 to either continue secukinumab or switch to placebo every 4 weeks for up to 100 weeks or until disease flare occurred. The trial was planned to continue until either 33 flare events occurred or randomized subjects completed 104 weeks. Subjects who experienced a disease flare during TP2 or completed TP2 without flaring immediately entered Treatment Period 3 (TP3), an open-label extension in which subjects received secukinumab every 4 weeks up to week 100.

The mean duration of exposure to secukinumab was approximately 601 days, totaling 141.5 Patient-Years. During the initial open-label phase (TP1), 56 subjects (65.1%) experienced adverse events (AEs), with only 2 subjects (2.3%) reporting serious adverse events (SAEs) and 1 subject (1.2%) discontinuing due to AEs. In the randomized withdrawal phase (TP2), the proportion of subjects with AEs increased, with 34 subjects (91.9%) in the secukinumab group and 29 subjects (76.3%) in the placebo group experiencing AEs, while SAEs occurred in 5 subjects (13.5%) receiving secukinumab and none in the placebo group. However, more subjects in the placebo group (5 subjects, 13.2%) discontinued due to AEs compared to the secukinumab group (2 subjects, 5.4%) during TP2. Across the entire secukinumab exposure period, 79 subjects (91.9%) reported at least one AE, 11 subjects (12.8%) experienced SAEs, and 8 subjects (9.3%) discontinued due to AEs, with no deaths reported throughout the trial. The most frequently reported treatment-emergent adverse events included infections and gastrointestinal symptoms: nasopharyngitis affected 27 subjects (31.4%), while nausea and upper respiratory tract infections each occurred in 19 subjects (22.1%), followed by diarrhea in 17 subjects (19.8%). Direct comparisons between the secukinumab and placebo groups in TP2 were not made due to the trial design and different exposure times, and potential spill-over effects from previous secukinumab treatment could not be ruled out for events occurring during placebo treatment. Overall, the safety profile was considered favorable, and the sBLA for ERA and JPsA was approved by the FDA in December 2021.

Trial F2304E1 served as a long-term extension of the core trial F2304, allowing subjects with ERA and JPsA to continue treatment with secukinumab for up to 4 additional years. A total of 55 subjects entered this extension trial and received secukinumab at doses of 75 mg (19 subjects), 150 mg (43 subjects), or 300 mg (16 subjects), with the primary objective of evaluating long-term efficacy, safety, and tolerability. The safety profile observed throughout the extension period (from Core Week 104/Extension Week 104E1 up to 4 years) remained

consistent with both the core trial findings (up to Week 104) and the established safety profile of secukinumab across all approved indications. Among the 55 subjects who participated in the extension trial, 85.2% experienced treatment-emergent adverse events (TEAEs), with infections and infestations representing the most frequently reported category, and the majority of adverse events were classified as mild to moderate in severity. Treatment-emergent serious adverse events occurred in 4 subjects (7.4%), while TEAEs leading to treatment discontinuation were reported in only 1 subject due to a serious adverse event of Crohn's disease, with no discernible trend or pattern identified among these events. No deaths occurred during the extension trial.

Summary of Leveraged Safety Information for JAS

A PK-based modeling approach was used to ensure that secukinumab exposures for the proposed JAS dosing regimen would match those achieved with the approved adult AS regimen for efficacy purposes and align with exposures observed in ERA, JPsA, and pediatric PsO subjects of equivalent body weight receiving the same approved pediatric regimens for safety purposes. Notably, the proposed JAS dosing regimen is identical to the approved regimen for ERA and JPsA.

Anticipated exposures in adolescent JAS fall within the range of efficacious exposures established in adult AS receiving the approved 150 mg dose. These exposure levels have been demonstrated to be safe in pediatric subjects with PsO, ERA, and JPsA receiving the same weight-based dosing regimen (75 mg for <50 kg; 150 mg for ≥50 kg).

Safety data from pediatric PsO, ERA, and JPsA demonstrate that the proposed dosing regimen aligns with the established safety profile of secukinumab across these pediatric indications. These pediatric data provide the primary basis for safety extrapolation to JAS and support the use of the proposed dosing regimen without requiring new clinical trials.

Data Specifically Submitted to Address Safety for AxJSpA

Safety Information for the Subject who Fulfilled Published Classification Criteria for AxJSpA

Only 1 subject ((b) (6) was identified by published classification criteria for AxJSpA. During the core trial F2304, this subject reported adverse events including esophagitis, bronchitis, and respiratory tract infection. During the extension trial, this subject reported nasopharyngitis, tonsillitis, and rhinitis. All these AEs were mild or moderate in severity, were non-serious, and did not result in treatment interruption or discontinuation.

Overview of Treatment-Emergent Adverse Events (TEAEs)

The table below presents an overview of TEAEs among the 5 subjects identified using the Applicant-defined criteria for signs and symptoms suggestive of AxJSpA during the core trial F2304 and extension trial F2304E1 in comparison to TEAEs reported among subjects who did not belong to the full AxJSpA analysis cohort.

Table 104. Overview of TEAEs in Trials F2304 and F2304E1 (Safety Set)

Adverse Event Category	**Core Trial AxJSpA subgroup N=5 n (%)**	**Extension Trial AxJSpA subgroup Total N=3 n (%)**	**Extension Trial Non-AxJSpA N=51 n (%)**
Number of participants with at least one AE	5 (100%)	3 (100%)	43 (84.3%)
Number of participants with at least one SAE	1 (20%)	0	4 (7.8%)
Number of participants with at least one AE related to study drug	1 (20%)	1 (33.3%)	10 (19.6%)
Number of participants with at least one AE leading to discontinuation of study treatment	0	0	1 (1.9%)
Deaths	0	0	0
Number of participants with at least one infections and infestations AE (SOC)	3 (60%)	1 (33.3%)	32 (62.7%)
Number of participants with at least one inflammatory bowel disease AE (NMQ)	0	0	2 (3.9%)
Number of participants with at least one hypersensitivity AE (SMQ)	2 (40%)	0	10 (19.6%)
Number of participants with at least one eczematous reactions AE (CMQ narrow)	0	0	0

Abbreviations: AE = Adverse Event; CMQ = Customized MedDRA Query; SAE = Serious Adverse Event; SMQ = Standard MedDRA query; SOC = System organ class; NMQ = Novartis MedDRA Query; AxJSpA = Axial Juvenile Spondyloarthritis. 'n' represents number of patients with events. All the adverse events/serious adverse events mentioned in the table above are treatment emergent adverse events. Source: [Appendix 1-Table 8-1.1],

[Appendix 1-Table 9-1.1], [Appendix 1-Table 10-1.1], [Study CAIN457F2304-Listing 16.2.7-1.1], [Study CAIN457F2304-Listing 16.2.7-1.2], [Appendix 1-Table 8-1.2], [Appendix 1-Table 9-1.2], [Appendix 1-Table 10-1.2], [Study CAIN457F2304E1-Listing 16.2.7-1.1], [Study CAIN457F2304E1-Listing 16.2.7-1.2]

In the core trial F2304, all 5 subjects who were in the subgroup identified by the Applicant-defined criteria experienced at least one TEAE during the entire treatment period. The TEAEs by PT were upper respiratory tract infection (2 incidents reported), splenomegaly, hydrocele, aphthous ulcer, diarrhea, pyrexia, non-alcoholic fatty liver disease, skin infection, viral infection, folliculitis, GI viral infection, post-operative wound infection, staphylococcal infection, foot fracture, injection related reaction, radius fracture, aspartate aminotransferase increased, blood uric acid increased, hypercholesterolemia, scrotal pain, varicocele and dermatitis. All AEs were mild or moderate in severity and none led to treatment discontinuation.

In the extension trial F2304E1, all 3 subjects were from the Applicant-defined subgroup and experienced at least one TEAE during the entire treatment period. TEAEs by PT included hypertension, uveitis, weight decreased, costochondritis, COVID-19, pneumonia, ear infection, generalized anxiety disorder, and sinusitis, 1 event each. All AEs were mild or moderate in severity and none led to treatment discontinuation.

There were no deaths reported during the core or extension trial, and only one treatment-emergent SAE with preferred term of post-operative wound infection.

Clinical Impression of Safety in the AxJSpA Analysis Cohort

Given the limited sample size of the AxJSpA analysis cohort (6 subjects, of whom only 1 met published classification criteria while 5 met Applicant-defined criteria for signs and symptoms suggestive of AxJSpA), it is difficult to draw definitive conclusions regarding the safety of secukinumab specifically from this population. However, the observed safety profile would be expected to be consistent with the known safety of secukinumab across its approved indications, including indications that appear to include patients with AxJSpA.

8. Advisory Committee Meeting

An Advisory Committee Meeting was not conducted for this application.

9. Labeling

For JAS, the Applicant proposed the following key changes to the USPI for Cosentyx (secukinumab):

- Revision of the AS indication from “adults with active ankylosing spondylitis (AS)” to “active ankylosing spondylitis (AS) in adults and pediatric patients 12 years of age and older.” This change expands the age range for approved use.

- Addition of a new Section 2.7 (Recommended Dosage in Pediatric Patients 12 Years of Age and Older with Juvenile Ankylosing Spondylitis) with recommended pediatric dosing for ankylosing spondylitis – "The recommended weight-based subcutaneous dosage in pediatric patients 12 years of age and older with AS at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter is as follows: For patients < 50 kg, the recommended dose is 75 mg. For patients ≥ 50 kg, the recommended dose is 150 mg."

- Addition of the following language to Section 8.4 (Pediatric Use) – "Juvenile Ankylosing Spondylitis - The safety and effectiveness of COSENTYX have been established for treatment of JAS in pediatric patients 12 years of age and older. Use of COSENTYX for this indication is supported by safety and efficacy data from adequate and well-controlled trials in adult subjects with AS. Additional evidence includes pharmacokinetic data from adult subjects with PsO, PsA, and AS and pediatric subjects with PsO, JPsA, and ERA, as well as safety data from clinical trials in pediatric subjects with PsO, JPsA, and ERA. The pharmacokinetics are predicted to be comparable between adult AS and pediatric subjects with JAS (b) (4) [redacted] [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]. (b) (4) [redacted] The safety and effectiveness of COSENTYX in pediatric patients with JAS below the age of 12 years old have not been established."

    - Labeling Negotiation – The Division recommended modifications to the Applicant's initial proposal for Section 8.4 (Pediatric Use) to remove the phrase "(b) (4) [redacted]" to align with the approach of relying on observed pharmacokinetic data comparisons rather than (b) (4) [redacted].

    - Agreed-Upon Language for Section 8.4 (Pediatric Use): "Juvenile Ankylosing Spondylitis - The safety and effectiveness of COSENTYX have been established for treatment of JAS in pediatric patients 12 years of age and older. Use of COSENTYX for this indication is supported by safety and efficacy data from adequate and well-controlled trials in adult subjects with AS. Additional evidence includes pharmacokinetic data from adult subjects with PsO, PsA, and AS and pediatric subjects with PsO, JPsA, and ERA, as well as safety data from clinical trials in pediatric subjects with PsO, JPsA, and ERA. The pharmacokinetics are predicted to be comparable between adult AS and pediatric subjects with JAS [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]. (b) (4) [redacted] The safety and effectiveness of COSENTYX in pediatric patients with JAS below the age of 12 years old have not been established."

- Addition of the following language to Section 12.3 (Pharmacokinetics) – "The observed pre-dose (trough) concentrations are generally comparable between adults

with AS, PsO, and PsA and pediatric patients with PsO, JPsA, and ERA. Based on (b) (4), secukinumab concentrations in pediatric patients (12 years of age and older) with JAS who received the recommended pediatric dosing regimen were predicted to be comparable to exposures observed in adult patients with AS (b) (4).”

- Labeling Negotiation – The Division recommended modifications to the Applicant's initial proposal for Section 12.3 (Pharmacokinetics) to replace "(b) (4)" with "PK comparison" to better reflect the use of observed PK data comparisons.

- Agreed-Upon Language for Section 12.3 (Pharmacokinetics): "The observed pre-dose (trough) concentrations are generally comparable between adults with AS, PsO, and PsA and pediatric patients with PsO, JPsA, and ERA. Based on PK comparison, secukinumab concentrations in pediatric patients (12 years of age and older) with JAS who received the recommended pediatric dosing regimen were predicted to be comparable to exposures observed in adult patients with AS."

For AxJSpA, the Applicant proposed the following key changes to the USPI for Cosentyx (secukinumab):

- Applicant’s Proposed Language – “Six pediatric patients with axial symptoms were participants in a study for JPsA and ERA (NCT03031782). Due to the limited number of patients (b) (4), the effectiveness of COSENTYX in AxJSpA has not been established. Safety was comparable to pediatric patients treated with COSENTYX for JPsA and ERA [see Adverse Reactions (6.1)].”

- Labeling Negotiation – The Division recommended modifications to the Applicant's initial proposal to: (1) use "uncertainty fulfilling Axial Juvenile Spondyloarthritis (AxJSpA) classification criteria" instead of "(b) (4)" to better reflect the limitations in patient identification; and (2) state that both "effectiveness and safety" have not been established, rather than only "effectiveness," to accurately reflect the limited data available. The Applicant agreed to the Division's recommended language on April 13, 2026.

- Agreed-Upon Language for Section 8.4 (Pediatric Use): “Axial Juvenile Spondyloarthritis - Six pediatric patients with axial symptoms were participants in a study for JPsA and ERA (NCT03031782). Due to the limited number of patients and uncertainty fulfilling Axial Juvenile Spondyloarthritis (AxJSpA) classification criteria, the effectiveness and safety of COSENTYX in AxJSpA has not been established. Safety was comparable to pediatric patients treated with COSENTYX for JPsA and ERA."

10. Postmarketing Recommendations

No postmarketing recommendations are recommended.

11. Recommendation/Risk Benefit Assessment

Juvenile Ankylosing Spondylitis (JAS)

The Division recommends approval of sBLA 125504 Supplement 98 to expand the ankylosing spondylitis indication to include patients 12 years of age and older with active ankylosing spondylitis. The proposed weight-based dosing regimen (75 mg SC for patients <50 kg; 150 mg SC for patients ≥50 kg at Weeks 0, 1, 2, 3, and 4, then every 4 weeks thereafter) is supported by a 4-way extrapolation strategy that leverages efficacy data from adult AS trials, PK data demonstrating comparable drug exposures across populations, and identical ASAS classification criteria that justify extrapolation of efficacy from adults to adolescents. Safety is supported by data from pediatric populations (PsO, ERA, and JPsA) receiving the identical weight-based dosing regimen.

The efficacy of secukinumab in adult AS was demonstrated in three randomized, placebo-controlled trials (F2305, F2310, and F2314). PK data demonstrate that the proposed dosing regimen results in steady-state exposures comparable to those achieved in adult AS patients treated with the approved 150 mg SC Q4W regimen, supporting extrapolation of efficacy. The safety profile is well-characterized and leveraged from pediatric PsO trials using the identical weight-based dosing regimen, with additional support from pediatric ERA and JPsA trials, demonstrating a consistent safety profile across indications with no new safety signals. The proposed indication addresses an unmet medical need, as no therapies are currently FDA-approved for JAS.

Axial Juvenile Spondyloarthritis (AxJSpA)

The Division recommends approval of sBLA 125504 Supplement 97 to add descriptive information about pediatric subjects with axial symptoms to Section 8.4 Pediatric Use of the label without establishing a new treatment indication. The retrospective analysis identified six pediatric subjects from trials F2304 and F2304E1 with axial symptoms, of whom four (66.67%) demonstrated improvement in disease activity measures and three achieved JIA ACR 100 response during long-term follow-up. However, the limited sample size and uncertainty in identifying subjects with AxJSpA preclude establishing effectiveness in this population. For these reasons, the effectiveness and safety of secukinumab in AxJSpA have not been established, though safety findings were generally comparable to those observed in pediatric patients treated for JPsA and ERA.

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/s/

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