CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761349Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	BLA 761349, BLA125504/S-73
Priority or Standard	Standard
Submit Date(s)	December 7, 2022
Received Date(s)	December 7, 2022
PDUFA Goal Date	October 7, 2023
Division/Office	Division of Rheumatology and Transplant Medicine
Review Completion Date	October 6, 2023
Established/Proper Name	Secukinumab
(Proposed) Trade Name	Cosentyx
Pharmacologic Class	Monoclonal antibody
Code name	
Applicant	Novartis Pharmaceuticals Corporation
Dosage form	125 mg/5 mL solution in a single-dose vial for intravenous administration
Applicant proposed Dosing Regimen	Intravenous Dosage: 6 mg/kg loading dose given at Week 0, followed by 1.75 mg/kg every 4 weeks thereafter (maintenance dosage). Total doses exceeding 300 mg per infusion are not recommended for the 1.75 mg/kg maintenance dose in adults.
Applicant Proposed Indication(s)/Population(s)	Psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adults with: • Active psoriatic arthritis (PsA) • Active ankylosing spondylitis (AS) • Active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation
Recommended Dosing Regimen	Intravenous Dosage • With a loading dosage: 6 mg/kg loading dose given at Week 0, followed by 1.75 mg/kg every 4 weeks thereafter (maintenance dosage). • Without a loading dosage: 1.75 mg/kg every 4 weeks. Total doses exceeding 300 mg per infusion are not recommended for the 1.75 mg/kg maintenance dose in adults.

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Reference ID: 5256774

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion

OSIS= Office of Study Integrity and Surveillance
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

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

NDA	new drug application
NME	new molecular entity
nr-axSpA	non-radiographic axial spondyloarthritis
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBO	Placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PsA	Psoriatic Arthritis
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SEC	Secukinumab
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Secukinumab (Cosentyx) is a recombinant selective fully human monoclonal anti-human Interleukin-17 (IL-17A, IL-17) antibody of the IgG1/κ-class. Secukinumab subcutaneous formulations was originally approved on January 21, 2015 (BLA 125504), for the indication of moderate to severe plaque psoriasis. Supplemental BLAs were later approved for the indications of, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Non-radiographic Axial Spondyloarthritis (nr-axSpA), pediatric plaque psoriasis (6 to <18 years old), and most recently pediatric PsA (age 2 years and older) and enthesitis-related arthritis (age 4 years and older).

COSENTYX subcutaneous (SC) formulation is currently supplied as a 150mg/mL or 75mg/0.5mL solution for injection in prefilled syringe and a 150mg/mL solution for injection in prefilled pen. Lyophilized powder for injection is also approved, however has never been marketed and an application for withdrawal of this dosage form has been approved on Jul 21, 2023 (BLA 125504 S-055).

The applicant is seeking the approval of Intravenous (IV) formulation and dosage of Cosentyx® [non-proprietary name: Secukinumab (AIN457)] for the treatment of psoriatic arthritis (PsA), ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) in adults. The IV formulation is provided as solution in a single-dose 125 mg/5 mL vial. BLA 125504 S-073 Cosentyx SC labeling supplement was also submitted to align label.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The substantial evidence of effectiveness of the proposed IV dosing regimen is based upon PK bridging to the efficacy of subcutaneous secukinumab established in adequate and well-controlled clinical trials in adults with PsA, AS, and nr-axial SpA[1], i.e. the indications sought for licensure of the IV dosing regimen. The secukinumab (SEC) IV regimen for PsA, AS and nr-axial SpA is with or without loading dose of 6 mg/kg followed by maintenance dosing of 1.75 mg/kg administered q4w. A capping of the IV maintenance dose to a maximum dose of 300 mg per infusion is also proposed to limit the Cmax,ss of subjects weighing >170 kg. Based on population PK modeling, the proposed IV dosing regimen, with or without loading dose, is predicted to achieve exposure of SEC to match the exposures of the approved subcutaneous (SC) doses of 150 mg and 300 mg with or without loading dose, respectively. Based on PK matching, efficacy and safety of the SC regimens approved in axSpA and PsA are extrapolated to the secukinumab IV regimen proposed for registration.

[1] FDA-approved secukinumab labeling

Clinical PK, safety, and efficacy data were available using the to-be-marketed IV formulation in previous clinical studies (P12301 and P12302), however, the proposed IV dosing regimen differs from that studied. The proposed IV dosing regimen better approximates the exposures for which efficacy and safety have been established for SC secukinumab for the indications sought for licensure with the IV dosing regimen. It is supported by a modeling and extrapolation approach as discussed with FDA during the presubmission meeting (08-Dec-2021) and in the Model-informed Drug Development (MIDD) program meeting correspondence dated 28-Jun-2022. FDA concluded that a dedicated confirmatory PK study with the proposed IV secukinumab dose is not necessary in this case, considering that secukinumab has linear PK; the dosing interval of the proposed IV dosing regimen is the same as the approved SC dosing regimen, and the extensive clinical experience and PK data available with the to-be-marketed IV formulation. The review team emphasizes that this approach was considered applicable in this unique case based on the totality of data available from the secukinumab extensive development program and may not be generalizable to other SC to IV conversion programs.

Based on modeling and simulation, the 1.75 mg/kg SEC IV Q4W dosing regimen is predicted to achieve steady-state exposures that were either comparable (Ctrough) or higher (Cave, Cmax) than the exposure established in PsA, AS and nr-axSpA patients with the approved 150 mg Q4W dosing regimens. The simulated time-concentration profile shows that the 1.75 mg/kg IV Q4W dosing regimen achieved comparable or higher SEC concentrations compared to the approved 150 mg Q4W SC dosing regimens throughout the dosing interval at steady state. Therefore, the PK data support the bridging of efficacy from SEC SC to SEC IV for the treatment of PsA, AS and nr-axSpA.

The efficacy of SEC IV in adult patients with PsA is based on PK bridging and extrapolation of the previously established efficacy of SEC SC in adult patients with PsA in studies F2306 and F2312, a randomized, double blind, placebo controlled studies that provided the efficacy and safety data to support the approval of BLA 125504/S-01 (b) (4) for SEC SC for PsA.

The efficacy of SEC IV in adult patients with AS is based on PK bridging and extrapolation of the previously established efficacy of SEC SC in adult patients with AS in Study F2305 and F2310, a randomized, double blind, placebo controlled studies that provided the efficacy and safety data to support the approval of BLA 125504/S-02 and S-031 for SEC SC for AS.

The efficacy of SEC IV in adult patients with nr-axSpA is based on PK bridging and extrapolation of the previously established efficacy of SEC SC in adult patients with nr-axSpA in Study H2315, a randomized, double blind, placebo controlled study that provided the efficacy and safety data to support the approval of BLA 125504/S-035 for SEC SC for nr-axSpA.

The recommended regulatory action is Approval for secukinumab IV for the treatment of psoriatic arthritis (PsA), ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis

(nr-axSpA) in adults. This recommendation is based on the full extrapolation of efficacy established in adults with secukinumab SC and leveraging of safety established with secukinumab SC, as well as supportive safety data from the Study P12301 and Study P12302.

APPEARS THIS WAY ON ORIGINAL

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriatic arthritis (PsA) is a chronic progressive inflammatory arthritis associated with psoriasis. The clinical manifestations of PsA may include peripheral and axial inflammatory arthritis, dactylitis and enthesitis. If left untreated, PsA may result in pain, disability, and permanent joint damage. Ankylosing Spondylitis (AS) is a serious medical condition. It is a chronic, progressive disease, that primarily affects joints and entheses, but can also involve other organs. If left untreated, disease progression can result in severe joint deformity, significant morbidity and increased mortality. Nonradiographic axial spondyloarthritis (nr-axSpA) is an inflammatory arthritis of the axial skeleton without evidence of sacroiliitis on conventional radiographs. Patients with nr-axSpA can have inflammatory back pain that can impact quality of life. These patients may or may not progress to evidence of radiographic sacroiliitis (AS).

Secukinumab (Cosentyx) is a recombinant selective fully human monoclonal anti-human Interleukin-17 (IL-17A, IL-17) antibody of the IgG1/κ-class, available as subcutaneous (SC) formulations. The safety and efficacy of SEC SC for the treatment of AS, nr-axSpA, and PsA is already established as reflected in the FDA-approved secukinumab labeling.

The applicant submitted this biologics license application (BLA 761349) to seek the approval of IV formulation and dosing regimen of Cosentyx® [non-proprietary name: secukinumab] for the treatment of PsA, AS and nr-axSpA in adults. The proposed dosing regimen is with or without loading dose of 6 mg/kg followed by maintenance dosing of 1.75 mg/kg administered q4w.

To support the application, the efficacy of SEC IV in adult patients with PsA, AS, and nr-axSpA is based on PK bridging and extrapolation of the previously established efficacy of SEC SC in adult patients with PsA, AS, and nr-axSpA. Based on modeling and simulation, the 1.75 mg/kg SEC IV Q4W dosing regimen is predicted to achieve steady-state exposures that were either comparable (Ctrough) or higher (Cave, Cmax) than the exposure established in PsA, AS and nr-axSpA patients with the approved 150 mg Q4W dosing regimens. Therefore, the PK data support the bridging of efficacy from SEC SC to SEC IV for the treatment of PsA, AS and nr-axSpA.

The safety of maintenance dose (1.75 mg/kg) of intravenous secukinumab is based on similar pharmacokinetic exposure and leveraging of the established safety of subcutaneous secukinumab in PsA and AS patients (150 mg and 300 mg doses), and nr-axSpA (150 mg dose). Based on modeling and simulation, the 1.75 mg/kg SEC IV Q4W dosing regimen is predicted to achieve steady-state exposures that were either comparable (Cmax) or lower (Cave, Cmin) than the exposure established in PsA and AS patients with the approved 300 mg Q4W dosing

Reference ID: 5256774

regimens. The simulated time-concentration profile shows that the 1.75 mg/kg IV Q4W dosing regimen achieved comparable or lower SEC concentrations compared to the approved 300 mg Q4W SC dosing regimens throughout the dosing interval at steady state. Therefore, the PK data support the leveraging of safety data from SEC SC to SEC IV for the treatment of PsA and AS. As the only approved maintenance SC dose for nr-axSpA is 150 mg, additional 52-week safety data in nr-axSpA subjects for IV secukinumab at a 3 mg/kg Q4W IV maintenance dose, i.e. higher than proposed in this submission, and for a 300 mg SC maintenance dose are provided to support the proposed IV maintenance dose of 1.75 mg/kg Q4W in nr-axSpA.

In addition, safety data from studies P12301 and P12302 are being summarized to support the approval of the IV route of administration. The safety of the loading dose (6 mg/kg) of intravenous secukinumab is based on the observed safety data in Studies P12301 and P12302, which included a 6 mg/kg loading dose at baseline, as well as 10 mg/kg IV loading doses in the registrational trials of SC secukinumab. The overall safety findings with IV secukinumab in studies P12301 and P12302 (SEC IV maintenance dose of 3mg/kg Q4W) did not show any new safety concerns when compared to placebo and are consistent with the known safety profile in registrational studies of subcutaneous secukinumab in AS, nr-axSpA, and PsA, and provide supportive evidence for the safety of the proposed SEC IV maintenance dose of 1.75 mg/kg Q4W.

The Applicant has provided adequate data to inform the benefit-risk assessment of SEC IV for the treatment of adult patients with AS, adult patients with nr-axSpA and adult patients with PsA. Overall, the efficacy and safety evidence provided in this submission supports a favorable benefit-risk profile of SEC IV for the treatment of adults with active PsA, AS, and nr-axSpA at the proposed IV dosing regimen. The safety of SEC IV in these indications is expected to be consistent with the known safety of SEC SC and offers an acceptable risk for the therapeutic benefits. We recommend approval of BLA 761349. The Division Signatory agrees with this assessment and the recommended action.

The approval SEC IV for the treatment of adults with active PsA, AS and nr-axSpA will provide additional treatment option that could be more convenient to some patients with these indications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Psoriatic arthritis (PsA) is a chronic progressive inflammatory arthritis associated with psoriasis. The clinical manifestations of PsA may include peripheral and axial inflammatory arthritis, dactylitis and enthesitis. • The estimated U.S. prevalence of PsA is 1-2 per 1,000 • The goals of PsA treatment are to improve signs and symptoms, physical function, and inhibit long-term structural damage. • Ankylosing spondylitis (AS) is a chronic and progressive disease of the axial skeleton manifested by back pain and progressive stiffness of the spine. • The disease can also involve the hips, shoulders, peripheral joints, entheses, and digits. • AS is a well-characterized form of spondyloarthritis (SpA), a family of disorders characterized by inflammation around entheses (the sites of ligament insertion into bone), an association with human leukocyte antigen (HLA)-B27, and radiographic sacroiliitis. • Patients with AS can also have extra-articular disease manifestations such as uveitis, psoriasis and inflammatory bowel disease. • As the disease progresses, AS results in serious impairment of spinal mobility and physical function, impacting the quality of life. • The estimated prevalence of AS in North America is 31.9 per 10,000 • The goal of treatment is to try to prevent functional impairment and irreversible joint damage. • Nonradiographic axial spondyloarthritis (nr-axSpA) is a diagnosis based on ASAS classification criteria. These criteria potentially allow for the	PsA is an inflammatory arthritis associated with psoriasis that may result in pain, disability, and permanent joint damage. AS is a serious medical condition. It is a chronic, progressive disease, that primarily affects joints and entheses, but can also involve other organs. If left untreated, disease progression can result in severe joint deformity, significant morbidity and increased mortality. Nonradiographic axial spondyloarthritis (nr-axSpA) is an inflammatory arthritis of the axial skeleton without evidence of sacroiliitis on conventional radiographs. Patients with nr-axSpA can have inflammatory back pain that can impact quality of life. These patients may or may not progress to evidence of radiographic sacroiliitis (AS).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	earlier diagnosis of axial spondyloarthritis (axSpA). AxSpA describes an inflammatory arthritis that affects the spine and/or sacroiliac joints. Patients classically have inflammatory back pain. Patients, who meet ASAS criteria for axSpA but do not meet radiographic criteria for ankylosing spondylitis (AS), are diagnosed with nr-axSpA. • ASAS criteria require that patients have back pain ≥ 3 months with the age of onset < 45 years. Patients could then be classified as having axSpA based on meeting clinical criteria or radiographic criteria. The clinical path requires HLA-B27 positivity and ≥ 2 additional features (e.g., inflammatory back pain, arthritis, enthesitis, response to NSAIDs, family history, elevated CRP). The radiographic path requires sacroiliitis on imaging and ≥ 1 clinical feature. Thus, patients with nr-axSpA could not have conventional radiographic evidence of sacroiliitis (i.e., meeting modified New York [mNY] criteria) but could have MRI evidence of sacroiliitis. • It has been suggested that nr-axSpA may be an early presentation of AS, but there are many patients who do not progress. Some risks for disease progression that have been considered include male gender, longer disease duration, elevation in CRP, and MRI evidence of sacroiliitis. • It is estimated that the prevalence of nr-axSpA in the US ranges from 0.31-0.35% of the US population (Strand 2013)	
Current Treatment Options	• The management of patients with PsA includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), systemic and/or intra-articular glucocorticoids, and small molecule and biologic disease modifying antirheumatic drugs (DMARDs) • FDA approved drugs for the treatment of PsA including TNFα-inhibitors;	PsA: At this time, there are a number of approved therapy for PsA, including SC secukinumab: • With a loading dosage: 150 mg at Weeks 0, 1, 2, 3, and 4 and every 4 weeks

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	apremilast, an oral small molecule inhibitor of phosphodiesterase 4; ustekinumab, an IL-12/23 inhibitor; secukinumab (SC route of administration), an IL-17A inhibitor; abatacept, a T-cell costimulation modulator; ixekizumab, an IL-17A inhibitor; guselkumab, an IL-23 inhibitor and, in patients who have had an inadequate response or intolerance to one or more TNF blockers, tofacitinib and upadacitinib, both oral janus kinase (JAK) inhibitors. • Current treatment options for AS include NSAIDs, corticosteroids, conventional DMARDs (csDMARDs), and biologic DMARDs (bDMARDs). • Currently, six Tumor necrosis factor (TNF) inhibitors are available for the treatment of AS: etanercept, infliximab, adalimumab, golimumab, certolizumab, and golimumab IV. Two IL-17 inhibitors—secukinumab and ixekizumab—re approved for the treatment of AS. Two JAKi—tofacitinib and upadacitinib—are approved for treatment of active AS in patients who have an inadequate response or intolerance to one or more TNF blockers. • Treatments approved for AS have demonstrated efficacy for multiple aspects of clinical disease activity in AS, but it is not yet known whether treatment has a beneficial effect on structural damage progression. • Recommendations for treatment of nr-axSpA are based on literature for ankylosing spondylitis (AS). • Currently approved therapies for adults with active nr-axSpA include the TNFi certolizumab pegol, the IL-17 inhibitors secukinumab and	thereafter • Without a loading dosage: 150 mg every 4 weeks • If a patient continues to have active PsA, consider a dosage of 300 mg every 4 weeks. AS: At this time, there are a number of approved therapy for AS, including SC secukinumab: • With a loading dosage: 150 mg at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter • Without a loading dosage: 150 mg every 4 weeks • If a patient continues to have active AS, consider a dosage of 300 mg every 4 weeks. nr-axSpA: At this time, there are a number of approved therapies for nr-axSpA, including SC secukinumab: • With a loading dosage: 150 mg at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter • Without a loading dosage: 150 mg every

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ixekizumab, and the JAKi upadacitinib in patients who have had an inadequate response to a biological DMARD. • Standard of care for nr-axSpA begins with treatment with NSAIDs. • According to several treatment guidelines (ACR/SPARTAN, EULAR/ASAS), patients with nr-axSpA who have persistent disease activity can be treated with TNF inhibitors or potentially other biologic DMARDs.	4 weeks
Benefit	• Following an intravenous administration of 1.75 mg/kg maintenance dose every four weeks, with or without a loading dose of 6 mg/kg at Day 0, the secukinumab concentrations [steady state trough secukinumab concentrations (Cmin,ss), mean secukinumab concentrations (Cavg,ss), and maximum secukinumab concentrations (Cmax,ss)] are expected to be within the range of the estimated steady state concentrations following subcutaneous administration of 150 mg and 300 mg doses of COSENTYX administered every four weeks. • The efficacy of treatment of PsA, AS, and nr-axSpA with IV secukinumab is leveraged from the completed studies with SC secukinumab. • The original registrational studies F2306 and F2312 were submitted as the primary source of efficacy data for secukinumab in the treatment of PsA. Both trials consisted of a 24-week, placebo controlled double-blind period at which time the primary efficacy endpoint was measured. At week 16 or 24, patients randomized to placebo were re-randomized to secukinumab without a loading dose. • The findings from the original supplemental BLA and later supplement resulted in approval of both 150 mg Q4W (with or without loading) and 300 mg Q4W (with or without loading) for the treatment of active	The efficacy of SEC IV in adult patients with PsA, AS, and nr-axSpA is based on PK bridging and extrapolation of the previously established efficacy of SEC SC in adult patients with PsA, AS, and nr-axSpA. PsA (basis for approval of SC secukinumab): The primary endpoint was ACR20 response at week 24. Secondary analyses were performed at Week 24. The trials were well controlled and had endpoints that were considered acceptable for efficacy evaluations in PsA. AS (basis for approval of SC secukinumab): The clinical development program demonstrated evidence of efficacy for the secukinumab 150 mg and 300 mg every 4 weeks over placebo for the treatment of ankylosing spondylitis in adults.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	psoriatic arthritis in adults. • Studies F2305 and F2310 were submitted as the primary source of efficacy data for SC secukinumab in the treatment of ankylosing spondylitis. In both studies, the primary endpoint was the proportion of patients achieving ASAS20 response at week 16 for both studies. The trials were well-controlled and had endpoints that are considered acceptable for efficacy evaluations in AS. • The clinical development program to support the efficacy and safety of the 150 mg dose of secukinumab for treatment of adults with nr-axSpA consisted of one randomized, double-blind, and controlled study (study H2315) that enrolled patients with active nr-axSpA who had baseline demographics and disease characteristics similar to the US patient population. The primary objective of study H2315 was to demonstrate that at least one of the dosing regimens of secukinumab (150 mg SC with or without load) at Week 16 or Week 52 is superior to placebo in patients with active nr-axSpA • Both secukinumab 150 mg Load and 150 mg No Load demonstrated efficacy for reducing the signs and symptoms in patients with active nr-axSpA. • At Week 52, ASAS40 response using non-responder imputation was numerically higher in both the no load and load secukinumab groups than in the placebo group (38% and 34% vs. 19%, respectively). • Secukinumab 150 mg provided statistically significant differences in key secondary endpoints.	Results demonstrated that treatment with secukinumab showed an improvement in clinical response (ASAS20) and other measures of disease activity (BASDAI, ASAS 5/6, hsCRP, and ASAS partial remission). Two doses of secukinumab were studied (150 mg every 4 weeks and 300 mg every 4 weeks). Both doses were effective in treating ankylosing spondylitis when compared with placebo. Proportions of ASAS20 responses were greater at week 16 for both doses of secukinumab when compared to placebo. nr-axSpA (basis for approval of SC secukinumab): The clinical development program demonstrated evidence of efficacy for the secukinumab 150 mg every 4 weeks over placebo for the treatment of nr-axSpA in adults. Results demonstrated that treatment with secukinumab showed an improvement in clinical response (ASAS40) and other

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		measures of disease activity (BASDAI, ASAS 5/6, hsCRP, and ASAS partial remission). Two doses regimens secukinumab were studied (150 mg No Load or 150 mg Load followed by 150 mg every 4 weeks). Both dosing regimens were effective in treating nr-axSpA when compared with placebo. Proportions of ASAS40 responses were greater at week 16 and week 52 for both dosing regimens of secukinumab when compared to placebo. Similar safety profile was seen for both dosing regimens.
Risk and Risk Management	• Secukinumab has well characterized risks of serious infections, hypersensitivity reactions, and inflammatory bowel disease. Risks associated with SC secukinumab are captured in the US prescribing information. • Following an intravenous administration of 1.75 mg/kg maintenance dose every four weeks, with or without a loading dose of 6 mg/kg at Day 0, the secukinumab concentrations [steady state trough secukinumab concentrations (Cmin,ss), mean secukinumab concentrations (Cavg,ss), and maximum secukinumab concentrations (Cmax,ss)] are expected to be within the range of the estimated steady state concentrations following subcutaneous administration of 150 mg and 300 mg doses of	The safety of maintenance dose (1.75 mg/kg) of intravenous secukinumab is based on similar pharmacokinetic exposure and extrapolation of the established safety of subcutaneous secukinumab in PsA and AS patients (150 mg and 300 mg doses), and nr-axSpA (150 mg dose). For nr-axSpA, safety of the maintenance dose of intravenous secukinumab is also supported by observed safety data in the blinded long-term extension period of study H2315 comparing 150 mg to 300 mg subcutaneous

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	COSENTYX administered every four weeks. • The safety of IV secukinumab in the treatment of PsA, AS, and nr-axSpA is extrapolated from the completed studies with SC secukinumab. • As the only approved maintenance SC dose for nr-axSpA is 150 mg, additional safety data in nr-axSpA subjects for IV secukinumab (study P12301) and for a 300 mg SC maintenance dose (extension study H2315) are provided to support the proposed IV maintenance dose of 1.75 mg/kg Q4W in nr-axSpA. • Supportive Safety information for the use of IV secukinumab in AS and nr-axSpA is based on 16-Week placebo-controlled data from study P12301. In study P12301, a total 526 adult subjects were randomized to receive either SEC IV or PBO IV, of which the ratio of patients with AS to nr-axSpA was approximately 4:1. Specifically, 208 AS and 56 nr-axSpA patients were randomized to receive SEC IV; 205 AS and 56 nr-axSpA patients were randomized to receive PBO IV. • Supportive Safety information for the use of IV secukinumab in PsA is based on placebo-controlled 16-Week data from study P12302. In study P12302, a total of 381 adult subjects with active PsA were randomized to receive either SEC IV (191 patients) or PBO IV (190 patients). • Both P12301 and P12302 included a 16-week placebo-controlled period (Treatment Period 1; TP1), followed by a 36-week period during which all subjects received open label IV secukinumab 3 mg/kg Q4W (Treatment Period 2; TP2), followed by an 8 week safety Follow Up period (FUP). • In the extension phase of study H2315, 294 subjects were rerandomized at a 1:1 ratio (147 in each arm) to either continue 150 mg SC SEC or	secukinumab. The safety of the loading dose (6 mg/kg) of intravenous secukinumab is based on the observed safety data in Studies P12301 and P12302, which included a 6mg/kg loading dose at baseline. No new safety signals were identified in IV studies of secukinumab in PsA, AS and nr-axSpA and in a study comparing 300 mg to 150 SC secukinumab in nr-axSpA. The overall safety data was consistent with the current Cosentyx® US prescribing information. A Risk Evaluation and Management Strategy (REMS) is not recommended for this product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	300 mg SC SEC every 4 weeks. Adverse events were recorded for this blinded, comparator-arm controlled extension phase for the period from Week 104 through Week 156. • There were no new safety signals.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

No new patient experience data was collected as the application provided PK modeling as the rationale to approve the IV doses for treatment of Adult PsA, AS, and nr-axSpA.

2 Therapeutic Context

2.1. Analysis of Condition

Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic progressive inflammatory arthritis associated with psoriasis that may result in permanent joint damage and disability.[2] The prevalence of PsA is approximately 0.3-1% of the population. PsA affects women and men equally, and the mean age of onset of PsA is around 40 years. Approximately 80% of patients with PsA have skin involvement with psoriasis prior to or at the time of diagnosis with PsA. Because of its tendency to involve the spine (occurring in up to 40% of PsA patients) and lack rheumatoid factor (RF), PsA is considered one of the seronegative spondyloarthropathies.

The clinical manifestations of PsA include peripheral and axial inflammatory arthritis. The peripheral arthritis may present as an asymmetric oligoarthritis, a symmetric polyarthritis of the small joints of the hands and feet, arthritis mutilans, or other patterns. Patients with PsA can also have involvement of the tendons, dactylitis and enthesitis, as well as spondyloarthritis. Some patients have only one clinical manifestation, while others have overlapping manifestations. Patients with PsA can develop destructive disease characterized by radiographic progression of structural damage.

The Classification Criteria for Psoriatic Arthritis (CASPAR)[3] criteria published in 2006 has been used for the diagnosis of psoriatic arthritis. A patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following five categories: evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis; typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination; a negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range; either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist; radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis

[2] Gladman DD, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64 suppl 2:ii14-17.
[3] Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006; 54(8): 2665-2673.

Ankylosing spondylitis (AS) is a chronic and progressive disease of the axial skeleton manifested by back pain and progressive stiffness of the spine. The disease can also involve the hips, shoulders, peripheral joints, entheses, and digits. AS is a well-characterized form of spondyloarthritis (SpA), a family of disorders characterized by inflammation around entheses (the sites of ligament insertion into bone), an association with human leukocyte antigen (HLA)-B27, and radiographic sacroiliitis. The mean AS prevalence per 10,000 is estimated to be 31.9 in North America[4].

The majority of research performed over the last two decades has used the modified New York Criteria to identify patients with AS (Table 1). In addition, these criteria were used in clinical trials performed to support product registration for AS in the United States. The AS criteria are anchored by radiographic changes of the sacroiliac (SI) joint.

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Table 1: Modified New York Criteria for Ankylosing Spondylitis (AS)

Clinical Criteria • Low Back pain and stiffness for longer than 3 months, which improve with exercise, but are not relieved by rest • Restriction of motion of the lumbar spine in both the sagittal and frontal planes • Restriction of chest expansion relative to normal values correlated for age and sex
Radiologic criterion • Sacroiliitis grade ≥2 bilaterally, or grade 3-4 unilaterally
Definitive ankylosing spondylitis is present if the radiologic criterion is associated with at least one clinical criterion

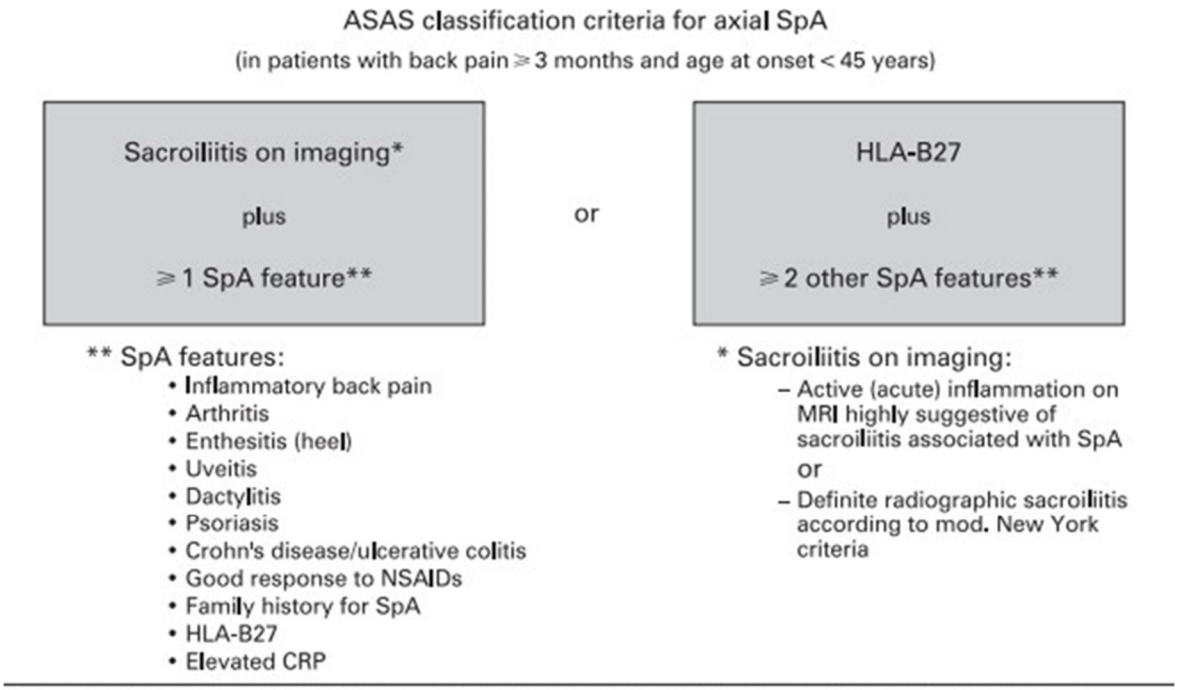
Source: van der Linden S. Arthritis Rheum 1984;27(4):361-8.

In 2009, the Assessment of SpondyloArthritis international Society (ASAS) developed a new set of classification for axSpA in order to describe a broader spectrum of inflammatory back pain, including those patients who do not have radiographic sacroiliitis (Rudwaleit et al., 2009). These criteria (Figure 1) require that patients must have back pain ≥ 3 months with the age of onset < 45 years. There are then 2 paths to meet criteria for axSpA. The clinical path requires positive HLA-B27 and ≥ 2 additional features (e.g., inflammatory back pain, arthritis, enthesitis, uveitis, etc.), whereas the radiographic path requires sacroiliitis on imaging and ≥ 1 clinical feature.

[4] Dean LE. Rheumatology (Oxford). 2014;53(4):650-7.

Sacroiliitis could either be x-ray findings consistent with the mNY criteria (thus, AS or radiographic axSpA) or MRI findings suggestive of sacroiliitis. The term nonradiographic axial spondyloarthritis is used to describe patients who meet ASAS criteria for axSpA but who do not meet mNY criteria for AS.

Figure 1: ASAS Classification Criteria for Axial Spondyloarthritis (axSpA)



Source: Rudwaleit M, et al. *Ann Rheum Dis*, Figure 2. 2009; 68:781.

Utilizing the ASAS criteria, it has been estimated that 0.7% of the population aged 18-44 years (slightly less than 1 million people) have axSpA (Strand et al., 2013). It is estimated that 0.31-0.35% of the US population has nr-axSpA (Strand et al., 2013). More females have nr-axSpA (2:1, female:male). For some patients, nr-axSpA may be an "early AS" or "pre-AS," while other patients with nr-axSpA have had disease for many years without progression (Ghosh & Ruderman, 2017). Some observational studies have suggested that progression is 10-12% in the first 2 years, 20-25% about 2-8 years after diagnosis, and 26-28% after ≥10 years (Ghosh & Ruderman, 2017). Male gender, elevated CRP, and MRI changes consistent with sacroiliitis may be predictors of progression (Ghosh & Ruderman, 2017). Additionally, buttock pain and absence of peripheral arthritis have been associated with progression.

2.2. Analysis of Current Treatment Options

Psoriatic Arthritis

The goals of PsA treatment are to improve signs and symptoms, improve physical function, and prevent radiographic progression. The treatment should also consider concomitant psoriatic skin involvement, enthesitis/dactylitis, and axial involvement. According to the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) Guideline for the Treatment of Psoriatic Arthritis,[5] the management of patients with PsA includes treatments with non-steroidal anti-inflammatory drugs (NSAIDs), intraarticular and/or systemic glucocorticoids, and small molecule and biologic disease modifying anti-rheumatic drugs. FDA approved drugs for the treatment of PsA include tumor necrosis factor alpha inhibitors (TNFα), an interleukin-17 inhibitor (IL-17), an IL-17A inhibitor, an IL-12/23 inhibitor, a phosphodiesterase 4 (PDE4) inhibitor, a T-cell costimulation modulator, and a janus kinase (JAK) inhibitor as shown in Table 2. Among the approved drugs, the TNFα-inhibitors, as well as secukinumab, ixekizumab, and upadacitinib have been shown to reduce the radiographic progression of peripheral arthritis in PsA.

Table 2: Drugs Approved for the Treatment of Psoriatic Arthritis (PsA)

Drug	Mechanism of Action	Date of Approval for PsA	Dosage and Administration
Etanercept (Enbrel)	TNFα-Inhibitor	1/15/2002	50 mg SC once weekly with or without methotrexate
Infliximab (Remicade)	TNFα-Inhibitor	5/18/2005	5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks
Adalimumab (Humira)	TNFα-Inhibitor	10/3/2005	40 mg SC every other week
Golimumab (SC) (Simponi)	TNFα-Inhibitor	4/24/2009	50 mg SC once per month
Ustekinumab (Stelara)	IL-12/23 Inhibitor	9/20/2013	45 mg SC initially and 4 weeks later, followed by 45 mg every 12 weeks
Certolizumab (Cimzia)	TNFα-Inhibitor	9/27/2013	400 mg SC initially and at week 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered
Apremilast (Otezla)	PDE4 Inhibitor	3/21/2014	30 mg PO twice daily after a 6 day titration schedule

[5] Jasvinder A. Singh, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis & Rheumatology Vol. 71, No. 1, January 2019, pp 5–32.

Secukinumab (Cosentyx)	IL-17 Inhibitor	1/15/2016	• With a loading dose: 150 mg SC at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter • Without a loading dose 150 mg every 4 weeks • If a patient continues to have active psoriatic arthritis, consider a dose of 300 mg
			• If a patient continues to have active psoriatic arthritis, consider a dose of 300 mg
Abatacept (Orencia)	T-Cell Costimulation Modulator	6/1/2017	• 500-1000 mg IV at 0, 2, and 4 weeks, then every 4 weeks • 125 mg SC once weekly
Golimumab (IV) (Simponi Aria)	TNFα-Inhibitor	10/20/2017	2 mg/kg IV over 30 minutes at weeks 0 and 4, then every 8 weeks
Ixekizumab (Taltz)	IL-17A Inhibitor	12/1/2017	160 mg SC at Week 0, followed by 80 mg every 4 weeks
Tofacitinib* (Xeljanz)	JAK-Inhibitor	12/14/2017	• 5 mg PO twice daily • XR: 11 mg PO once daily
Guselkumab (Tremfya)	IL-23 Inhibitor	7/13/2020	• 100 mg SC at Week 0, Week 4 and every 8 weeks thereafter
Upadacitinib* (Rinvoq)	JAK-inhibitor	6/25/2021	15 mg PO once daily

Abbreviations: TNF=tumor necrosis factor; PDE4=phosphodiesterase 4; IL=interleukin; JAK=janus kinase; SC=subcutaneous; IV=intravenous; PO=by mouth; mg=milligram; kg=kilogram; XR=extended release
*JAK-inhibitors Tofacitinib and Upadacitinib Indication for PsA is limited to active psoriatic arthritis with an inadequate response or intolerance to one or more TNF blockers.

Ankylosing Spondylitis and non-radiographic Axial Spondyloarthritis

The American College of Rheumatology (ACR), together with the Spondyloarthritis Research and Treatment Network (SPARTAN) and the Spondylitis Association of America (SAA), published 2015 recommendations for the treatment of AS and nr-axSpA[6]. These guidelines were updated

[6] American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol. 2016 Feb;68(2):282-98.

in 2019 in response to new treatments available for axSpA[7], and rely on the literature from AS, as the data on treatment for nr-axSpA were limited. In general, the treatment recommendations for nr-axSpA are similar to those for AS.

Since 2003, six Tumor necrosis Factor (TNF) inhibitors have been approved for the treatment of AS: etanercept, infliximab, adalimumab, golimumab, certolizumab, and golimumab IV. In addition, one IL-17 inhibitor (secukinumab), one IL-17A Inhibitor (ixekizumab), and one JAK inhibitor (tofacitinib) are approved for the treatment of AS (Table 3); there are four FDA-approved treatments for nr-axSpA (Table 4).

Table 3: Drugs Approved for the Treatment of Ankylosing Spondylitis (AS)

Drug	Mechanism of Action	Date of Approval for AS	Dosage and Administration
Etanercept (Enbrel)	TNFα-Inhibitor	7/ 2003	50 mg SC once weekly
Infliximab (Remicade)	TNFα-Inhibitor	12/ 2004	5 mg/kg IV at 0, 2 and 6 weeks, then
Adalimumab (Humira)	TNFα-Inhibitor	7/ 2006	40 mg SC every other week
Golimumab (SC)	TNFα-Inhibitor	4/ 2009	50 mg SC once per month
Certolizumab (Cimzia)	TNFα-Inhibitor	10/ 2013	400 mg SC initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks
Secukinumab (Cosentyx)	IL-17 Inhibitor	1/ 2016	• With a loading dose: 150 mg SC at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter • Without a loading dose: 150 mg every 4 weeks
Golimumab (IV) (Simponi Aria)	TNFα-Inhibitor	10/ 2017	2 mg/kg IV over 30 minutes at weeks 0 and 4, then every 8 weeks
Ixekizumab (Taltz)	IL-17A Inhibitor	8/ 2019	160 mg SC at Week 0, followed by 80 mg every 4 weeks
Secukinumab (Cosentyx)	IL-17 Inhibitor	1/ 2020	**Addition of higher dosage:** If a patient continues to have active ankylosing spondylitis, consider a dosage of 300 mg every 4 weeks
Tofacitinib (Xeljanz and Xeljanz XR)	JAK Inhibitor	12/ 2021	5 mg twice daily or XR 11 mg once daily
Upadacitinib* (Rinvoq)	JAK-inhibitor	4/2022	15 mg PO once daily

[7] 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol. 2019 Oct;71(10):1599-1613.

*JAK-inhibitors Tofacitinib and Upadacitinib Indication for AS is limited to active psoriatic arthritis with an inadequate response or intolerance to one or more TNF blockers.

Table 4: Drugs Approved for the treatment of non-radiographic axial spondyloarthritis (nr-axSpA)

Drug	Mechanism of Action	Date of Approval for nr-axSpA	Dosing/ Administration
Certolizumab (Cimzia)	TNF Inhibitor	3/2019	400 mg SC initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks
Ixekizumab (Taltz)	IL-17A Inhibitor	5/2020	80 mg SC every 4 weeks
Secukinumab (Cosentyx)	IL-17A Inhibitor	6/2020	Administer with or without a loading dosage: - With a loading dosage: 150 mg SC at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter - Without a loading dosage: 150 mg SC every 4 weeks
Upadacitinib* (Rinvoq)	JAK-inhibitor	10/2022	15 mg PO once daily

*JAK-inhibitors Tofacitinib and Upadacitinib Indication for AS is limited to active psoriatic arthritis with an inadequate response or intolerance to one or more TNF blockers.

3 Regulatory Background Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The original BLA was approved on January 21, 2015, for the indication of moderate to severe plaque psoriasis. Supplemental BLAs were later approved for the indications of, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Non-radiographic Axial Spondyloarthritis (nr-axSpA), pediatric plaque psoriasis, and most recently juvenile PsA and enthesitis-related arthritis.

COSENTYX® is currently supplied as a 150mg/mL or 75mg/0.5mL solution for injection in prefilled syringe and a 150mg/mL solution for injection in prefilled pen. Lyophilized power for injection is also approved, however has never been marketed and an application for withdrawal of this dosage form is in process (BLA 125504 S-055).

The currently approved and US marketed Cosentyx drug product formulations include the 150 mg/mL solution for injection in pre-filled syringe (PFS), the 150 mg/mL solution for injection in auto-injector (AI), and the 75 mg/0.5 mL solution in PFS, all of which are administered subcutaneously (BLA 125,504).]

The purpose of this submission is to provide evidence supporting the registration of a newly developed secukinumab intravenous (IV) formulation (secukinumab 125 mg/5 mL concentrate for solution for infusion) also called Liquid in Vial (LIVI) and IV regimen for the treatment of adult patients with axial spondyloarthritis (axSpA: including both ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)) plus psoriatic arthritis (PsA).

3.2. Summary of Presubmission/Submission Regulatory Activity

A higher dose of the IV formulation than what is currently proposed was studied in two large Phase III trials in adults with axSpA ((P12301; enrolled 526 subjects with AS and nr-axSpA) and PsA (P12302; enrolled 381 subjects), with a dosing regimen of an initial dose of 6 mg/kg followed by 3 mg/kg every four weeks (q4w) starting at Week 4. The 16-week primary endpoint analysis from both studies demonstrated that treatment with the secukinumab IV regimen was efficacious, with a safety profile similar with that seen previously with subcutaneous use in authorized indications. No new safety signals were observed. These studies have been conducted by the applicant and informed the discussions about the IV dosing regimen that ultimately informed the approach used in the current submission.

Previous consultations with the Agency are summarized as below:

1) Novartis had a Type B pre-submission meeting with the Agency on December 08, 2021 to discuss an IV formulation of secukinumab for PsA.
   - The efficacy and safety results of study P12302 were summarized; in this study adult PsA patients were treated with placebo or a regimen of secukinumab consisting of an IV loading dose of 6mg/kg at baseline followed by 3mg/kg every 4 weeks thereafter.

- Novartis's position was that the efficacy and safety data from study P12302 supported a regulatory filing for secukinumab IV (6mg/kg at baseline and (b)(4) mg/kg Q4W thereafter).
- FDA did not accept the proposed plan for regulatory filing proposed by Novartis due to the fact that the proposed IV dosing regimen appeared to result in significantly higher Cmax and AUC than the 300 mg Q4W SC dosing regimen than the approved SC dosing regimens. Further, the PK parameters were estimated to be significantly higher than the initially approved SC dosing regimen in PsA of 150 mg Q4W. FDA raised concerns that the proposed IV loading/maintenance dosing regimen was not supported by sufficient safety information to support the benefit-risk assessment and that the short-term placebo-controlled comparisons from study P12302 are unlikely to address those concerns.
- In order to address FDA concerns, FDA recommended an alternative approach. Noting that SC secukinumab is currently approved for PsA with a two-tiered dosing regimen of 150 mg Q4W or 300 mg Q4W for patients who continue to have active PsA, FDA suggested that safety and efficacy information from these two SC dosing regimens could be leveraged to support approval of an IV dosing regimen. Further, FDA advised that lower IV doses could be targeted that would achieve an AUC in the range of 150 mg SC to 300 mg SC doses. The estimated exposures with the lower IV dosing regimen could be based on a model-informed drug development (MIDD) approach. FDA advised that this approach would better support an IV dosing regimen(s) that can leverage relevant safety information from the currently approved SC dosing regimens, for which the benefit-risk has been established, without the need for comparative long-term safety assessments. Using this approach, efficacy could be extrapolated, with appropriate justification, from the efficacy established with the SC dosing regimens.
- FDA included additional advice based on the observation that exposures of secukinumab tended to be higher in patients with very high body weight and recommended that Novartis include a maximum absolute dose for the IV dosing regimen (e.g. 300 mg IV).
- Novartis was encouraged to submit a proposal under the MIDD pilot (https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program)

2) Novartis requested an MIDD meeting, which was granted for June 28, 2022. FDA provided detailed responses to Novartis's questions on June 24th. After receiving these written responses, Novartis canceled the meeting.

- Novartis asked if the proposed model-derived IV dosing regimen of 6 mg/kg at baseline followed by 1.75 mg/kg Q4W would deliver exposures that lie between the approved 150 mg and 300 mg SC regimens of secukinumab so that established efficacy and safety of the SC secukinumab dosage could be leveraged to support approval of this IV regimen in PsA and axSpA indications. FDA responded that the established efficacy and safety of the SC secukinumab dosage form can be leveraged to support the approval of the IV regimen in the proposed indications if the secukinumab concentrations lie between the approved 150 mg and 300 mg SC regimens of secukinumab. Based on the information provided, the proposed IV dosing regimen of 6 mg/kg at baseline followed by 1.75 mg/kg administered every 4

weeks starting at week 4 appears to result in exposures that lie between the approved 150 mg and 300 mg SC regimens of secukinumab.

- Novartis also asked if the information provided sufficient evidence for the PK modeling to support the proposed IV dosing regimen without the need for a dedicated PK study in patients. FDA responded that the information provided in the meeting package appears to support the sufficiency of the PK modeling to support the proposed lower IV dosing regimen, without the need for a dedicated PK study in patients provided that you have established the PK bridging between the proposed IV regimen and the approved SC regimen.
- FDA advised that final acceptance of the PK modeling would be made after review of the data and modeling and simulation results.
- FDA also advised that, given that the approved SC dosing regimen for nr-AxSpA is 150 mg, Novartis should consider what additional information would be needed to support the safety of the IV dosing regimen, and also consider providing a justification of the relevance of the safety information available for other indications, such as PsA and AS, for which safety information is available with the 300 mg SC dosing.

3) Novartis also obtained a Type C meeting written feed-back from FDA on October 15, 2021, regarding CMC aspects of the submission.

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

4.1. Office of Scientific Investigations (OSI)

OSI inspection was not requested. Office of Study Integrity and Surveillance (OSIS) inspection was requested for the bioanalytical sites for Study CAIN457P12301 (P12301) and Study CAIN457P12302 (P12302).

OSIS determined that an inspection is not needed for the site (b) (4) As OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4) The RRA was conducted under the following submission: BLA (b) (4) OSIS concluded that data from the reviewed studies were reliable.

Similarly, OSIS determined that an inspection is not needed for (b) (4) (b) (4) site. As OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4) The inspection was conducted under the following submissions: BLA Non-responsive There were minor objections, and after review of the objectionable conditions and the written response from the site OSIS determined that the observations were isolated in nature and did not impact the reliability of data.

Hence, for this BLA, the data from the reviewed studies were considered reliable. For additional details, refer to OSIS review in DARRTS dated Mar 28, 2023 and May 12, 2023.

4.2. Product Quality

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761349 for Cosentyx (intravenous formulation) manufactured by Novartis Pharmaceutical Corporation. The data submitted in this application are adequate to support the conclusion that the manufacture of Cosentyx is well-controlled and leads to a product that is pure and potent. OPQ microbiology review team concluded that the information of the drug product microbial quality control is adequate.

The OPQ team has recommended that this product be approved for human use under conditions specified in the package insert. For additional details, refer to the Integrated Quality Assessment in DARRTS dated August 29, 2023.

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

N/A

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Secukinumab is a human monoclonal antibody directed against interleukin-17A (IL-17A, also known as IL-17). IL-17A levels are elevated in many inflammatory and autoimmune conditions. By binding to IL-17A, secukinumab inhibits the interaction of IL-17A with its receptor and prevents subsequent release of proinflammatory cytokines, chemokines, and mediators of tissue damage. The nonclinical program to support the use of secukinumab for the treatment of psoriasis and subsequent indications was reviewed previously for its initial approval (refer to the Pharmacology-Toxicology review for BLA 125504 by Dr. Jill Merrill dated August 7, 2014). Included in that review are studies that support the safety of intravenous administration of secukinumab although an IV marketing application was not prepared at that time. Early studies established compatibility between solutions of secukinumab for intravenous (IV) dosing and both cynomolgus monkey and human blood. In toxicological studies of up to 26 weeks with once weekly IV dosing, there were no adverse events, and the NOAEL was the highest administered dose in all studies. The safety of the IV route of administration was demonstrated in the nonclinical studies with appropriate safety margins to support human administration.

There were no proposed changes to the prescribing information for pharmacology-toxicology-related topics and none were necessary.

IV Formulation of Secukinumab
The proposed IV formulation of secukinumab (AIN457), 125 mg/5 mL Concentrate for solution for infusion, contains the same drug substance and excipients as the marketed Cosentyx (AIN457) 150 mg/mL Solution for injection. The infusion solution contains a lower secukinumab concentrations 25 mg/mL versus 150 mg/mL for the approved SC administration. The excipient, trehalose dihydrate, which is used as a (b) (4) has a slightly higher concentration (225 mM) in the IV formulation than the SC formulation (200 mM) (b) (4) Neither of these alterations are expected or appeared in nonclinical or clinical studies to influence safety of secukinumab.

Table 5. Comparison of the composition per 1 mL of solution of the existing Cosentyx presentations and the new AIN457 125 mg/5 mL Concentrate for solution for infusion presentation.

	Cosentyx® 150 mg Powder for solution for injection [1]	Cosentyx® 150 mg/1 mL Solution for injection in pre-filled syringe	AIN457 125 mg/5 mL Concentrate for solution for infusion
AIN457 (mg/mL)	150	150	25
Sucrose (mM)	270	-	-
Trehalose-dihydrate (mM)	-	200	225
Histidine (b) (4) (mM)	(b) (4)		(b) (4)
pH	5.8	5.8	5.8
Polysorbate 80 (%)	(b) (4)		
Methionine (mM)	-	5	5
Water for injection	1 mL	up to 1 mL	up to 1 mL

[1] After reconstitution with 1.0 mL water for injection

(Source: Module 2.3, Quality Overall Summary - Drug Product, Table 2-1 page 8)
There were no new secukinumab impurities present in the IV formulation.

Extractables and Leachables
The drug product container closure system consisting of a 6 mL glass vial (type 1), grey (b) (4) -rubber stopper coated on the product contact side with (b) (4) and an aluminum cap seal with flip-off disk.

Table 6. AIN457 125 mg/5 mL concentrate for solution for infusion - Identity of materials of construction

Component	Description	Identity of material	Compliance status
Vial	6 mL / 13 mm, colourless	Glass (b) (4)	Complies with Ph. Eur., USP requirements for (b) (4) glass
Stopper	13 mm, grey	(b) (4)	Complies with Ph. Eur. requirements for 'Rubber closures for containers for aqueous preparations for parenteral use', USP requirements for 'Elastomeric closures for injection'
Flip-off cap	13 mm	Aluminum flip-off cap with a plastic flip-off disk (b) (4)	Not applicable (non-product contact)

(Source: Pharmaceutical development - Container closure system, Module 3.2.P.2, SD-009, Table 2-1, page 3.)

Extractable and leachable studies (described in Module 3.2.P.2, SD-009 of the BLA 761349) were conducted without incorporating the aluminum cap since there is no contact of the cap with the drug product. The Analytical Evaluation Threshold (AET), was set at (b) (4) µg/mL based on PQRI recommendations (using a SCT of (b) (4) µg/day) with adjustments for dosing frequency for 70 year lifetime. Two compounds, (b) (4) (b) (4) were found in the extractables that had AET greater than (b) (4) µg/mL as indicated in the following table; however, both compounds were present at levels well below the maximum daily intake defined in ICH Q3C (R6) for (b) (4) (b) (4) in which amounts less or equal to (b) (4) mg per day are considered acceptable without justification. (b) (4) was detected in the incubation experiment with 20% isopropanol/water (exaggerated extracted condition) with an MDI of (b) (4) µg, below the MDI of (b) (4) µg/day evaluated in a dedicated toxicological assessment (not described or referenced).

Table 7. Summary of compounds exceeding the AET (VOCs, SVOCs, NVOCs).

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Compounds (CAS no.)	Incubation solvent	Concentration in the incubation extracts (µg/mL)	Maximum daily intake (µg/day)
(b) (4)			

[1] SVOCs (semi-volatile organic compounds)
[2] VOCs (volatile organic compounds)
[3] Maximum daily intake [µg/day] was only calculated for the highest concentration of (b) (4) found in the (b) (4)

(Source: Pharmaceutical development - Container closure system, Module 3.2.P.2, SD-009 Table 2-2, page 6.)

No volatiles, semi-volatiles and non-volatiles extractables above the respective analytical evaluation thresholds (AETs) for the particular process material were detected in the filter extracts and in the extracts of the majority of different tubing, connectors and gaskets.

Leachables were studied for secukinumab containing vials (three pre-validation / registration stability batches, SXW48, SXW50 and SYE80, manufactured at Novartis Pharma Stein AG and fully representative for the commercial product) stored up to 24 months. No leachable at or above the AET and 3-fold above the respective blank sample were detected in VOC, SVOC, or NVOC screenings. An (b) (4) derivative leachable at higher level than the AET was detected after 6-month of storage, (b) (4)

(b) (4)

(b) (4)

Toxicological Safety of IV Secukinumab

Secukinumab (0.62-2.5 mg/ml) was negative in a hemolysis assay using human and cynomolgus monkey whole blood and showed compatibility with human and cynomolgus monkey serum and plasma. [NVP-AIN457-NX-1: hemolytic potential and blood compatibility (Study RD-2005-00699) Reviewed May 28, 2009 for IND 100418 by Dr Barbara Hill].

Reviews of IV dosing studies were conducted for IND 100418 for psoriasis by Drs Barbara Hill (dated January 4, 2007, May 28, 2009, and March 29, 2012) and Carmen Booker (dated February 4, 2010), and IND 12678 by Maria Rivera, (2007, filed in the Division File System (DFS) prior to DARRTS) for rheumatoid arthritis. Also refer to the initial secukinumab BLA 125504 nonclinical review by Dr. Jill Merrill dated August 7, 2014. In toxicological studies of up to 26 weeks with once weekly IV dosing, there were no adverse events, and the NOAEL was the highest administered dose in all studies. The major studies are listed in the following table:

Table 8 Pivotal repeat dose intravenous toxicology studies with secukinumab

Table 4-5 Repeated dose toxicity studies

Species (Strain)	Method of administration (Vehicle / Formulation)	Duration of dosing (Weeks)	Dose levels (mg/kg)	Gender and No. per group	Major findings
Cynomolgus monkey GLP	Intravenous Sp2/0 material	4 with 8-week recovery	0, 10, 30, 100	3m/3f 2m/2f for recovery	NOAEL= 100 mg/kg/week
Cynomolgus monkey GLP	Intravenous CHO material	4 with 10-week recovery	0, 15, 50, 150	3m/3f 2m/2f for recovery	NOAEL = 150 mg/kg
Cynomolgus monkey GLP	Intravenous CHO material	26 with 13-week recovery	0, 15, 50, 150	4m/4f 2m/2f for recovery	NOAEL = 150 mg/kg
Cynomolgus monkey GLP	Subcutaneous CHO material	13 with 13-week recovery	0, 15, 50, 150	3m/3f 2m/2f for recovery	NOAEL = 150 mg/kg

Abbreviations: NOAEL=no observed adverse effect level;

(Source: Excerpted from the Sponsor's submission)

6 Clinical Pharmacology

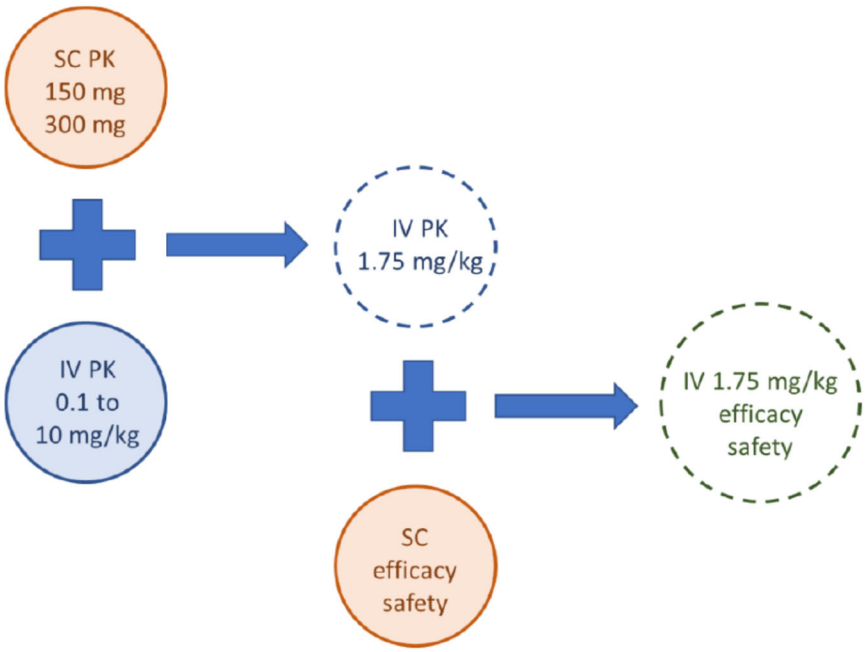
6.1. Executive Summary

The applicant is seeking the approval of IV formulation of Cosentyx® [non-proprietary name: Secukinumab (AIN457)] for the treatment of, psoriatic arthritis (PsA), ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) in adults.

The focus of this submission is on the adult indications of PsA, AS and nr-axSpA for LIVI formulation using MIDD approach. The key clinical pharmacology findings for LIVI secukinumab in patients with PsA, AS and nr-axSpA are summarized below:

- The applicant has used PK data from SC and IV administration to develop a PK model and conducted simulations exploring a range of IV dosing regimens that approximate the exposures of the approved SC dosing regimens (150 and 300 mg) and result in similar PK (Cmin,ss, Cmax,ss and Cavg,ss [AUCtau/dosing interval]) parameters. With an IV dosing regimen that would target the same q4w dosing interval and has similar PK parameters falling within the range of the two approved SC regimens, the established efficacy and safety of the approved SC regimens can be leveraged to extrapolate the safety and efficacy of the proposed simulated IV regimen without the need of conducting additional PK, efficacy, or safety studies.

Figure 2. Overview of MIDD Approach



Note: Red solid circles represent observed PK or efficacy/safety of SC doses, blue solid circles represent observed PK of IV doses and open circles with dashed lines represent simulated data for PK or efficacy/safety of proposed IV dosing regimen.

(Source: Summary of Clinical Pharmacology, Figure 1-1, page 10)

The presented IV regimens were determined by modeling and simulation from a PopPK model developed using data from a large pool of PsA, AS and nr-axSpA studies. The PK information included in this pool allows for a robust estimation of PK parameters, and the population PK model underwent thorough internal and external validation.

- Based on population PK modeling, the proposed IV dosing regimen of 1.75 mg/kg, with or without loading dose of 6 mg/kg, is predicted to achieve exposure of SEC to match the exposures of the approved SC doses of 150 mg and 300 mg with or without loading dose, respectively.

- Based on modeling and simulation, the 1.75 mg/kg SEC IV Q4W dosing regimen is predicted to achieve steady-state exposures that were either comparable (Ctrough) or higher (Cave, Cmax) than the exposure established in PsA, AS and nr-axSpA patients with the approved 150 mg Q4W dosing regimens. The simulated time-concentration profile shows that the 1.75 mg/kg IV Q4W dosing regimen achieved comparable or higher SEC concentrations compared to the approved 150 mg Q4W SC dosing regimens throughout the dosing interval at steady state. Therefore, the PK data support the bridging of efficacy from SEC SC to SEC IV for the treatment of PsA, AS and nr-axSpA.

- Based on modeling and simulation, the 1.75 mg/kg SEC IV Q4W dosing regimen is predicted to achieve steady-state exposures that were either comparable (Cmax) or lower (Cave, Cmin) than the exposure established in PsA and AS patients with the approved 300 mg Q4W dosing regimens. The simulated time-concentration profile shows that the 1.75 mg/kg IV Q4W dosing regimen achieved comparable or lower SEC concentrations compared to the approved 300 mg Q4W SC dosing regimens throughout the dosing interval at steady state. Therefore, the PK data support the leverage of safety data from SEC SC to SEC IV for the treatment of PsA and AS. For nr-axSpA, safety of the maintenance dose of intravenous secukinumab is also supported by observed safety data in the placebo-controlled long-term extension period of study H12315 comparing 150 mg to 300 mg subcutaneous secukinumab.

- The maximum recommended maintenance IV dose is 300 mg. To leverage safety information from SEC SC, a maximum IV dose of 300 mg is recommended so that the SC safety data can provide adequate safety coverage. The 6 mg/kg loading dose was studied in the two IV Phase III studies (Study P12301 and Study P12302). The safety profile in these two studies was overall similar to the safety profile seen with secukinumab given SC. Therefore, no dose capping of the loading dose is recommended.

- The exposure-response analyses for PsA and AS support that both the efficacy and safety of the proposed IV regimen are consistent with the approved SC regimens.

- A dedicated confirmatory PK study with the proposed IV dose is not necessary based on the following prerequisites. This decision is based on the totality of data available for secukinumab program and may not be generalized to other SC to IV conversion programs.

    1) Secukinumab has dose proportional PK properties over a dose range of 25 mg to 300 mg following SC administration and 1 mg/kg to 10 mg/kg following IV administration.
    2) The two clinical studies (CAIN457P12301 and CAIN457P12302) used the new liquid in vial (LIVI) formulation with 6 mg/kg IV as a loading dose at baseline and 3 mg/kg IV q4w as a maintenance dose. In addition, there is extensive experience with iv administration in previous clinical studies.
    3) The proposed dosing frequency (q4w) is the same between the proposed IV doses and the SC and IV doses studied in clinical studies.
    4) A robust popPK model was built based on abundant observed PK data of secukinumab from a wide dose range of both SC and IV formulations across multiple indications. External validation from study P12301 showed close agreement between observed and predicted Cmax,ss and Cmin,ss.
    5) These evidences suggest the population PK model is credible and should be able to adequately predict secukinumab PK for the proposed IV dosing regimen with minimal uncertainty. Even though the 'model influence' is high, an additional study to confirm the PK of secukinumab at the proposed IV doses would be of minimal value and as such the 'decision consequence' can be considered low.

- No treatment-emergent ADA were observed in P12302, and incidence of treatment-emergent ADA was approximately 1% in P12301 which is close to the incidence observed in studies with SC administration. As there is no available immunogenicity data with the proposed dose of SEC IV, we recommend no updates in the labeling immunogenicity section.

- The to-be-marketed LIVI formulation was used to study an IV regimen with an initial 6 mg/kg IV loading dose at Week 0 followed by 3 mg/kg IV administered q4w starting at Week 4 in two large Phase 3 studies, Study CAIN457P12301 (further referred to as P12301) in subjects with axSpA (AS and nr-axSpA) and Study CAIN457P12302 (further referred to as P12302) in subjects with PsA.

Recommendations
The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under BLA 761349. This BLA is recommended for approval from a clinical pharmacology perspective.

Post marketing requirement/Post marketing commitment
The Pediatric Research Equity Act (PREA) PMR studies need to be completed. Please refer to section 10 for more details.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics Following Subcutaneous Administration
The pharmacokinetic (PK) properties of secukinumab administered subcutaneously is similar in PsA, AS and nr-axSpA adult patients. See Cosentyx USPI for details of PK for secukinumab SC.

Pharmacokinetics Following Intravenous Administration
Following an intravenous administration of 1.75 mg/kg maintenance dose every four weeks, with or without a loading dose of 6 mg/kg at Day 0, the secukinumab concentrations [steady state trough secukinumab concentrations (Cmin,ss), mean secukinumab concentrations (Cavg,ss), and maximum secukinumab concentrations (Cmax,ss)] are estimated to be within the range of the steady state concentrations following subcutaneous administration of 150 mg and 300 mg doses of COSENTYX administered every four weeks.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed intravenous dosages are: With a loading dosage: 6 mg/kg given at Week 0 as a loading dose, followed by 1.75 mg/kg every 4 weeks thereafter (max. maintenance dose 300 mg per infusion). Without a loading dosage: 1.75 mg/kg every 4 weeks. (max. maintenance dose 300 mg per infusion).

Therapeutic Individualization

Intrinsic factors were not found to have a clinically meaningful effect on secukinumab PK in moderate-to-severe PsA, and AS patients. Therefore, no dose adjustment is necessary for these factors.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Review Issues	**Recommendations and Comments**
Mechanism of Action	Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines.
Active Moieties	Secukinumab is a human IgG1 monoclonal antibody (MAb) and it is the active moiety.
General Information	
Bioanalysis	Secukinumab serum concentrations were measured using validated enzyme-linked immunosorbent assay (ELISA).
Healthy Volunteers vs. Patients	The pharmacokinetic (PK) parameters were comparable among healthy subjects and PsA and axSpA subjects. PK properties of secukinumab administered subcutaneously, observed in PsA, AS and nr-axSpA patients were similar to the PK properties of secukinumab administered subcutaneously observed in plaque psoriasis patients.
Drug exposure at steady state following the therapeutic dosing regimen	<u>With Loading Dose (6 mg/kg), and 1.75 mg/kg q4w IV:</u> steady-state was already reached at Week 4 <u>Without Loading Dose, and 1.75 mg/kg q4w IV:</u> The median concentration of the 1.75 mg/kg q4w IV regimen with no loading increases during the first 16 weeks, where it nearly reaches steady state.
Maximal tolerated dose or exposure	In clinical studies in prior BLA submissions and this submission, the PK of secukinumab was assessed at following dose range: • IV doses over a range of 0.1 to 10 mg/kg, and • SC doses over a range of 25 to 300 mg.
Dose Proportionality	The PK of secukinumab is linear, dose proportional and has been well characterized across a wide range of doses and with SC (25 to 300 mg) and IV (0.1 to 10 mg/kg) routes of administration.
Absorption	
Bioavailability	In healthy subjects and subjects with plaque psoriasis, secukinumab bioavailability ranged from 55% to 77% following subcutaneous dose of 150 mg or 300 mg. For IV administration secukinumab bioavailability will be 100%.
t_{max}	Secukinumab reached peak mean (± SD) serum concentrations

	by approximately 6 days post dose after SC administration.
Distribution	
Volume of 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 plaque psoriasis subjects.
Metabolism	
Primary metabolic pathway(s)	Secukinumab is a mAb and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs.
Elimination	
Mean Terminal Elimination half-life	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 plaque psoriasis subjects following intravenous and subcutaneous administration across all psoriasis trials. For IV studies, mean half-life was estimated to be 28.5 days in patients with PsA, and axSpA based on popPK analysis.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The substantial evidence of effectiveness of the proposed IV dosing regimen is based upon PK bridging to the efficacy of SEC SC established in adequate and well-controlled clinical trials in adults with PsA, AS, and nr-axial SpA , i.e. the indications sought for licensure of the IV dosing regimen. The SEC IV regimen for PsA, AS and nr-axial SpA is with or without loading dose of 6 mg/kg followed by maintenance dosing of 1.75 mg/kg administered q4w. A capping of the IV maintenance dose to a maximum dose of 300 mg per infusion is also proposed to limit the Cmax,ss of subjects weighing >170 kg. Based on population PK modeling, the proposed IV dosing regimen, with or without loading dose, is predicted to achieve exposure of SEC to match the exposures of the approved SC doses of 150 mg and 300 mg with or without loading dose, respectively. Based on PK matching, efficacy and safety of the SC regimens approved in axSpA and PsA are extrapolated to the secukinumab IV regimen proposed for registration.

The efficacy of the proposed IV regimen in PsA, AS and nr-axSpA (6 mg/kg at baseline followed by 1.75 mg/kg q4w) is demonstrated based on extrapolation of the efficacy of the approved SC regimens in the same indications. This extrapolation approach is based on closely matched PK profiles of the proposed IV regimen with the approved SC regimens. The efficacy of the SC regimens was established previously in multiple phase 3 studies, which formed the basis of the approval of the SC regimens in each indication.
Exposure-response analyses for PsA and AS further support that the efficacy of the IV regimen at the proposed dose is consistent with the efficacy of the approved SC regimens in each indication. While only a 150 mg SC q4w dosing regimen is approved in nr-axSpA, commonalities between AS (also termed r-axSpA) and nr-axSpA, with both diseases being part of the spectrum

of axSpA allow applying the conclusions from E-R analysis conducted with AS data to the nr-axSpA population providing additional support.

The safety of maintenance dose (1.75 mg/kg) of intravenous secukinumab is based on similar pharmacokinetic exposure and leveraging of the established safety of subcutaneous secukinumab in PsA and AS patients (150 mg and 300 mg doses), and nr-axSpA (150 mg dose). Based on modeling and simulation, the 1.75 mg/kg SEC IV Q4W dosing regimen is predicted to achieve steady-state exposures that were either comparable (Cmax) or lower (Cave, Cmin) than the exposure established in PsA and AS patients with the approved 300 mg Q4W dosing regimens. The simulated time-concentration profile shows that the 1.75 mg/kg IV Q4W dosing regimen achieved comparable or lower SEC concentrations compared to the approved 300 mg Q4W SC dosing regimens throughout the dosing interval at steady state. Therefore, the PK data support the leveraging of safety data from SEC SC to SEC IV for the treatment of PsA and AS. As the only approved maintenance SC dose for nr-axSpA is 150 mg, additional 52-week safety data in nr-axSpA subjects are provided to support the proposed IV maintenance dose of 1.75 mg/kg Q4W in nr-axSpA. The overall safety in nr-axSpA was consistent across studies H2315 (150 mg subcutaneous secukinumab in the core study), the P12301 study of intravenous secukinumab in nr-axSpA subjects, and the extension phase of H2315 in which subjects were treated with subcutaneous secukinumab at both 150 and 300 mg doses. Refer to Section 8 for details of safety assessment for patients with nr-axSpA.

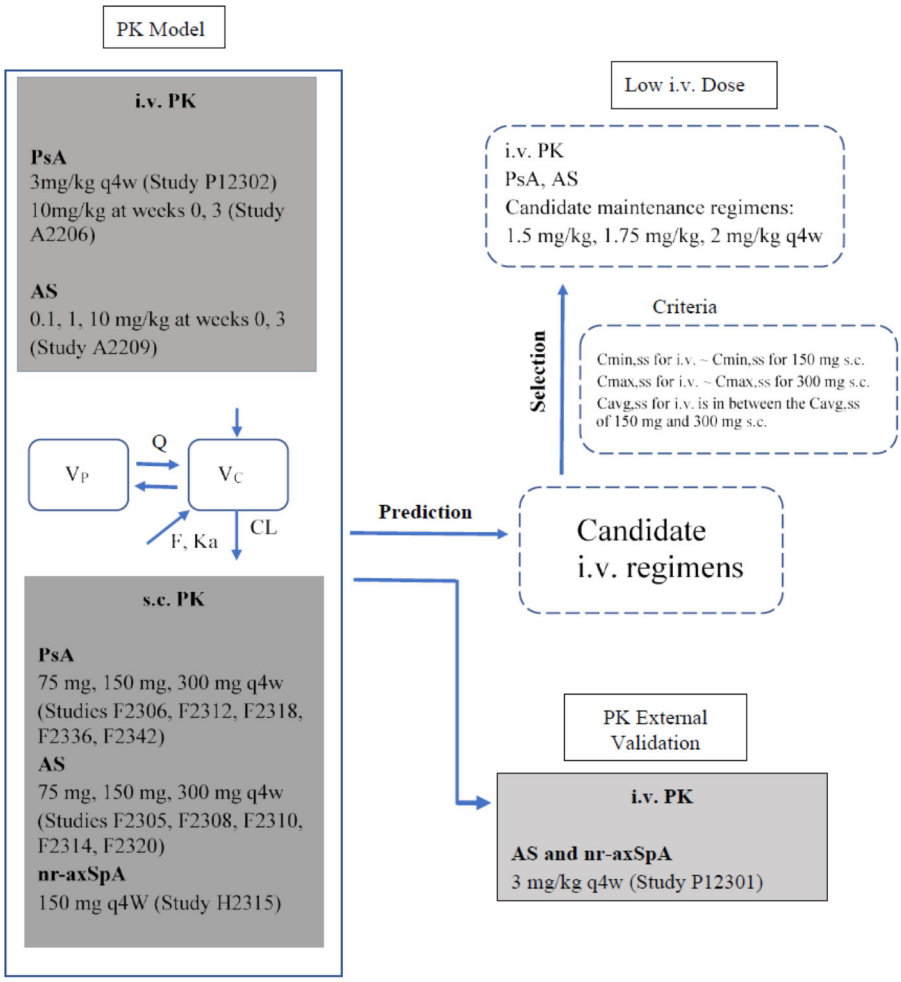
Additionally, the safety and tolerability of the to-be-marketed SEC IV formulation were assessed in PsA and AS subjects in Study P12302 and Study P12301 at a higher IV dose (6 mg/kg loading dose, followed by 3 mg/kg q4w) than the proposed dose for this submission. Refer to Section 8 for details of safety assessment for the to-be-marketed IV formulation in these two studies.

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

Yes. The SEC IV regimen for PsA, AS and nr-axial SpA is with or without loading dose of 6 mg/kg followed by maintenance dosing of 1.75 mg/kg administered q4w. A capping of the IV maintenance dose to a maximum dose of 300 mg per infusion is also proposed to limit the Cmax,ss of subjects weighing >170 kg. Based on population PK modeling, the proposed IV dosing regimen, with or without loading dose, is predicted to achieve exposure of SEC to match the exposures of the approved SC doses of 150 mg and 300 mg with or without loading dose, respectively. Based on PK matching, efficacy and safety of the SC regimens approved in axSpA and PsA are extrapolated to the secukinumab IV regimen proposed for registration.

Clinical PK, safety, and efficacy data were available using the to-be-marketed IV formulation in previous clinical studies (P12301 and P12302), however, the proposed IV dosing regimen is lower than that studied. The identification of the IV regimens were based on a population PK model as provided in Figure 3 below.

Figure 3. Schematic overview of identification of the model-informed IV regimens.



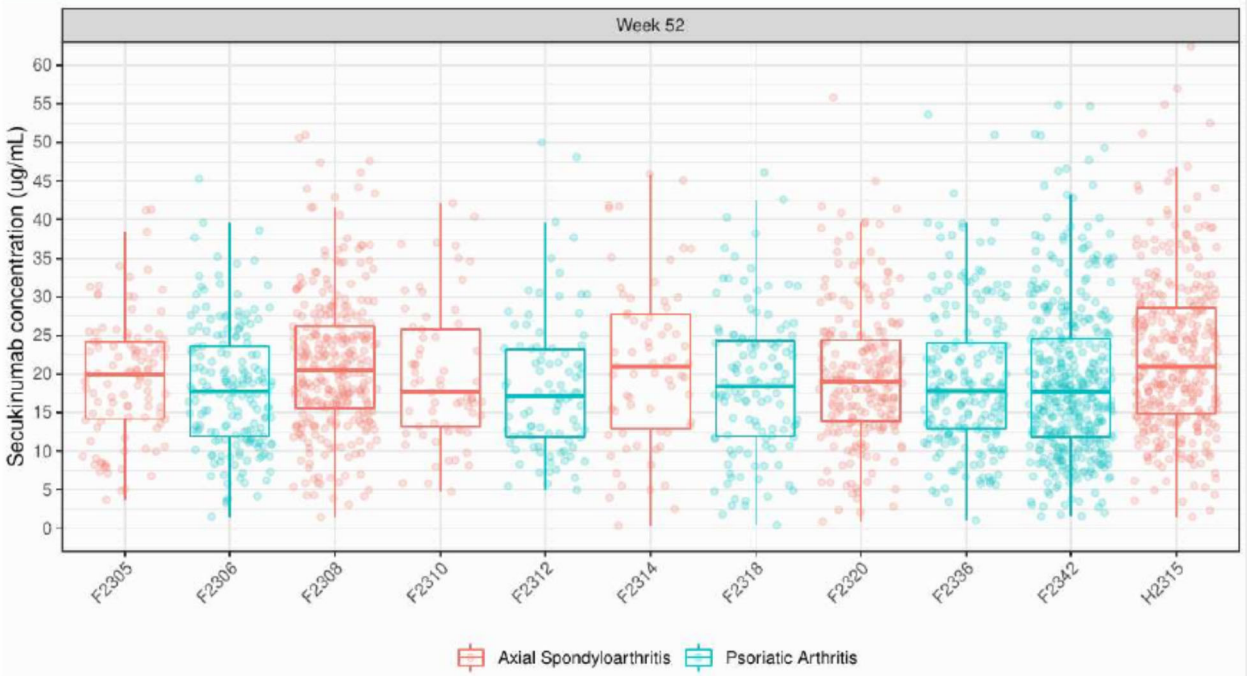
Vc is volume of central compartment, Vp is volume of peripheral compartment, Q is intercompartmental exchange flow rate, CL is clearance, Ka is absorption rate constant, and F is bioavailability

(Source: Summary of Clinical Pharmacology, Figure 3-3, page 34).

The PK parameters of the population PK model for secukinumab were estimated utilizing data from SC studies in PsA, AS and nr-axSpA and IV studies in PsA and AS/ nr-axSpA. The PK properties of secukinumab observed in PsA, AS and nr-axSpA patients were similar (Figure 4). Therefore, it is reasonable to pool the available PK data for this analysis, and the conclusion of the modeling/simulation analysis is applicable to all three indications. The SC studies utilized maintenance dose regimens of 75, 150 and 300 mg SC q4w. The IV phase 3 studies utilized 3 mg/kg q4w as maintenance dosing and a 6 mg/kg IV loading dose. Additionally, data from 0.1, 1, and 10 mg/kg IV dosing at Weeks 0, 2 and 4 in AS subjects as well as 10 mg/kg IV at Weeks 0, 2 and 4 in PsA subjects were also included in the analysis. The results of the population PK modeling and simulation were generally acceptable due to the agreement of prediction and

observation and abundant PK data in both IV and SC dosing regimen. See section 16.3 for details.

Figure 4. Distribution of secukinumab predose concentrations (Cmin,ss) at Week 52 by study in subjects treated with the 150 mg SC q4w regimen



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. The dots represent the pediatric secukinumab concentration data; the data is horizontally jittered to ensure legibility.

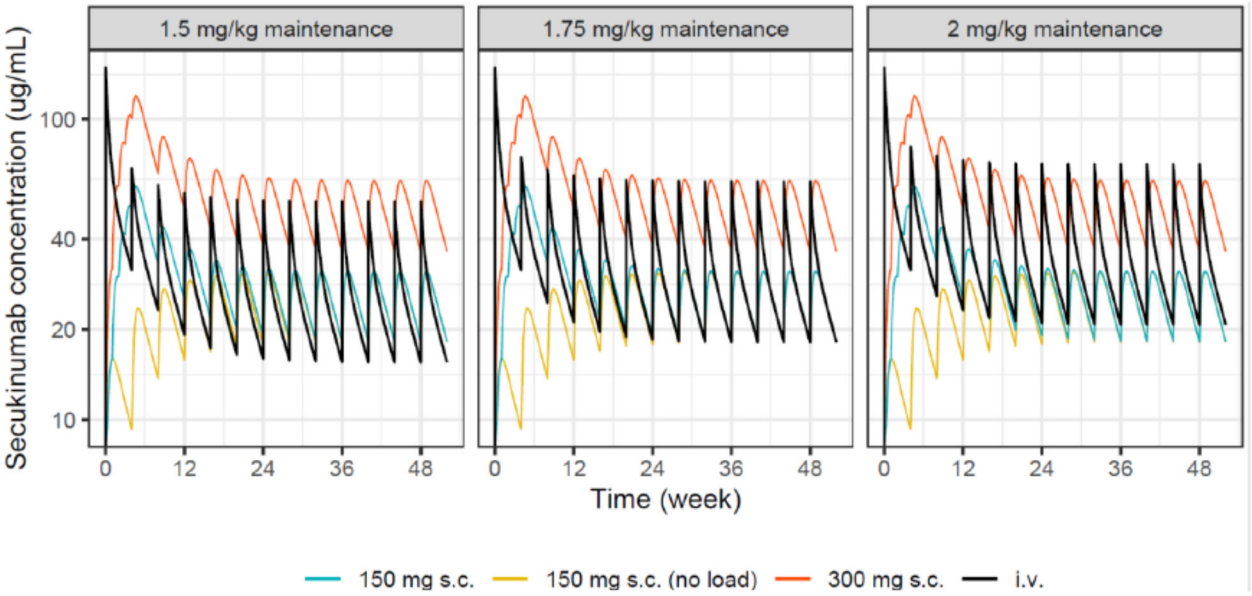
(Source: Summary of Clinical Pharmacology, Figure 2-1, page 17)

Maintenance regimen

Three secukinumab IV maintenance regimens, i.e., 1.5, 1.75, or 2 mg/kg administered q4w, were considered by modeling and simulation to approximate the PK of the approved secukinumab 150 and 300 mg SC regimens in PsA and axSpA subjects.

The median time-concentration profiles of the three IV q4w maintenance regimens when preceded by one 6 mg/kg IV loading dose at Week 0 are presented in Figure 5. This figure overlays the median time-concentration profiles of the approved SC q4w regimens in PsA and axSpA subjects (150 mg SC regimen with and without weekly loading doses and the 300 mg SC regimens with weekly loading doses) for comparison purposes. The profiles were predicted from the final population PK model for a population representative of PsA and axSpA subjects from Study P12301 and Study P12302, as secukinumab PK appeared consistent across those two populations.

Figure 5. Median predicted concentration-time profiles of three IV maintenance regimens that approximate the 150 mg and the 300 mg SC regimens.



The three IV regimens comprise a 6 mg/kg loading dose at Week 0 followed by a maintenance with 1.5, 1.75, or 2 mg/kg administered q4w starting on Week 4. The lines represent the median of the secukinumab concentration-time profiles predicted for 3000 PsA and 3000 axSpA subjects for each secukinumab regimen, as obtained from the final popPK model. The simulated subjects' weights were obtained by bootstrapping from Study P12301 and Study P12302.

(Source: Summary of Clinical Pharmacology, Figure 3-4, page 35)

The steady-state PK parameters (predose concentration (Cmin,ss), maximum concentration (Cmax,ss) and average concentration (Cavg,ss) at steady-state) are summarized in Table 9.

Table 9: Summary of predicted steady-state PK parameters of the IV and SC secukinumab regimens.

Maintenance regimen	Median (90% PI)		
	Cmin,ss (µg/mL)	Cavg,ss (µg/mL)	Cmax,ss (µg/mL)
1.5 mg/kg i.v. q4w	15.6 (7.6, 29.9)	25.1 (13.7, 45.7)	53.3 (34.0, 83.0)
1.75 mg/kg i.v. q4w	18.1 (8.9, 34.8)	29.2 (16, 53.4)	62.1 (39.6, 96.9)
2 mg/kg i.v. q4w	20.7 (10.2, 39.7)	33.4 (18.2, 61.0)	71.0 (45.3, 110.7)
150 mg s.c. q4w	18.2 (8.6, 36.5)	25.1 (12.3, 50.6)	31.3 (18.0, 54.3)
300 mg s.c. q4w	36.4 (17.2, 73.2)	50.1 (24.6, 101.2)	62.6 (36.1, 108.7)

Cmin,ss = predose concentration at steady-state. Cmax,ss = maximum concentration at steady-state. Cavg,ss = average concentration at steady-state. The statistics (median and 90% PI) have been obtained by simulation from the final popPK model: 9000 PsA and 9000 axSpA subjects for each IV regimen, 6000 PsA and 6000 axSpA subjects for the 150 mg SC regimen, and 3000 PsA and 3000 axSpA subjects for the 300 mg SC regimen. The 90% PI is the 5th and 95th percentiles of the simulations. The simulated subjects' weights were obtained by bootstrapping from Study P12301 and Study P12302.

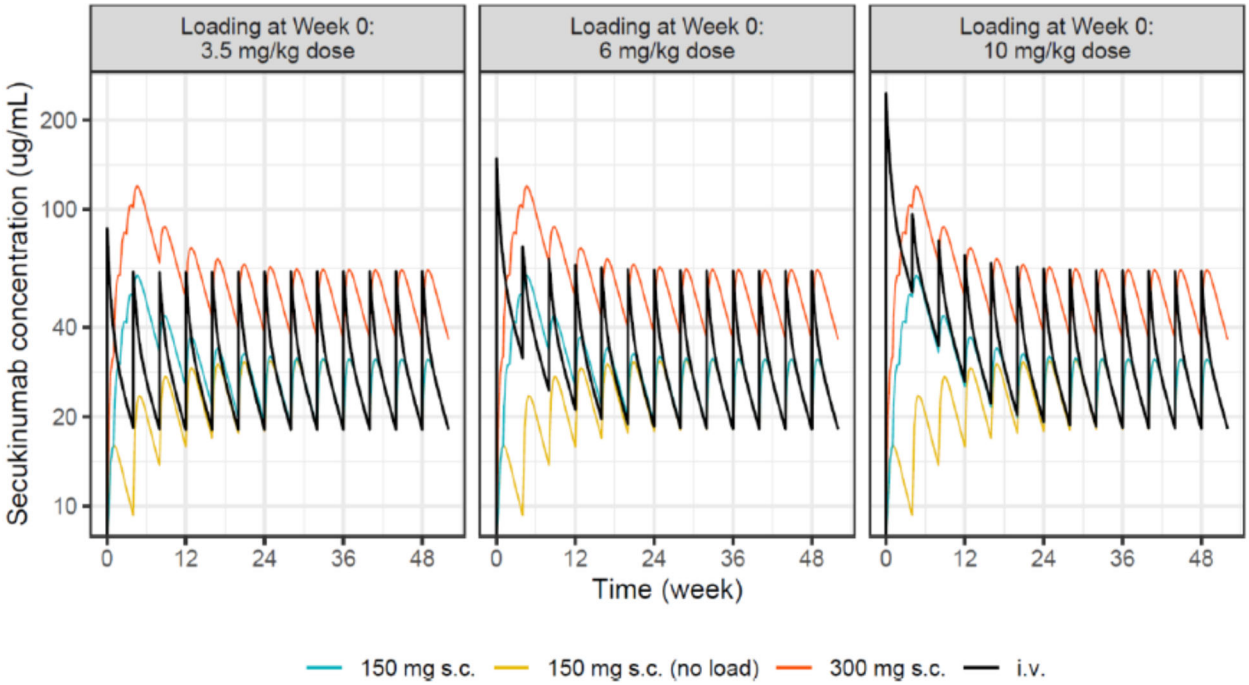
(Source: Summary of Clinical Pharmacology, Table 3-1, page 37)

Among the three modeled IV regimens, the 1.75 mg/kg IV maintenance regimen best approximates the steady-state exposure achieved by the two approved SC regimens: median Cmin,ss (18.1 µg/mL) is comparable to that of the 150 mg SC regimen (18.2 µg/mL), median Cmax,ss does not exceed that of the 300 mg SC regimen, and median Cavg,ss is in between those of the two SC regimens (Table 9). The simulated time-concentration profile shows that the 1.75 mg/kg IV Q4W dosing regimen achieved comparable or higher SEC concentrations compared to the approved 150 mg Q4W SC dosing regimens, and comparable or lower SEC concentrations compared to the approved 300 mg Q4W SC dosing regimens throughout the dosing interval at steady state (Figure 5). For the other two explored maintenance regimens, the median Cmin,ss of the 1.5 mg/kg IV regimen (15.6 µg/mL) is approximately 14% lower than that of the 150 mg SC regimen and the median Cmax,ss of the 2 mg/kg q4w IV regimen slightly exceeds the Cmax,ss of the 300 mg SC regimen by 13%. Therefore, 1.75 mg/kg IV q4w regimen is proposed as the maintenance dose.

Loading regimen
Three secukinumab IV loading regimens (3.5 mg/kg, 6 mg/kg, and 10 mg/kg) at Week 0 were considered. Clinical data from SC studies demonstrated that subjects receiving the 150 mg SC regimen with loading doses tended to have earlier efficacy responses compared to those receiving 150 mg without loading doses; therefore, the current USPI provides an option for secukinumab to be administered with loading. The 6 mg/kg loading dose at Week 0 is studied in both Phase 3 IV studies (Study P12301 and Study P12302). It can be noted that in some legacy Phase 3 studies that supported approval of SEC SC in PsA and AS (Study F2305, Study F2306 and Study F2314), an IV loading regimen of three q2w doses of 10 mg/kg IV was utilized.

The median time-concentration profiles of the 1.75 mg/kg maintenance regimen with different loading doses (3.5 mg/kg, 6 mg/kg, and 10 mg/kg) are presented in Figure 6. Following a loading dose of 3.5 mg/kg, the concentration levels remained lower initially compared to the initial exposures achieved by the approved 150 mg SC regimen with weekly loading. The median Cmin at Week 16 (Cmin, 16W) for the 1.75 mg/kg maintenance regimen following a loading dose of 3.5 mg/kg of the IV regimen is 18.0 µg/mL, which is approximately 17% lower than the Cmin, 16W of the 150 mg SC regimen with loading (21.6 µg/mL) as shown in Table 10. A higher loading dose of 6 mg/kg at Week 0 results in comparable initial concentration levels although with a slightly lower (approximately 9%) Cmin, 16W of 19.6 µg/mL compared to the 150 mg SC regimen with loading. A higher IV loading dose of 10 mg/kg, will lead to much higher Cmax compared to the approved 150 mg and 300 mg SC regimens with loading dose(**Figure 6**).

Figure 6. Impact of three different loading doses at Week 0 on the median predicted concentration-time profiles of the 1.75 mg/kg IV maintenance regimen.



The three IV regimens comprise one loading dose at Week 0 (3.5, 6, and 10 mg/kg) followed by a maintenance with 1.75 mg/kg administered q4w starting at Week 4. The lines represent the median of the secukinumab concentration-time profiles predicted for 3000 PsA and 3000 axSpA subjects for each secukinumab regimen, as obtained from the final popPK model. The simulated subjects' weights were obtained by bootstrapping from Study P12301 and Study P12302.

(Source: Summary of Clinical Pharmacology, Figure 3-7, page 39)

Table 10. Summary of predicted Cmin at Week 16 for various IV and SC loading regimens

	Cmin (µg/mL, 16W
	Median (90% PI)
Loading regimens (at Week 0) with 1.75 mg/kg as maintenance	
3.5[a] mg/kg	18.0 (9.1, 32.4)
6 mg/kg	19.6 (9.3, 37.3)
10 mg/kg	22.1 (10.0, 44.5)
For comparison purpose: s.c. regimens	
150 mg without loading	16.9 (8.3, 31.9)
150 mg with loading	21.6 (9.8, 43.7)
300 mg with loading	43.1 (19.7, 87.4)

Cmin,16W = predose concentration at Week 16. The statistics (median and 90% PI) have been obtained by simulation for 3000 PsA and 3000 axSpA subjects from the final popPK model. The 90% PI is the 5th and 95th percentiles of the simulations. The simulated subjects' weights were obtained by bootstrapping from Study P12301 and Study P12302.

(Source: Summary of Clinical Pharmacology, Table 3-1, page 37)

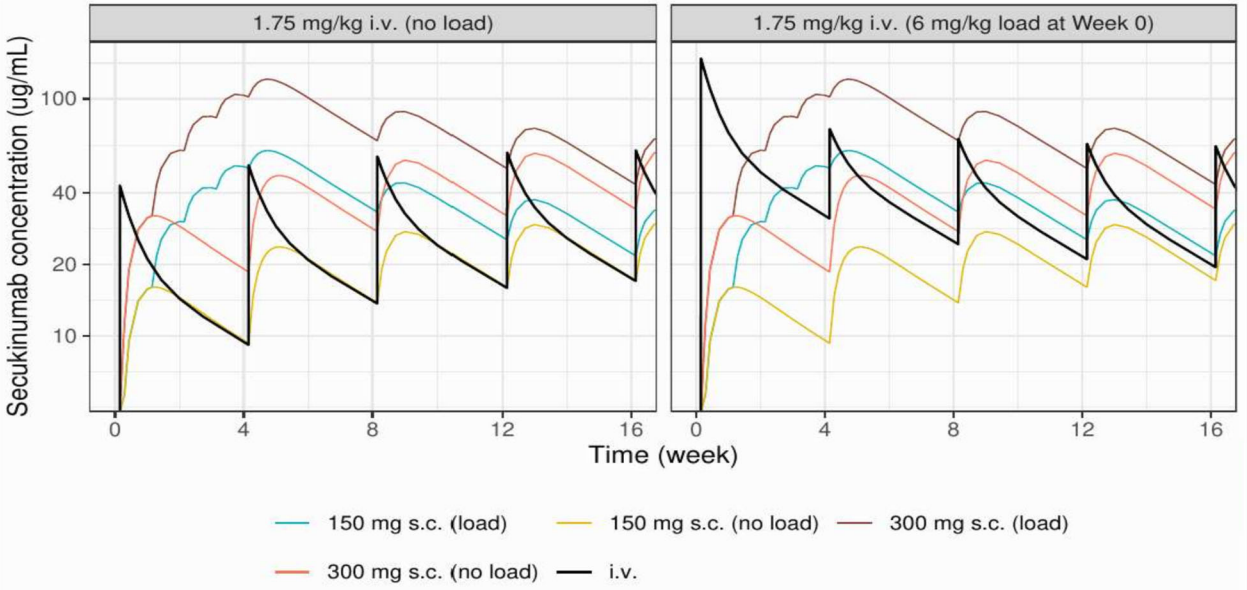
The 6 mg/kg is recomended as a loading dose given that it is predicted to achieve comparable exposures to the approved SC doses with loading and was studied in the two IV Phase III studies (Study P12301 and Study P12302). These two clinical trials conducted with 907 adult subjects

(381 with PsA in one study, and 413 with AS and 113 with nr-axSpA in the other study) evaluated the 6 mg/kg loading dose without a cap/maximum dose and a higher IV maintenance dose (3 mg/kg every 4 weeks) which were higher than the recommended IV dosage. The safety profile during the 16-week placebo-controlled period in these studies using higher dose of secukinumab administered IV was overall similar to the safety profile seen with secukinumab given SC. In addition, 10 mg/kg IV loading doses in the registrational trials of SC secukinumab provide supportive safety data. For instance, in Study F2306, loading doses of 10 mg/kg IV at Weeks 0, 2 and 4 were given to a subject with a body weight of 163 kg (maximum body weight in this study), in a total dose of 4890 mg during the first month of treatment without any impact on new or unexpected safety signals. Therefore, no dose capping of the loading dose is needed.

Maintenance dose without loading dose:
In the initial submission, only the dosing regimen with a single 6 mg/kg loading dose at Week 0 was proposed as it was studied in both Phase 3 IV studies (Study P12301 and Study P12302). During the review, FDA review team asked applicant to conduct simulations which shows direct comparison of proposed IV dosing regimen 1.75 mg/kg q4w without loading dose exposures versus observed PK exposures with 150 mg and 300 mg SC administration with and without loading dose.

In response, the applicant submitted the IR response on Aug 11,2023. The median of the secukinumab concentration time-profiles of patients treated with the 1.75 mg/kg q4w IV regimen with no loading dose and the subcutaneous 150 and 300 mg q4w regimens with and without loading are displayed in the Figure 7 for first 16 weeks.

Figure 7. Median predicted concentration time-profiles (Week 0 to 16) for the 1.75 mg/kg IV maintenance regimen with and without loading, along with the 150 and 300 mg SC regimens with and without loading.

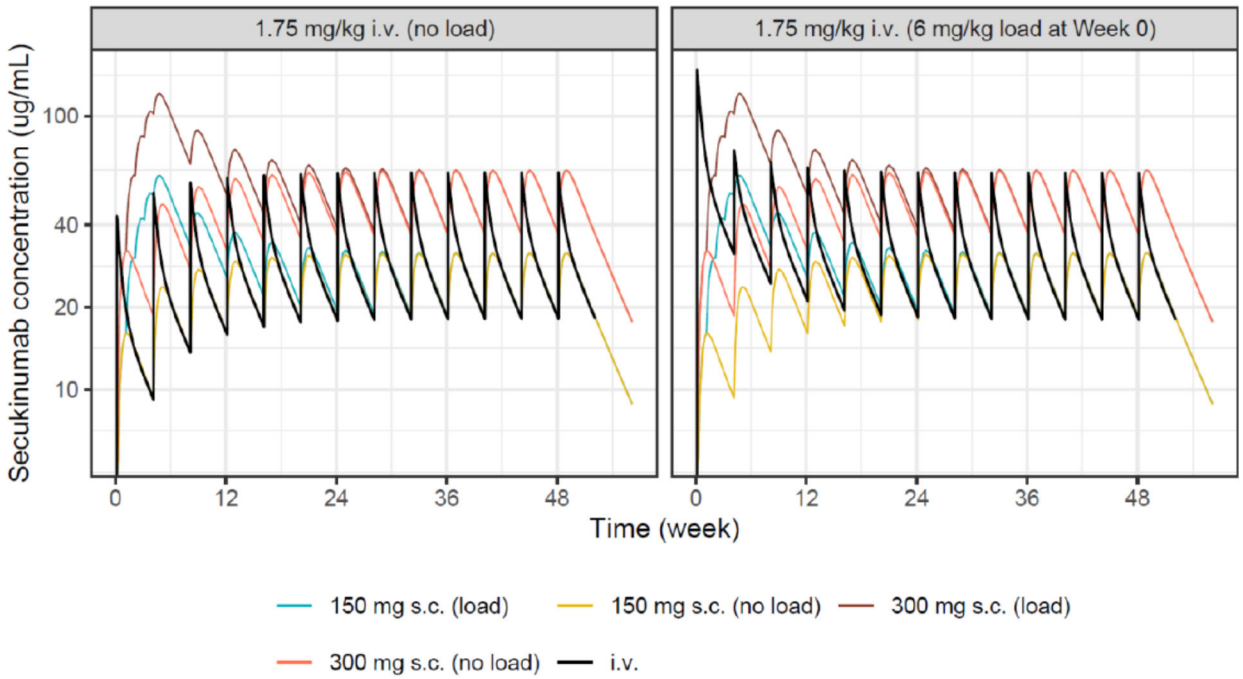


The lines represent the median of the secukinumab concentration time-profiles for two IV and four SC treatments, as predicted from the final popPK model included in SN 0000 for patients with same characteristics (body weight and race) as patients from studies P12301 and P12302.

(Source: Response to Clinical Pharmacology IR dated 8-11-2023, Figure 1-1, page 6)

Similarly, the median of the secukinumab concentration time-profiles of patients treated with the 1.75 mg/kg q4w IV regimen with no loading dose and the subcutaneous 150 and 300 mg q4w regimens with and without loading at steady state are displayed in the Figure 8.

Figure 8. Median predicted concentration time-profiles (Week 0 to 52) for the 1.75 mg/kg IV maintenance regimen with and without loading, along with the 150 and 300 mg SC regimens with and without loading.



The lines represent the median of the secukinumab concentration time-profiles for two IV and four SC treatments, as predicted from the final popPK model included in SN 0000 for patients with same characteristics (body weight and race) as patients from studies P12301 and P12302.

(Source: Response to Clinical Pharmacology IR dated 8-11-2023, Figure 1-3, page 8)

The above figures demonstrate that proposed 1.75 mg/kg q4w dose without loading dose most closely approximates the exposures falling within the range of both approved SC dosing regimens without loading dose (150 and 300 mg). Therefore, efficacy and safety of the SEC SC regimens without loading dose can be extrapolated to the SEC IV regimen without loading dose, and the SEC IV dosing regimen without loading dose is recommended for approval in PsA, AS and nr-axSpA.

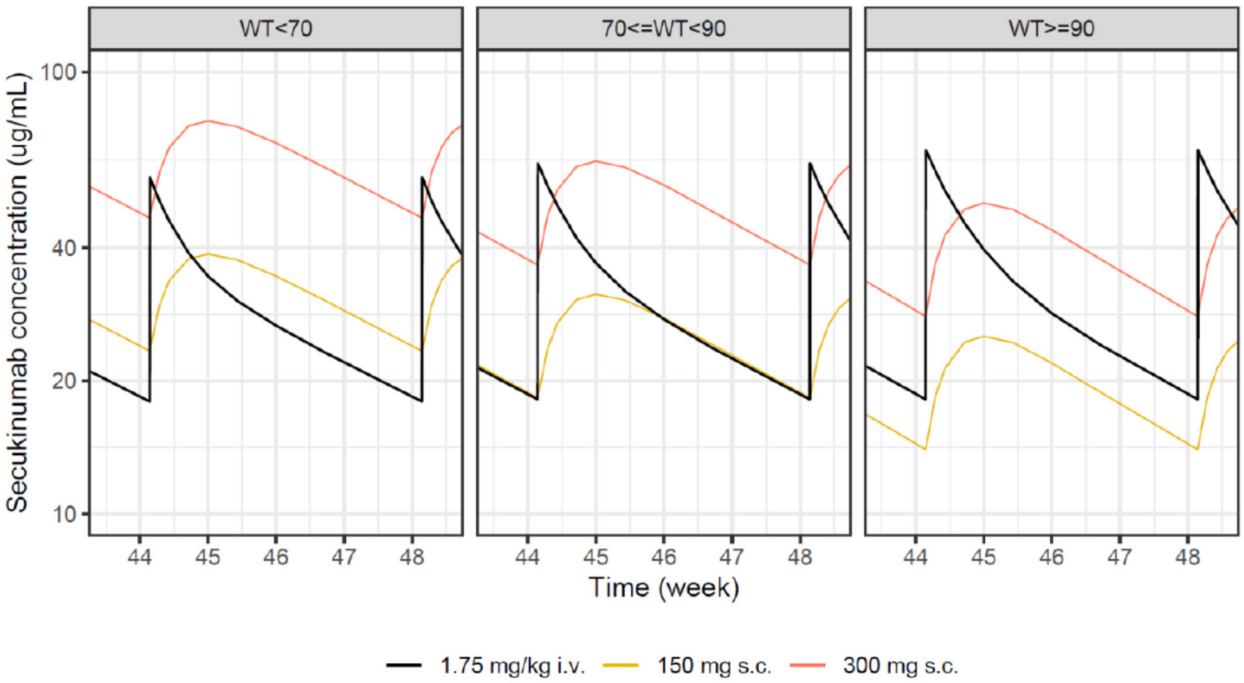
Consideration of the impact of body weight on PK, and Maintenance dose capping

The proposed secukinumab IV dosing regimen is proportional to patient's body weight (1.75 mg/kg q4w), resulting in an increase in Cmax with increasing body weight. In the ≥70 and <90 kg category, the IV regimens achieve similar Cmin,ss levels as the corresponding SC regimens (150 mg q4w SC with and without loading); but slightly lower (23%) in the <70 kg category and slightly higher (29%) in the ≥90 kg category with a large overlap of Cmin distribution between SC and corresponding IV regimens. Of note the higher Cmax,ss with IV dosing in the ≥90 kg subgroup is similar to Cmax,ss following administration of 300 mg SC in the <70 kg subgroup

(Figure 9), and no differential safety profile is expected in patients ≥90 kg with dose capping at 300 mg.

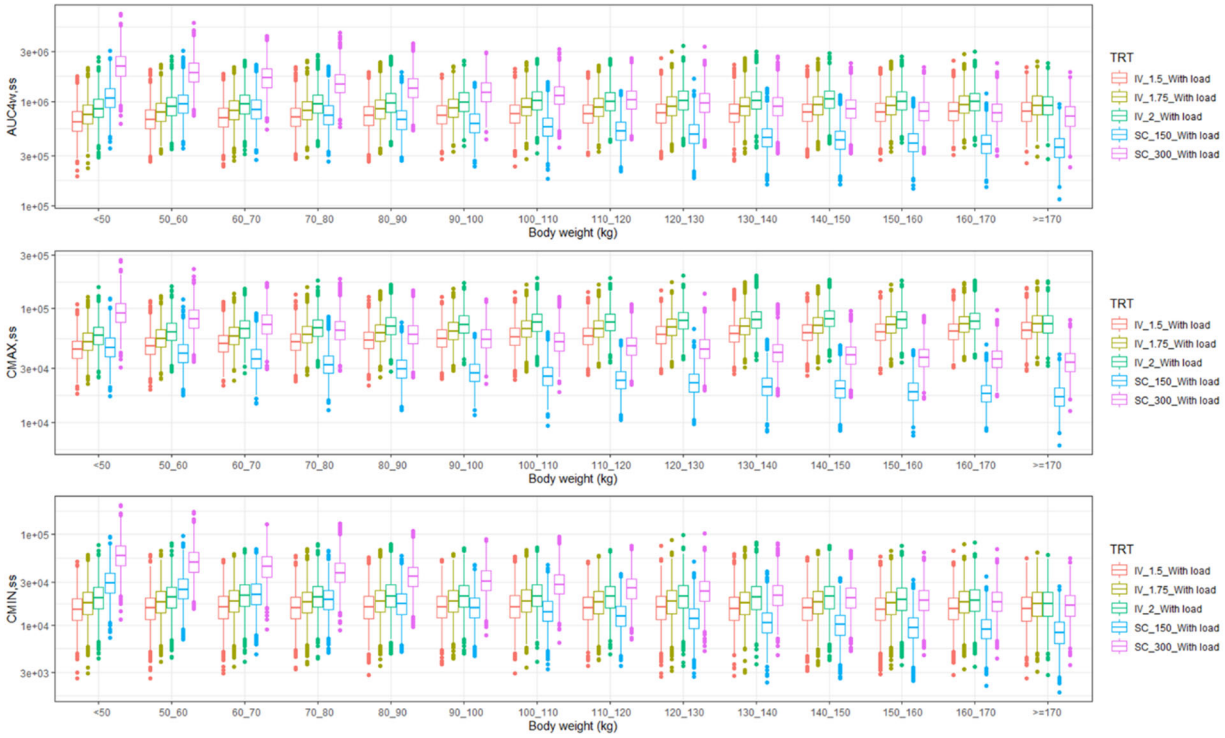
Overall, such findings are expected for any monoclonal antibody that is administered as a body weight-based IV dose versus a flat SC dose. As a benefit of using weight-based dosing, the IV regimens achieve similar Cmin levels across the three presented body weight categories and are predicted to ensure similar therapeutic effects regardless of the body weight (Figure 9). Comparison of secukinumab steady-state exposures under different doses in bodyweight groups is shown in Figure 9.

Figure 9. Median predicted concentration time-profiles (steady state) for the 1.75 mg/kg IV maintenance regimen, along with the 150 and 300 mg SC regimens, by body weight.



WT=Body weight
The lines represent the median of the secukinumab concentration time-profiles for two IV and four SC treatments, as predicted from the final popPK model included in SN 0000 for patients with same characteristics (body weight and race) as patients from studies P12301 and P12302.
(Source: Response to Clinical Pharmacology IR dated 8-11-2023, Figure 2-5, page 18)

Figure 10. Comparison of secukinumab steady-state exposures under different doses in bodyweight groups.



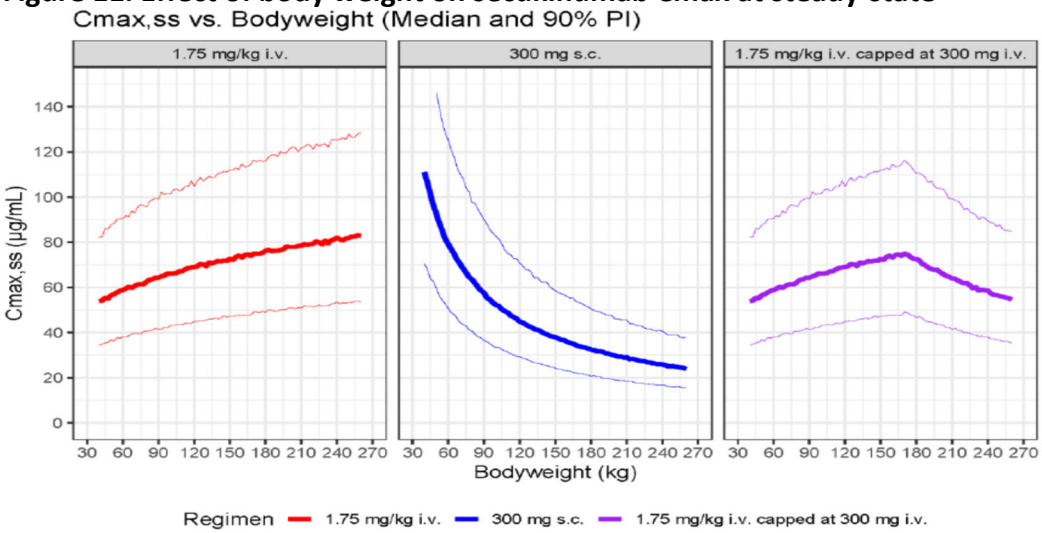
(Source: FDA Analysis, Appendix 16.3.2, Population PK-PD Analysis, Figure 33.)

A maximum limit for the maintenance dose per infusion is considered for subjects with high body weight because the weight-based IV dose led to an increase in steady-state Cmax with increasing body weight (**Figure 11** left panel). This contrasts with the decreasing exposure when body weight increases following administration of the approved 300 mg q4w SC regimen (**Figure 11** middle panel).

In particular, the steady-state Cmax levels achieved by subjects with body weight >170 kg treated with 1.75 mg/kg q4w IV regimen is substantially higher than those achieved if treated with 300 mg q4w SC regimen. To leverage safety information from SEC SC, a maximum IV dose of 300 mg is recommended so that the SC safety data can provide adequate safety coverage. The 6 mg/kg loading dose was studied in the two IV Phase III studies (Study P12301 and Study P12302). The safety profile in these two studies was overall similar to the safety profile seen with secukinumab given SC. Therefore, no dose capping of the loading dose is recommended.

Reviewer's Comments:
In order to reduce the exposure of subjects weighing >170 kg and as recommended by FDA, it is therefore proposed by applicant to cap the maximum IV maintenance dose administered to 300 mg. This results in the median Cmax,ss not exceeding 75 µg/mL in high body weight subjects (Figure 11 right panel) while maintaining efficacy by ensuring that steady-state trough and average concentrations are maintained relatively close to those of the approved 300 mg SC q4w regimens (comparison of middle and right panels in Figure 12 and Figure 13).

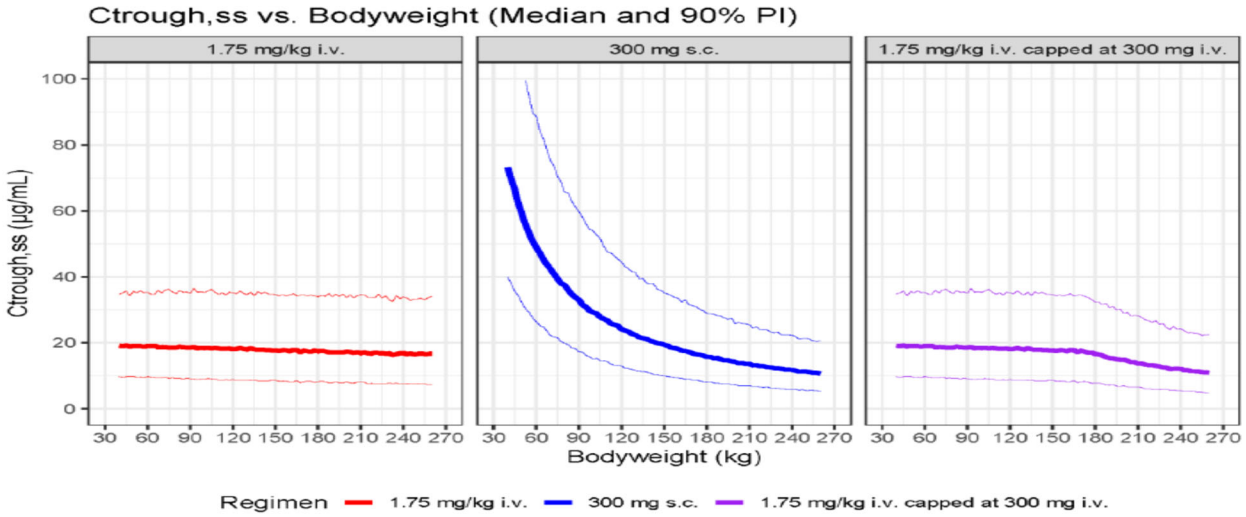
Figure 11. Effect of body weight on secukinumab Cmax at steady-state



The thicker line represents the median and the thinner lines the 5th and 95th percentiles of the simulated secukinumab concentration-time profiles. Simulation obtained from the population PK model for 5000 subjects with specific body weights between 40 and 260 kg at 2.5 kg intervals.

(Source: Summary of Clinical Pharmacology, Figure 3-7, page 39)

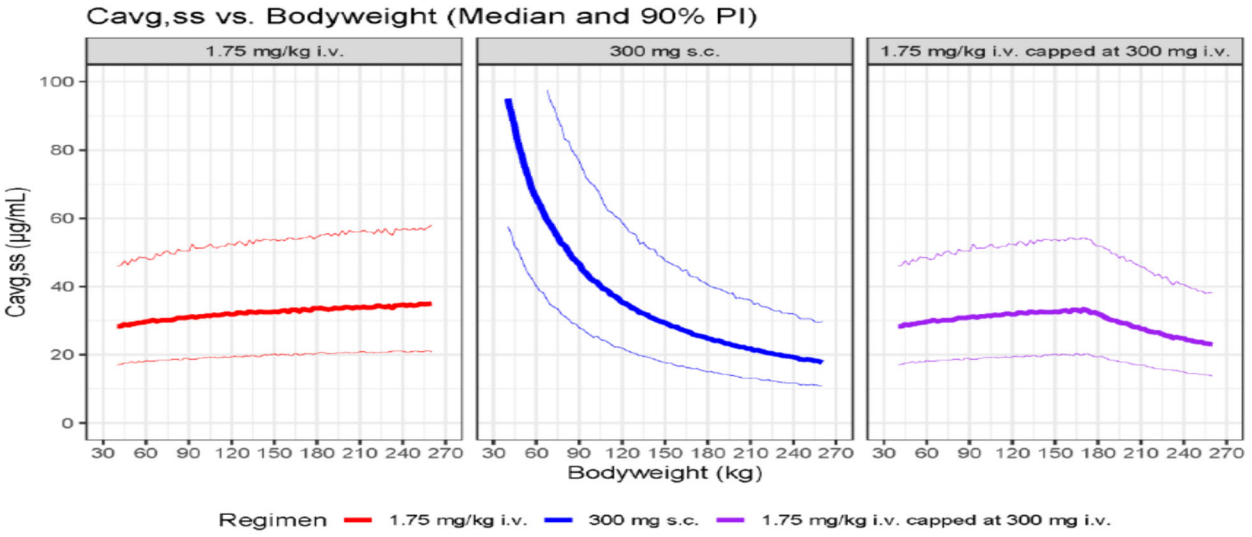
Figure 12. Effect of body weight on trough secukinumab at steady-state.



The thicker line represents the median and the thinner lines the 5th and 95th percentiles of the simulated secukinumab concentration-time profiles. Simulation obtained from the population PK model for 5000 subjects with specific body weights between 40 and 260 kg at 2.5 kg intervals.

(Source: Summary of Clinical Pharmacology, Figure 3-9, page 42)

Figure 13. Effect of body weight on average secukinumab at steady-state.



The thicker line represents the median and the thinner lines the 5th and 95th percentiles of the simulated secukinumab concentration-time profiles. Simulation obtained from the population PK model for 5000 subjects with specific body weights between 40 and 260 kg at 2.5 kg intervals.

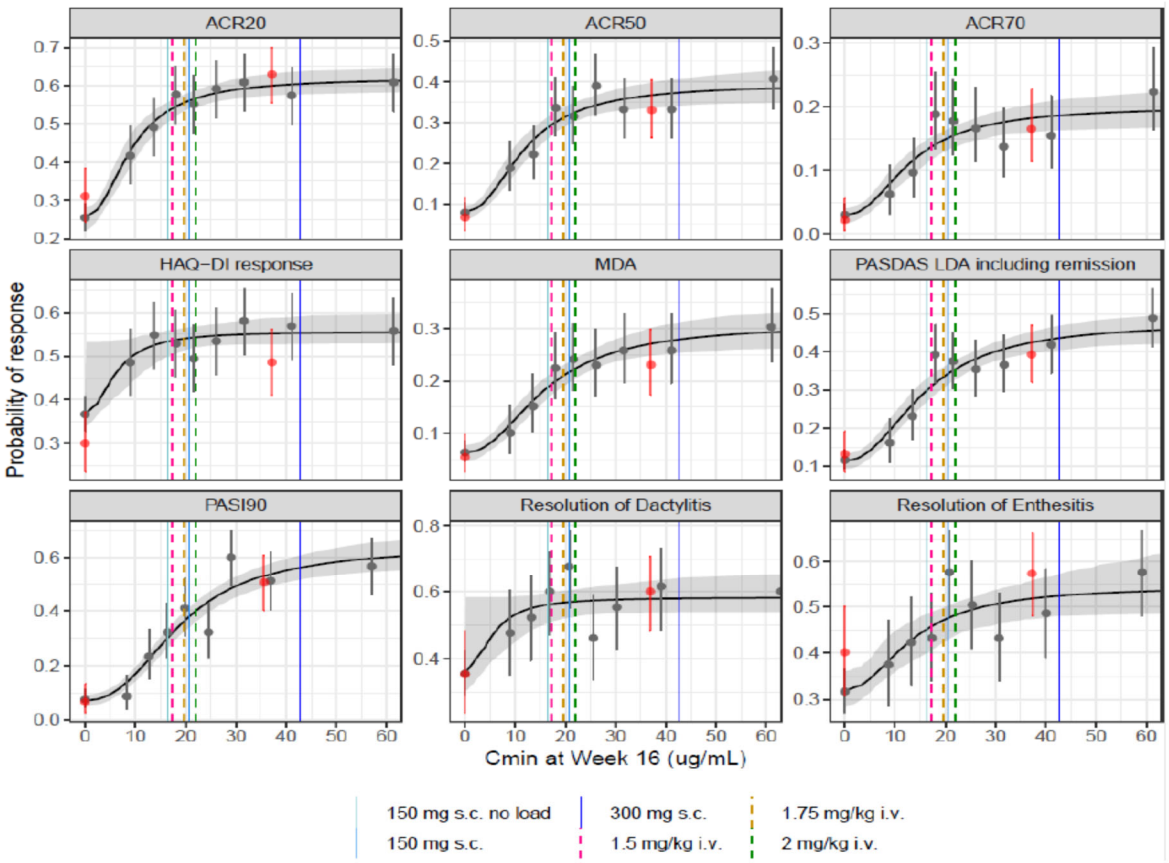
(Source: Summary of Clinical Pharmacology, Figure 3-10, page 43)

Exposure-efficacy response analyses

The exposure-response relationships between secukinumab exposure and the efficacy endpoints were estimated using data from subjects treated with SC regimens in the data pool. Available data from the two Phase III IV studies (P12301 (AS subjects only) and P12302) were used to assess consistency of results with the estimated exposure-response relationships, in order to support the validity of the PK bridging approach. The analyses were performed separately in PsA subjects and in AS subjects. No exposure-efficacy analyses were performed for nr-axSpA subjects because only the dose of 150 mg SC was tested in that indication (Study H2315), thus providing only a narrow exposure range.

The relationship between the efficacy response at Week 16 and the concentration at the same timepoint (Cmin W16) was estimated for the selected efficacy endpoints. Studies using the multi-dose 10 mg/kg IV loading regimen were not included in this analysis to avoid possible influence of the high exposures on efficacy at Week 16. The efficacy of the three IV regimens was predicted by combining the estimated exposure-response relationships with the simulated distribution of secukinumab at Week 16. The results of this analysis are shown in Figure 14 (PsA) and Figure 15 (AS).

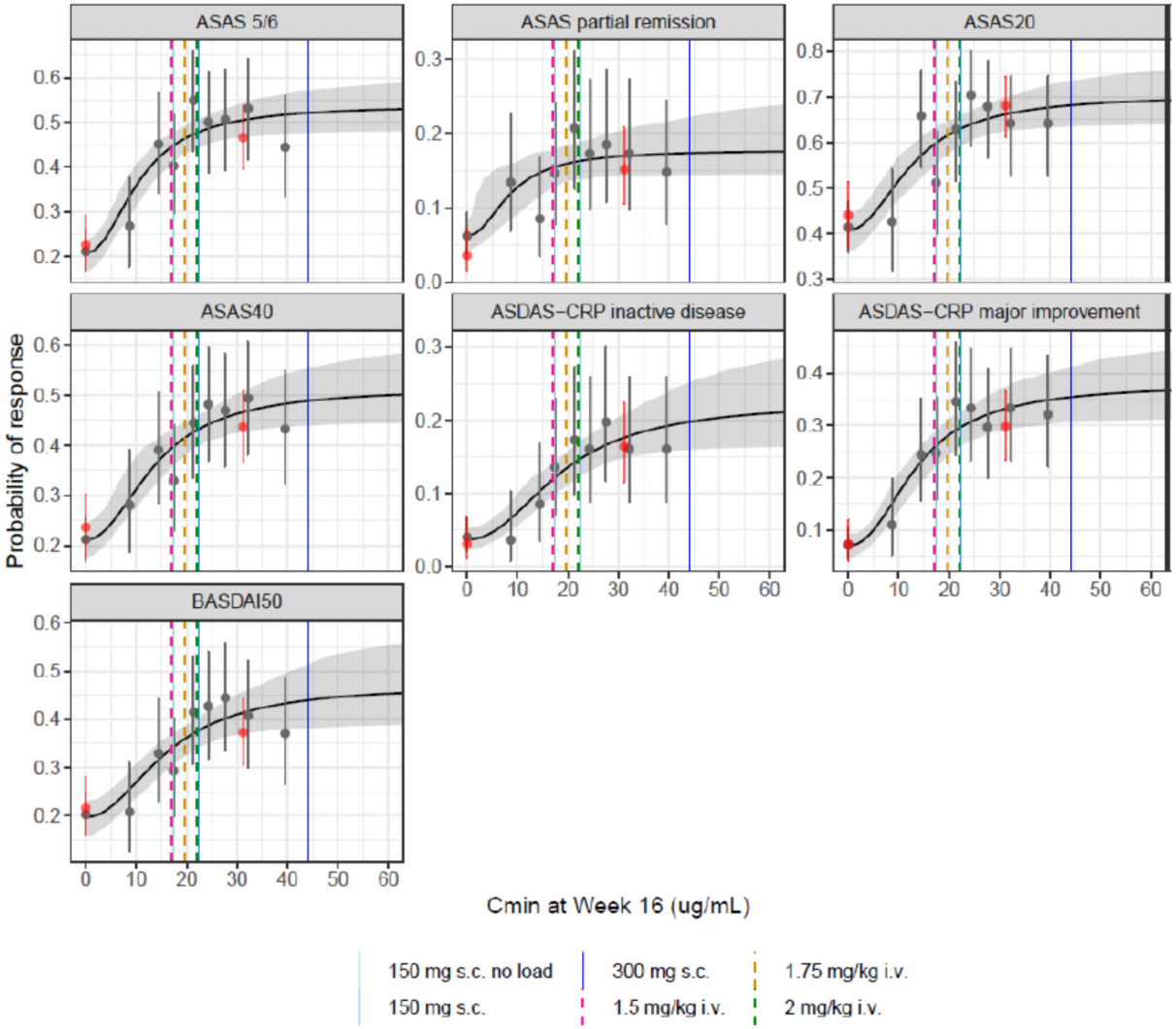
Figure 14. Exposure-response relationship for binary efficacy endpoints at Week 16 – PsA.



The black curves represent the estimated exposure-response relationship at Week 16. The analysis includes subjects randomized to placebo or secukinumab treatment in Study F2312, Study F2318, Study F2336, and Study F2342. This analysis only includes subjects with available Week 16 efficacy data (i.e., no imputation), and the secukinumab concentration was predicted by the final popPK model at the time of the efficacy measurement. The grey ribbons represent the 90% CI for the relationships and were obtained via bootstrapping (250 bootstrap samples). The grey dots represent the proportion of responders in the analysis dataset in equally sized bins of concentration and are plotted versus the median concentration in the bin; the vertical grey error bars represent the corresponding 90% CIs. The red dot and vertical error bar represent the proportion of responders in Study P12302 and the corresponding 90% CI, and are plotted versus the median concentration in that study. The vertical color lines are plotted at the median value of concentration in each of the six regimens indicated in the legend, as obtained from the final popPK model on a sample of 2000 subjects randomly selected from Study P12302.

(Source: Summary of Clinical Pharmacology, Figure 3-13, page 51)

Figure 15. Exposure-response relationship for binary efficacy endpoints at Week 16 –AS



The black curves represent the estimated exposure-response relationship at Week 16. The analysis includes subjects randomized to placebo or secukinumab treatment in Study F2308, Study F2310, and Study F2320. This analysis only includes subjects with available Week 16 efficacy data (i.e., no imputation), and the secukinumab concentration was predicted by the final popPK model (Model pka0003) at the time of the efficacy measurement. The grey ribbons represent the 90% CI for the relationships and were obtained via bootstrapping (250 bootstrap samples). The grey dots represent the proportion of responders in the analysis dataset in equally sized bins of concentration and are plotted versus the median concentration in the bin; the vertical grey error bars represent the corresponding 90% CIs. The red dot and vertical error bar represent the proportion of responders in Study P12301 and its 90% CI, and are plotted versus the median concentration in that study. The vertical color lines are plotted at the median value of concentration in each of the six regimens indicated in the legend, as obtained from the final popPK model on a sample of 2000 subjects randomly selected from Study P12301(AS subjects only).

(Source: Summary of Clinical Pharmacology, Figure 3-14, page 52)

There were small efficacy differences between solid light/medium blue (150 mg without/with load), dashed orange (1.75 mg/kg) and dashed green (2 mg/kg) vertical lines. The observed efficacy data in subjects randomized to placebo and to secukinumab in Study P12301 and Study

P12302 (red dot and red vertical error bar) are consistent with the estimated E-R relationships, which supports the adequacy of the PK bridging strategy used to select the IV regimen.

Exposure-safety response analyses
The exposure-response analyses were conducted to explore the relationship between secukinumab exposure and adverse events (AE) incidence during the first year of treatment, for 6 types of AEs (General infections and infestations, Candida infections, lower respiratory tract infections, hypersensitivity reactions, serious infections and infestations, and all serious or severe AEs) in the range of concentration of the three IV regimens (1.5 mg/kg, 1.75 mg/kg and 2 mg/kg q4w) in the PsA, AS, and nr-axSpA populations. The predicted incidences of most AEs are similar between the proposed IV regimen and approved SC regimens. Slight increase for Candida infections and hypersensitivity reactions were predicted for IV regimen over 150 mg SC regimen.

Hence overall, the PK of the proposed IV regimen (1.75 mg/kg q4w) closely approximates the exposure of the approved SC regimens. This allows for leveraging relevant efficacy and safety information from the currently approved SC dosing regimens. The exposure-response analyses for PsA, AS and nr-axSpA support that both the efficacy and safety of the proposed IV regimen are consistent with the approved SC regimens.

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

No.

No clinically relevant differences were observed for gender, ethnicity, and age (adults > 18 years). No formal studies were conducted to examine the impact of impaired renal function on secukinumab. Hepatic impairment is not expected to influence the metabolism and excretion of secukinumab, and thus, no formal studies were conducted to examine the impact of impaired hepatic function on secukinumab.

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

Food-Drug Interactions:

As secukinumab is administered intravenously, no food effect studies are required and thus have not been conducted.

Drug-Drug Interactions:
No new drug-drug interaction studies have been conducted with secukinumab. No new DDI information was submitted in this BLA submission.

What was the Impact of Immunogenicity on Lebrikizumab Exposure?

The immunogenicity profile of secukinumab for SC administration across indications and over time was extensively characterized throughout its clinical development. Regardless of the indication, SC formulation used, frequency and dose administered, the development of treatment-emergent anti-drug antibody (TE-ADA) and neutralizing antibodies (NAbs) in subjects treated with secukinumab is rare (<1% up to 52 weeks of treatment and up to 5 years in PsO).

A total of 5 Phase 3 clinical studies with IV administration of secukinumab in PsA and axSpA (AS and nr-axSpA) are included in the immunogenicity assessment. Across all secukinumab-exposed subjects evaluated for TE-ADA in the 5 Phase 3 studies, 11 of 1843 subjects showed TE-ADA. This resulted in a TE-ADA incidence of 0.6% (Table 11), which is in line with the secukinumab immunogenicity observed after SC administration (<1%).

Table 11 Number of TE-ADA subjects and TE-ADA incidence across studies.

	P12301	P12302	F2314	F2305	F2306	Total
TE-ADA (n/M) [1]	5/353	0/357	1/217	2/351	3/565	11/1843
TE-ADA incidence (%)	1.4	0.0	0.5	0.6	0.5	0.6
Nab positive (n) [2]	0	0	0	0	1	1

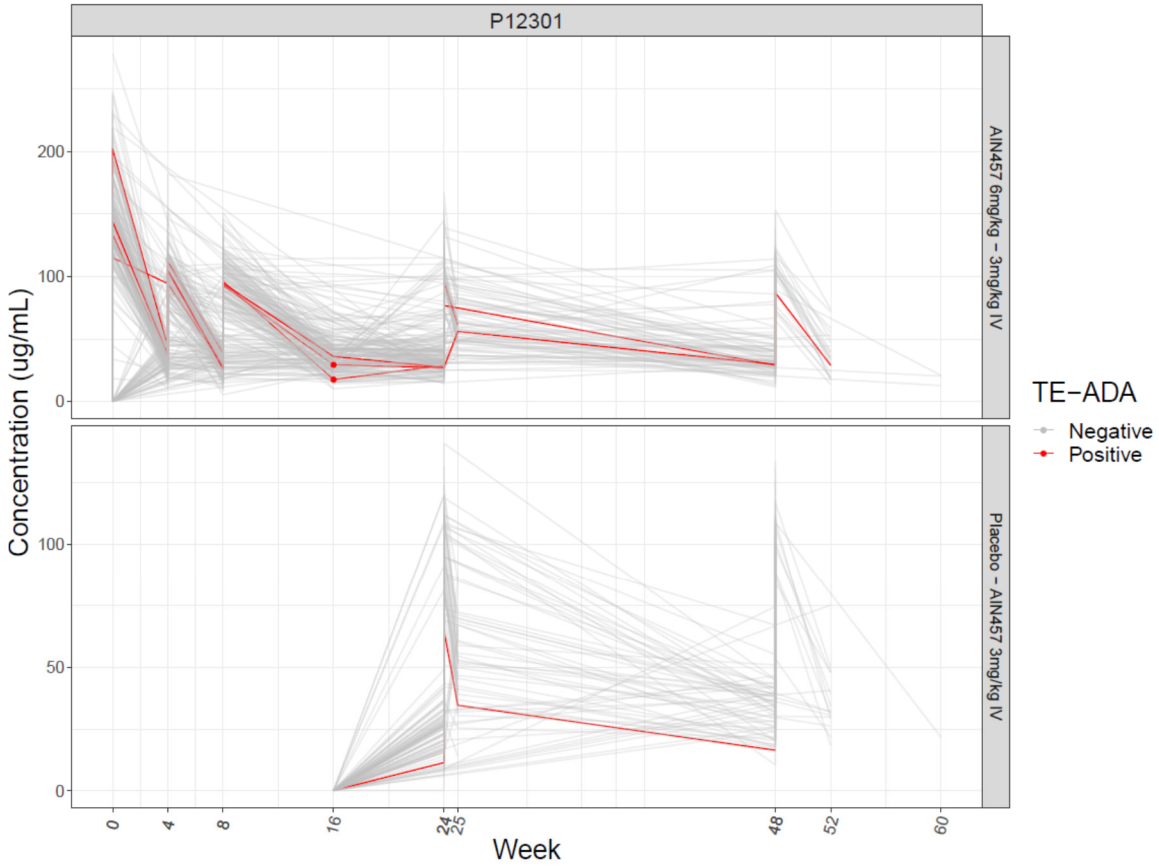
1 M is number of subjects who are ADA-negative at baseline and have at least one post-baseline sample. Subjects who were randomized to placebo and did not switch to secukinumab are not counted in M.
2 Only the number of NAb-positive subjects in the group of subjects with TE-ADA is counted. Samples with "not reportable" status were excluded from the analysis. P12301 Week 16 DBL data was used. All other studies used final DBL data
(Source: Integrated Summary of Immunogenicity, Table 5-3, page 32)

Following Figure 16 shows the PK trajectories in TE-ADA-positive subjects (red lines) compared with ADA-negative subjects (grey lines) in Study P12301 with the loading regimen of 6 mg/kg IV at Week 0 followed by 3 mg/kg IV q4w until Week 48 (last dose).

Reviewer's Comments:
PK and Immunogenicity results as shown in Figure 16 *result from an interim analysis at Week 16 with measurement of all available PK and IG samples beyond Week 16 at the cutoff date of 17-Feb-2022. Therefore, some of the PK and IG results beyond Week 16 are missing. The individual PK trajectories show Cmax at Week 0, Cmax,ss and Cmin,ss at Weeks 4, 24 and 48, and Cmin,ss only at Week 16. Further, concentrations at Week 25, i.e., one week after the dose at Week 24, were collected and plotted. Secukinumab concentrations in the 4 TE-ADA-positive subjects fit into the observed range for all ADA-negative subjects during the treatment period of 52 weeks.*

Overall, it appears that TE-ADA were not associated with altered PK profiles in Study P12301 with a continuous IV regimen. Study P12302 is not discussed in this section since no TE-ADA were detected in this study.

Figure 16 Spaghetti plots of secukinumab trough concentrations vs. time in TEADA- positive subjects and ADA-negative subjects in Study P12301 with a continuous IV regimen.



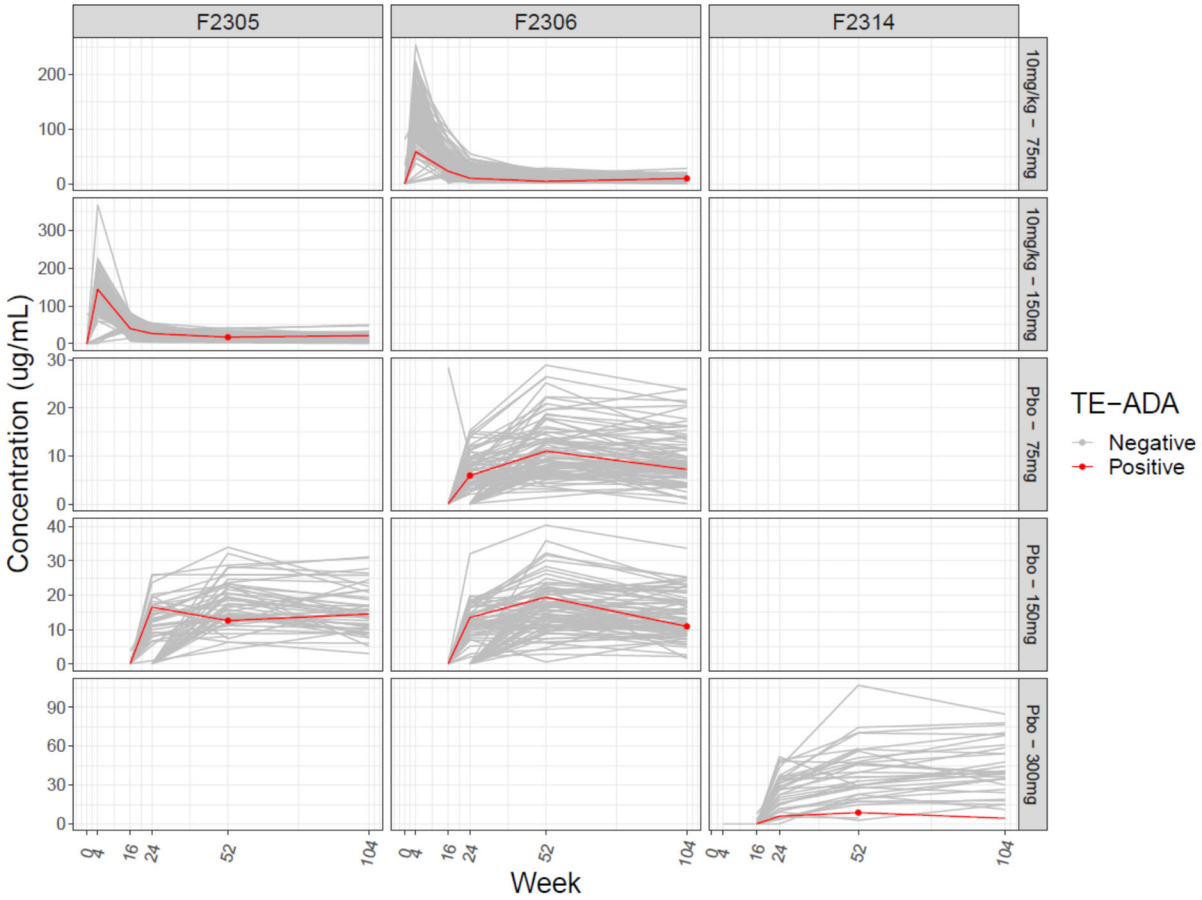
Red closed circles show subjects who are TE-ADA positive at the specific time point and red lines correspond to their trajectory of serum concentrations over time. P12301: PK sampling at Baseline, Week 4, 8, 16, 24, 25, 52, 60; IG sampling at Baseline, Week 16, 52, 60

(Source: Integrated Summary of Immunogenicity, Figure 5-1, page 37.)

Figure 17 shows the PK trajectories in TE-ADA-positive subjects (red lines) compared with ADA-negative subjects (grey lines) in the 3 studies with IV loading regimens of 10 mg/kg at Weeks 0, 2, and 4, followed by SC regimens with q4w dosing intervals (Studies F2314, F2305, and F2306). In these 3 studies, secukinumab concentrations in the 6 TE-ADA positive subjects fit into the observed range for all ADA-negative subjects during the treatment period of 104 weeks. Further, steady-state PK behavior is observed in these 6 subjects from Week 24 onwards. Of note, 4 of 6 subjects were placebo-switchers at Week 16 and did not experience the IV loading regimen, which leaves only 2 subjects with an IV loading regimen being TE-ADA-positive across these 3 studies.

In conclusion, TE-ADA were not associated with altered PK profiles in these Phase III studies with IV loading regimens followed by SC regimens.

Figure 17. Spaghetti plots of secukinumab trough concentrations vs. time in TEADA- positive subjects and ADA-negative subjects in studies with IV loading.



Red closed circles show subjects who are TE-ADA positive at the specific time point and red lines correspond to their PK trajectory of trough concentrations over time. F2305, F2306: PK sampling at Baseline, Week 4, 16, 24, 52, 104; IG sampling at Baseline, Week 24, 52, 104 F2314: PK sampling at Baseline, Week 4, 16, 24, 52, 104; IG sampling at Baseline, Week 16, 24, 52, 104

(Source: Integrated Summary of Immunogenicity, Figure 5-2, page 38.)

No loss of efficacy was observed in any of the subjects who developed TE-ADA. In Study F2314 using LIVI formulation for IV loading doses (10 mg/kg) at Weeks 0, 2 and 4, followed by SC regimen, 1 subject (300 mg secukinumab) with TE-ADA detected at Week 52, but with no NAb, did not achieve an ASAS20 or ASAS40 response at Week 52. However, the subject achieved ASAS20 and ASAS40 responses at all subsequent assessments at Weeks 60, 68, and 76. Thus, this subject was deemed to have not experienced loss of efficacy as per definition.

In Study F2305 using LYO formulation for IV loading doses (10 mg/kg) at Week 0, 2, and 4, followed by SC regimen, 1 subject with TE-ADA experienced an AE possibly related to immunogenicity. It was a non-serious AE of urticaria at Day 549, 26 weeks after the single positive ADA sample. This subject showed no NAbs and no loss of efficacy or PK abnormalities.

Reviewer's Comments:
It is important to acknowledge the limitations of assessing the impact of immunogenicity on clinical outcomes based on descriptive analyses. The TE-ADA-positive and NAb-positive subgroups were very small. Furthermore, the limited serum sampling schedule in the studies precludes any definitive assessment of the timing of ADA relative to PK, efficacy and safety outcomes. Given these limitations, the available evidence does not indicate there were altered PK, efficacy or safety profiles directly attributable to ADA development after IV administration of secukinumab.

In summary, the immunogenicity of secukinumab after IV dosing regimens was investigated in 5 Phase 3 clinical studies in subjects treated with secukinumab for the PsA and axSpA indications, 2 studies using the LIVI formulation with IV loading and IV maintenance regimens, and 3 studies with an IV loading regimen using LIVI or LYO formulations followed by SC maintenance regimens. Overall, the incidence of anti-secukinumab-Abs was low and not considered to have a clinically meaningful impact on PK, efficacy, or safety in subjects treated with secukinumab. Across all 5 clinical studies, the overall incidence of TE-ADA was less than 1% among 1843 TE-ADA-evaluable subjects. NAbs were detected in only 1 of 11 subjects with TE-ADA and did not have a relevant impact on clinical outcomes. Overall, the immunogenicity profile of the IV regimens was broadly comparable with that observed in the clinical Phase III program with SC regimens.

As there is no available immunogenicity data with the proposed dose of SEC IV, we recommend no update in the labeling immunogenicity section.

Are the bioanalytical methods properly validated to measure PK and PD in plasma samples?
A well validated ELISA assays were used for the bioanalytical analysis of secukinumab in serum, with a lower limit of quantification (LLOQ) of 80 ng/mL at (b) (4) and 160 ng/mL at (b) (4) (b) (4) The same ELISA method was used for the measurement of secukinumab serum concentrations as in previous submissions. The additional details of bioanalytical methods are provided in Appendix 16.3 .

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

APPEARS THIS WAY ON ORIGINAL

Table 12: Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support PK AND Safety						
CAIN457P12301 (P12301)	NCT04156620	R, DB, PC, PG, P3 IV Secukinumab to compare efficacy at 16 Weeks and to assess safety and tolerability up to 52 Weeks in active Ankylosing Spondylitis (AS) or non-radiographic axial spondyloarthritis (nr-axSpA)	6 mg/kg IV followed by 3 mg/kg IV Q4W starting at Week 4 (1:1 SEC or PBO) After 16 Weeks, all PBO patients switched to SEC 3 mg/kg IV Q4W	**PK and Safety are the Primary Endpoints for the purposes of this review** Efficacy: ASAS40 response at Week 16, defined as improvement of ≥ 40% and an absolute improvement from baseline of ≥20 units (range 0-100) in ≥ 3 of the following 4 domains: back pain [10 cm visual analogue scale (VAS)], patient global assessment of disease activity (10 cm VAS), physical function (BASFI; range 0-100) and inflammation (mean score of items 5 and 6 of the BASDAI; both 10 cm VAS) without any worsening in the remaining domain	Total Treatment duration of 60 weeks including 16 week DB Treatment Period 1 (**TP1**); 36 week OL Treatment Period 2 (**TP2**); 8 week Safety Follow Up Period	526 264 randomized to receive IV load and Q4W SEC during **TP1** 262 randomized to PBO for **TP1**	Subjects with active axSpA despite current or previous NSAID, DMARD and/or anti Tumor Necrosis Factor (TNF) therapy	United States (25) Belgium (2) Brazil (6) Bulgaria (5) Columbia (6) Czechoslovakia (5) Greece (2) Guatemala (4) India (6) Italy (2) South Korea (4) Malaysia (5) Philippines (4) Poland (5) Russian Federation (12) Sweden (2) Thailand (4) Turkey (3)
CAIN457P12302 (P123012)	NCT04209205	R, DB, PC, PG, P3 IV Secukinumab to compare efficacy at 16 Weeks and to assess safety and tolerability up to 52 Weeks in active Psoriatic Arthritis (PsA)	6 mg/kg IV followed by 3 mg/kg IV Q4W starting at Week 4 (1:1 SEC or PBO) After 16 Weeks, all PBO patients switched to SEC 3 mg/kg IV Q4W	**PK and Safety are the Primary Endpoints for the purposes of this review** Efficacy: ACR50 response at Week 16; The ACR50 is a composite measure defined as both improvement of 50% in the number of tender and number of swollen joints, and a 50% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure [most often Health Assessment Questionnaire (HAQ)], visual analog pain scale, and	Total Treatment duration of 60 weeks including 16 week DB Treatment Period 1 (**TP1**); 36 week OL Treatment Period 2 (**TP2**); 8 week Safety Follow Up Period	381 191 randomized to receive IV load and Q4W SEC during **TP1** 190 randomized to PBO for **TP1**	Subjects with active psoriatic arthritis (PsA) despite current or previous Non-steroidal anti-inflammatory drugs (NSAIDs), Disease-modifying antirheumatic drugs (DMARDs) and/or anti-tumor necrosis factor (TNF) therapy	United States (31) Brazil (2) Bulgaria (5) Columbia (4) Czechoslovakia (4) Greece (2) Guatemala (3) India (4) Malaysia (3) Philippines (4) Poland (5) Russian Federation (7) South Africa (2) Thailand (4) Turkey (1)

Reference ID: 5256774

				erythrocyte sedimentation rate or C-reactive protein (CRP)				
CAIN457H2315 (H2315) Extension Phase	NCT02696031	R, DB, PC, PG, P3 of Secukinumab 150 mg SC in active nr-axSpA up to 2 years with an optional extension phase of either 150 mg or 300 mg SC for up to another 2 years	DURING Extension Phase: At Week 104, subjects receiving SEC 150 mg SC every 4 weeks were given the option to enter an extension phase in which ASAS20 responders were randomized to 150 mg or 300 mg secukinumab by subcutaneous injection every 4 weeks. Treatment was blinded through Week 156.	The purpose of Study CAIN457H2315 was to demonstrate the clinical efficacy, safety and tolerability of two different regimens of secukinumab, 150 mg SC with loading and without loading, compared to placebo in patients with nr-axSpA at Week 16 as well as Week 52. Primary for the Feeder study: ASAS40 at Week 52; Stratification by TNF naïve versus TNF-IR This study also observed the long term efficacy, safety, and tolerability of secukinumab and the evolution of radiographic correlates of inflammation and structural progression based on the MRI and X-ray results up to Week 104. After the core study phase, patients could participate in an optional 16 week randomized dose escalation treatment period, which assessed if a treatment escalation from 150 mg to 300 mg secukinumab was of further benefit to patients, as compared to continuous treatment with 150 mg secukinumab. The long term results up to Week 104 and the results for the dose escalation treatment extension phase are presented for both efficacy and safety in this Final CSR.	Extension Phase Treatment Duration was 52 weeks, followed by a Safety Follow Up Period of at least 8 weeks	294 147 subjects randomized to remain on 150 mg SC Q4W dose 147 subjects randomized to remain on 300 mg SC Q4W dose	At Week 104, subjects who had received 150 mg SC Q4W during the first 2 years of the study were given the option to enter an extension phase in which ASAS20 responders were randomized to 150 mg or 300 mg SC secukinumab	United States (18) Australia (5) Austria (2) Belgium (3) Bulgaria (3) Czechoslovakia (6) France (8) Germany (13) Hungary (6) Israel (4) Italy (5) Japan (6) South Korea (2) Mexico (4) Netherlands (3) Norway (2) Poland (6) Portugal (5) Russian Federation (8) Spain (15) Sweden (3) Switzerland (2) Turkey (1) United Kingdom (9)
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
CAIN457F2306	NCT01392326	A randomized, double-blind, placebo-controlled,	Loading Dose: 10 mg/kg IV (weeks 0, 2, and 4) or PBO, then SC starting at Week 8	Efficacy: ACR20 at Week 24 Safety: Through Week 104	Duration: 104 weeks - Treatment period	606 Groups: 3	Subjects with active psoriatic arthritis who are intolerant	Countries: Argentina, Australia, Belgium,

		multicenter study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the long-term safety, tolerability and efficacy up to 2 years in patients with active psoriatic arthritis.	Maintenance Dose Groups: 1. 75 mg SC Q4W 2. 150 mg SC Q4W 3. Placebo Placebo through Wk 16: if non-responder, then 150 or 75 mg (1:1) SC q4w starting at Wk 16; if placebo responder, go to Wk 24 then 150 or 75 mg (1:1) SC q4w starting at Wk 24		1 of 52 weeks. - Treatment period 2 of 52 weeks. - Safety follow-up: 8 weeks after EOT	1. 202 2. 202 3. 202	to or have had an inadequate response to NSAIDs, DMARDs and / or TNFα inhibitor therapy	Brazil, Bulgaria, Canada, Czech Republic, Germany, Israel, Italy, Philippines, Poland, Romania, Russia, Singapore, Slovakia, Thailand, United Kingdom, United States Start: 08-Sep-2011 End: 08-Apr-2015
CAIN457F2312	NCT01752634	A Phase III randomized, double-blind, placebo-controlled, multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 24 weeks and to assess the long-term efficacy, safety and tolerability up to 5 years in patients with active psoriatic arthritis.	Loading Dose: 75, 150, or 330 mg SC OR PBO at baseline and Weeks 1,2, 3, and 4 Maintenance Dose Groups: 1. 75 mg SC Q4W 2. 150 mg SC Q4W 3. 300 mg SC Q4W 4. PBO SC Q4W Placebo through Wk 16: if non-responder, then 150 or 300 mg (1:1) SC q4w starting at Wk 16; if placebo responder, go to Wk 24 then 150 or 300 mg (1:1) SC q4w starting at Wk 24	Efficacy: ACR20 at Week 24 Safety: Through Week 260	Duration: 52 weeks with up to 260 weeks long-term therapy.	397 Groups: 4 1. 99 2. 100 3. 100 4. 98	Subjects with moderate to severe active PsA despite current or previous NSAIDs, DMARDs and/or TNFα inhibitor therapy	Countries: Australia, Belgium, Canada, Czech Republic, Germany, Poland, Russia, Thailand, United Kingdom, United States Start: 14-Apr-2013 End: 09-Jan-2019
CAIN457F2305	NCT01350804	A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 16 weeks and to assess the long-term safety, tolerability and	Loading Dose: 10 mg/kg IV (weeks 0, 2, and 4) or PBO, then SC starting at Week 8 Maintenance Dose Groups: 1. 75 mg SC Q4W 2. 150 mg SC Q4W 3. Placebo	Efficacy: ASAS 20 at Week 16 Safety: Through Week 104	Duration: 104 weeks - Treatment phase 1: Week 1 to week 52 - Treatment phase 2: Week 56 to week 104 - Follow-up visit: 12 weeks after EOT for	371 Groups: 3 1. 124 2. 125 3. 122	Subjects with moderate to severe AS despite current or previous Non Steroidal Anti-Inflammatory Drugs (NSAIDs), Disease Modifying Anti Rheumatic Drugs (DMARDs) and/or	Countries: Belgium, Bulgaria, Canada, France, Germany, Italy, Mexico, Netherlands, Peru, Russia, Taiwan, Turkey, United Kingdom, United States

Reference ID: 5256774

		efficacy up to 2 years in patients with active Ankylosing Spondylitis	Placebo through Wk 16: if non-responder, then 150 or 75 mg (1:1) SC q4w starting at Wk 16; if placebo responder, go to Wk 24 then 150 or 75 mg (1:1) SC q4w starting at Wk 24		all subjects		TNFα inhibitor therapy	Start: 19-Oct-2011 End: 18-Dec-2014
CAIN457F2310	NCT01649375	A randomized, double-blind, placebo-controlled Phase III multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 16 weeks and to assess the long-term efficacy, safety and tolerability up to 5 years in patients with active Ankylosing Spondylitis	Loading Dose: 75 mg, 150 mg or PBO SC once weekly at baseline and at Weeks 1, 2, 3, and 4 Maintenance Dose Groups: 1. 75 mg SC Q4W 2. 150 mg SC Q4W 3. PBO Placebo through Wk 16: rerandomization to either secukinumab 75 mg or 150 mg SC Q4W	Efficacy: ASAS 20 at Week 16 Safety: Through Week 260	Treatment period 1: 52 weeks Long term treatment: 4 years Follow-up: 8 weeks	219 Groups: 3 1. 73 2. 72 3. 74	Subjects with active moderate-to-severe AS despite current or previous NSAIDs, DMARDs and/or TNFα inhibitor therapy	Countries: Austria, Canada, Czech Republic, Finland, Germany, Italy, Netherlands, Russia, Singapore, Spain, Switzerland, United Kingdom, United States Start: 18-Oct-2012 End: 18-Sep-2018
CAIN457F2314	NCT02008916	A randomized, double-blind, placebo-controlled phase III multicenter study of secukinumab to demonstrate the efficacy at 16 weeks and to assess the long-term safety, tolerability and efficacy up to 3 years in subjects with active Ankylosing Spondylitis	Loading Dose: 10 mg/kg IV (weeks 0, 2, and 4) or PBO, then SC starting at Week 8 Maintenance Dose Groups: 1. 150 mg SC Q4W 2. 300 mg SC Q4W 3. Placebo Placebo through Wk 16; rerandomized to 150 or 300 mg SC Q4W	Efficacy: ASAS 20 at Week 16 Safety: Through Week 156	Duration: 156 weeks	226 Groups: 3 1. 74 2. 76 3. 76	Subjects with moderate to severe AS despite current or previous NSAIDs, DMARDs and/or TNFα inhibitor therapy	Countries: Belgium, Czech Republic, Germany, Greece, Mexico, Portugal, Russia, Spain, United Kingdom, United States Start: 14-Jan-2014 End: 11-Dec-2017
CAIN457H2315	NCT02696031	A randomized, double-blind, placebo-controlled	1. 150 mg SC load at baseline, Weeks 1, 2, and 3 and then Q4W	Efficacy: ASAS40 at Week 16 and at Week 52	Duration: - Core phase: up to Week 104	555	Subjects with active nr-axSpA and with objective signs of	Countries: Australia, Austria, Belgium, Bulgaria,

		multicenter study of secukinumab 150 mg in patients with active nonradiographic axial spondyloarthritis to evaluate the safety, tolerability and efficacy up to 2 years, followed by an optional phase of either 150 mg or 300 mg randomized dose escalation for up to another 2 years.	starting at Week 4 2. 150 mg SC at baseline, PBO at Weeks 1, 2, and 3, 150 mg SC at Week 4 and then Q4W 3. PBO at baseline, Weeks 1, 2, 3 and then Q4W starting at Week 4 PBO non-responders option to switch to OL 150 mg SC Q4W after Week 20		- Treatment extension phase: Week 104 to Week 208 - Follow-up visit: 12 weeks after end of treatment (EOT) for all subjects	Groups Core Phase: 3 1. 185 2. 184 3. 186	inflammation (MRI or CRP) despite treatment with NSAIDs, DMARDs and/or TNFα inhibitor therapy	Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, Norway, Poland, Portugal, Russia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States Start: 29-Apr-2016 End: 11-Mar-2021

7.2. Review Strategy

The efficacy and safety of subcutaneous (SC) secukinumab has been previously established based on reviewed data from studies in active PsA (F2306 and F2312); AS (F2305, F2310, and F2314); and nr-axSpA (H2315 Core Study). These registrational trials are summarized above in Table 12 and, together with the completed studies of intravenous (IV) secukinumab in PsA (P12302) and AS/nr-axSpA (P12301), form the basis for the pharmacokinetic exposure detailed in Section 6 (and Appendix) that support the extrapolation of efficacy from the approved SC to the proposed IV doses in PsA, AS and nr-axSpA.

As summarized in Section 6, following an intravenous administration of 1.75 mg/kg maintenance dose every four weeks, with or without a loading dose of 6 mg/kg at Day 0, the secukinumab concentrations [steady state trough secukinumab concentrations (Cmin,ss), mean secukinumab concentrations (Cavg,ss), and maximum secukinumab concentrations (Cmax,ss)] are estimated to be within the range of the steady state concentrations following subcutaneous administration of 150 mg and 300 mg doses of secukinumab administered every four weeks.

The safety of IV secukinumab in PsA and AS is based on similar pharmacokinetic exposure and extrapolation of the established safety of SC secukinumab in PsA and AS patients.

However, for nr-axSpA, the only approved SC dose is 150 mg. Therefore, additional data is necessary to support the proposed IV maintenance dose of 1.75 mg/kg Q4W, which is estimated to achieve a steady state dose that is between 150 and 300 mg SC doses. This data is provided from two sources—study P12301, in which an IV maintenance dose higher than the proposed dose was studied with placebo-controlled data for nr-axSpA through Week 16; and the extension phase of study H2315, in which 150 mg SC Q4W was compared in a blinded fashion to 300 mg SC Q4W for 52 weeks.

Additional safety data from studies P12301 and P12302 is reviewed as supportive evidence for the proposed IV doses in AS and PsA, respectively.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy of treatment of PsA, AS, and nr-axSpA with IV secukinumab is extrapolated from the completed adequate and well-controlled studies with SC secukinumab, [8] informed by PK-based bridging, as detailed in Section 6. The efficacy results of studies P12301 and P12302 will be only summarized here for completeness as they studied a higher dose than the proposed IV dosing regimen. Additional details on the design and results of studies P12301 and P12302 can be found in an appendix (170; 16.5 Efficacy Results of IV studies P12301 and P12302).

8.1.1. Study CAIN457P12301

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of treatment with intravenous secukinumab (initial dose of 6 mg/kg followed thereafter with 3 mg/kg administered every four weeks starting at Week 4) in subjects with active axSpA.

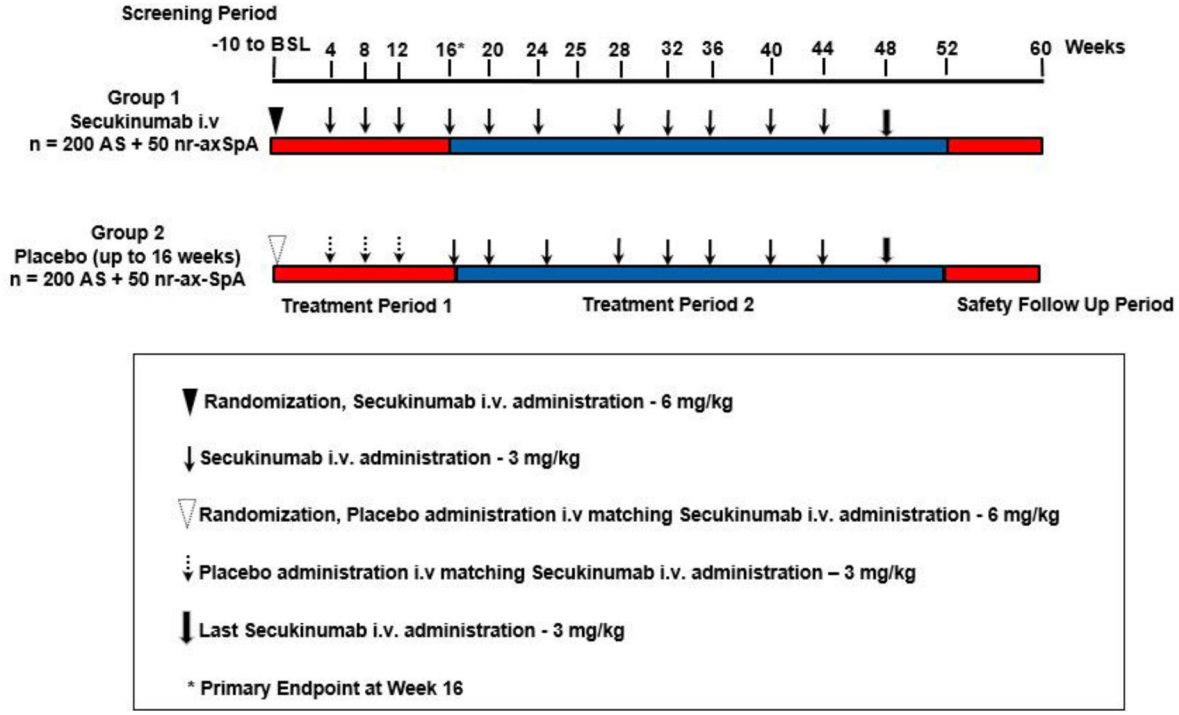
The study population consists of approximately 400 subjects with active AS and approximately 100 subjects with active nr-axSpA, with an inadequate response or intolerance to previous NSAID, conventional DMARD and/or TNF inhibitor therapy. Subjects were randomized to one of the following two treatment groups in a 1:1 ratio, stratified according to disease condition (i.e., AS or nr-axSpA):

- Group 1 (200 AS subjects and 50 nr-axSpA subjects): secukinumab 6 mg/kg IV at BSL, followed by the administration of secukinumab 3 mg/kg IV every four weeks starting at Week 4 through Week 48 (exposure through Week 52).
- Group 2 (200 AS subjects and 50 nr-axSpA subjects): placebo at BSL, Weeks 4, 8, and 12, followed by the administration of secukinumab 3 mg/kg IV at Week 16 and every four weeks through Week 48 (exposure through Week 52).

The design of the trial is shown in the following figure (Figure 18). The current review is based on the CSR week 16 analyses and includes efficacy data up to Week 16 in treatment period 1. The safety data includes information from all visits up to the data cut-off point of 2/17/2022 (data lock point 4/19/2022), when the last enrolled participant completed the Week 16 visit.

[8] FDA-approved secukinumab labeling

Figure 18 Study Design – Study P12301



Source: Figure 9-1 of the Clinical Study Report CAIN457P12301

The study population consisted of male and female subjects aged at minimum 18 years at time of consent, with active axSpA (AS or nr-axSpA). The diagnosis of axSpA fulfilled the ASAS criteria of inflammatory back pain for at least 6 months and onset before 45 years of age. Subjects with AS fulfilled the Modified New York criteria with prior documented radiological evidence and subjects with nr-axSpA fulfilled ASAS classification criteria for axSpA criteria (sacroiliitis on MRI with ≥1 SpA feature OR HLA-B27 is positive with ≥2 SpA features AND objective signs of inflammation at screening evident by either MRI with SI joint inflammation AND/OR hsCRP >ULN) and had no definitive radiographic evidence for AS by Modified New York Criteria. Subjects had to have active disease despite current or previous NSAIDs, DMARDs and/or anti-TNF therapy. Concomitant therapy with MTX (≤25 mg/week) or sulfasalazine (≤3 g/day) was acceptable, if dose and route of administration had been stable for at least 4 weeks prior to the randomization visit.

Subjects fulfilling any of the following key criteria were not eligible for inclusion in this study: subjects with total ankylosis of the spine; chest x-ray or MRI with evidence of ongoing infectious or malignant process obtained within 3 months of screening and evaluated by a qualified physician; subjects taking moderate and high potency opioid analgesics (e.g. methadone, hydromorphone, morphine); any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization; active ongoing inflammatory diseases

other than axSpA that might confound the evaluation of the benefits of secukinumab therapy, including inflammatory bowel disease or uveitis.

The primary efficacy variable was response to treatment according to the ASAS40 criteria at Week 16:

- The ASAS Response Criteria (ASAS40) response is defined as a ≥ 40% improvement and an ≥2 units on a scale of 10 in at least three of the following 4 domains: back pain, patient global assessment of disease activity, physical function (BASFI) and inflammation (mean score of items 5 and 6 of the BASDAI) without any worsening in the remaining domain.

The primary analysis was conducted via logistic regression with treatment and stratification factor (disease condition) as factors and baseline weight as a covariate. Missing data and intercurrent events for ASAS40 response for data up to Week 16 were considered as non-responders from the time they dropped out through Week 16.

8.1.2. **Study Results - P12301**

In total, 526 subjects were randomized in a 1:1 ratio to receive secukinumab 6 mg/kg - 3 mg/kg (n=264) or placebo (n=262). The 97% of randomized subjects in both the treatment groups completed Treatment period 1.

Subject demographics were comparable between treatment groups and consistent with the intended target population (Table 13).

Table 13 Baseline subject demographics (Randomized set)

Demographic Parameters	**Secukinumab IV** (N= 264)	**Placebo** (N= 262)
Sex, n (%)		
Male	165 (62.5)	178 (67.9)
Female	99 (37.5)	84 (32.1)
Age		
Mean years (SD)	39.8 (12.4)	39.1 (11.7)
Median (years)	38	39
Min, max (years)	18 - 78	18 - 79
Age Group, n (%)		
<65 years	253 (95.8)	257 (98.1)
65 - 74 years	8 (3.0)	4 (1.5)
≥ 75 years	3 (1.1)	1 (0.4)
Race, n (%)		
White	180 (68.2)	179 (68.3)
Black or African American	7 (2.7)	6 (2.3)
Asian	59 (22.4)	47 (17.9)
American Indian or Alaska Native	17 (6.4)	25 (9.5)
Multiple	1 (0.4)	5 (1.9)
Ethnicity, n (%)		
Hispanic or Latino	35 (13.3)	44 (16.8)
Not Hispanic or Latino	225 (85.2)	214 (81.7)
Unknown	4 (1.5)	4 (1.5)
BMI (kg/m^2)		
Mean (SD)	26.8 (5.7)	27.0 (5.9)
Median	26.2	25.8
Min - Max	15.8 – 53.8	15.1 – 57.1
Smokers at baseline, n (%)		
No	222 (84.1)	208 (79.4)
Yes	42 (15.9)	54 (20.6)

Source: Statistical Reviewer and Table 10-4 of Clinical Study Report CAIN457P12301

As the primary basis for approval of the proposed IV dosing regimen of 6 mg/kg single loading dose, followed by 1.75 mg/kg every four weeks thereafter with a maximum dose of 300 mg IV is the modeled exposure of secukinumab to match the approved subcutaneous (SC) doses of 150 mg and 300 mg with or without loading, the efficacy results of this study, which has dose of secukinumab 6 mg/kg IV at BSL, followed by the administration of a higher dose of secukinumab, 3 mg/kg IV, every four weeks starting at Week 4, will be considered supportive only. However, there was no concern noted with the primary efficacy results of this trial (Table 14).

Table 14 ASAS40 response using non-responder imputation* at Week 16 (FAS)

Treatment	Responder, n (%) 95% CI	Response rate difference compared to Placebo (95% CI) / P-value
Secukinumab IV N=264	108 (40.9) (34.9, 46.8)	17.9 (10.1, 25.7) <0.0001
Placebo N=262	60 (22.9) (17.9, 28.0)	

* There were 12 subjects (3 on secukinumab and 9 on placebo) who were non-responders due to missing data and 14 subjects (8 on secukinumab and 6 on placebo) who were non-responders due to treatment/study discontinuation.
Source: Statistical Reviewer and Table 14.2-1.1 of Clinical Study Report CAIN457P12301

8.1.3. **Study CAIN457P12302**

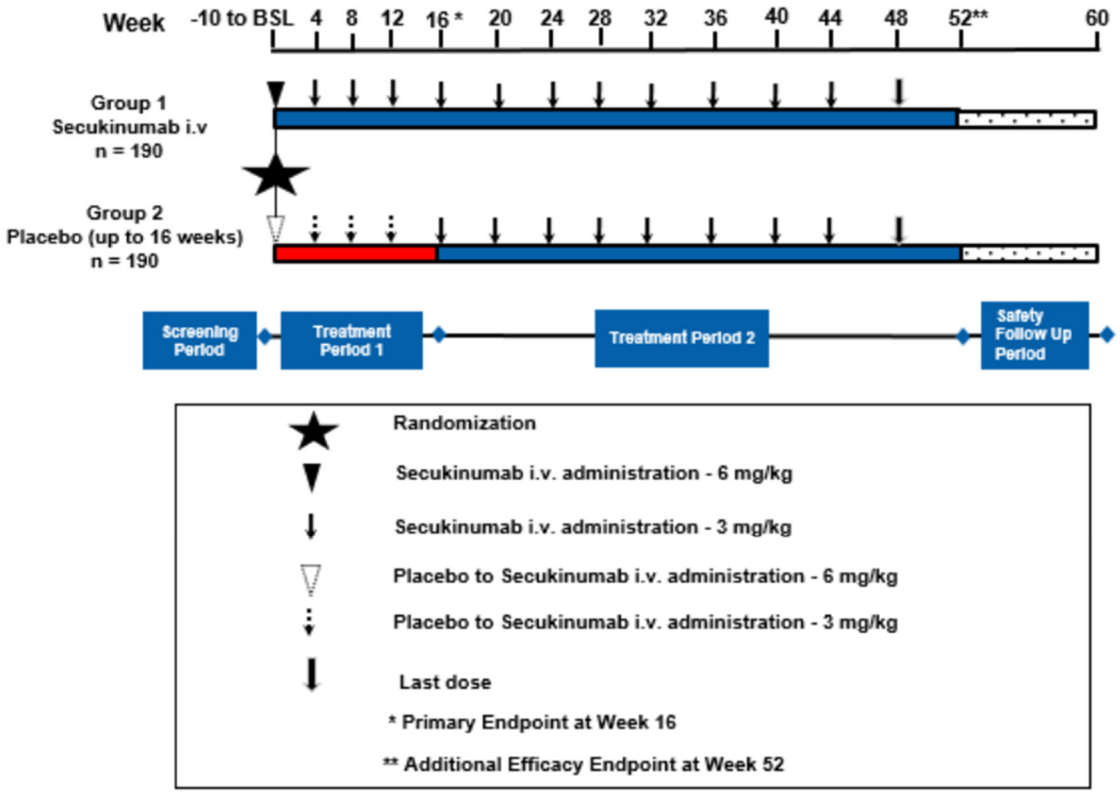
Study 12302 was a randomized, double-blind, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of treatment with intravenous secukinumab in patients with active PsA. The study population comprises 381 subjects with active PsA, despite current or previous NSAID, DMARD and/or TNF inhibitor therapy or intolerance to these therapies. Subjects were randomized to one of the following two treatment groups in a 1:1 ratio:

- Group 1: secukinumab 6 mg/kg IV at baseline, followed by the administration of secukinumab 3 mg/kg IV every four weeks starting at Week 4.

- Group 2: placebo at baseline, Weeks 4, 8, and 12, followed by the administration of secukinumab 3 mg/kg IV every four weeks starting at Week 16.

This study design is outlined in the figure below (Figure 19). The current review is based on the CSR week 16 analyses and includes efficacy data up to Week 16 in treatment period 1 and safety data up to a cut-off of 7/14/2021 when the last enrolled participant completed the Week 16 visit.

Figure 19 Study Design – Study P12302



Source: Figure 9-1 of Clinical Study Report CAIN457P12302

The study population consisted of male and female subjects aged at minimum 18 years at time of consent, with diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who had at Baseline ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each). Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs. Subjects taking corticosteroids must have been on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should have remained on a stable dose up to Week 16.

The main exclusion criteria include chest X-ray or chest MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician; subjects taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine); ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization; any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization; any therapy by intra-articular injections (e.g.

corticosteroid) within 4 weeks before randomization; subjects who had ever received biologic immunomodulating agents, investigational or approved except for those targeting TNF-alpha.

The primary efficacy variable was ACR50 response at Week 16. A subject was defined as an ACR50 responder if, and only if, the following three conditions held:

1. they had a ≥ 50% improvement in the number of tender joints (based on 78 joints)
2. they had a ≥ 50% improvement in the number of swollen joints (based on 76 joints)
3. they had a ≥ 50% improvement in three of the following five domains: Patient's global assessment of disease activity (measured on a VAS scale, 0-100), Physician's global assessment of disease activity (measured on a VAS scale, 0-100), Patient's assessment of PsA pain (measured on a VAS scale, 0-100), Health Assessment Questionnaire – Disability Index (HAQ-DI®) score, Acute phase reactant (hsCRP or ESR)

The primary endpoint was evaluated using a logistic regression with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate. Missing data for ACR50 response were handled using a non-responder imputation.

8.1.4. **Study Results – P12302**

In total, 381 subjects were randomized 1:1 to receive secukinumab (n=191) or placebo (n=190). The majority of randomized subjects in both the secukinumab (186/191; 97.4%) and placebo (183/190; 96.3%) groups completed Treatment period 1 (until 16 weeks). The remaining 12 subjects discontinued during Treatment period 1.

Subject demographics were comparable between treatment groups and consistent with the intended target population as specified in the inclusion criteria (Table 15).

Table 15 Baseline subject demographics (Randomized set – Study P12302)

Demographic Parameters	**Secukinumab IV** (N= 191)	**Placebo** (N= 190)
Sex, n (%)		
Male	87 (45.6)	85 (44.7)
Female	104 (54.5)	105 (55.3)
Age		
Mean years (SD)	47.5 (13.5)	48.1 (13.7)
Median (years)	47	48
Min, max (years)	20 - 81	19 - 76
Age Group, n (%)		
<65 years	170 (89.0)	165 (86.8)
65 - 74 years	17 (8.9)	24 (12.6)
≥ 75 years	4 (2.1)	1 (0.5)

Race, n (%)		
White	148 (77.5)	153 (80.5)
Black or African American	5 (2.6)	1 (0.5)
Asian	25 (13.1)	26 (13.7)
American Indian or Alaska Native	10 (5.2)	9 (4.7)
More than one race	3 (1.6)	1 (0.5)
Ethnicity, n (%)		
Hispanic or Latino	34 (17.8)	25 (13.2)
Not Hispanic or Latino	155 (81.2)	163 (85.8)
Unknown	2 (1.0)	2 (1.1)
BMI (kg/m^2)		
Mean (SD)	29.7 (6.8)	30.0 (7.4)
Median	28.9	28.7
Min - Max	16.1 – 58.3	16.9 – 59.8
Smokers at baseline, n (%)		
No	165 (86.4)	158 (83.2)
Yes	26 (13.6)	32 (16.8)

Source: Statistical Reviewer and Table 10-3 of Clinical Study Report CAIN457P12302

As mentioned earlier in the review, the primary basis for approval of the proposed IV dosing regimen of 6 mg/kg single loading dose, followed by 1.75 mg/kg every four weeks thereafter with a maximum dose of 300 mg IV is the modeled exposure of SEC to match the approved subcutaneous (SC) doses of 150 mg and 300 mg with or without loading. Hence the efficacy results of this study, which has dose of secukinumab 6 mg/kg IV at baseline, followed by the administration of a higher dose of secukinumab, 3 mg/kg IV, every four weeks starting at Week 4, will be considered supportive only. However, there was no concern noted with the primary efficacy results of this trial (Table 16).

Table 16 ACR50 response using non-responder imputation* at Week 16 (FAS)

Treatment	Responder, n (%) 95% CI	Response rate difference compared to Placebo (95% CI) / P-value
Secukinumab IV N=191	60 (31.4) (24.8, 37.9)	25.0 (17.6, 32.4) <0.0001
Placebo N=190	12 (6.3) (2.9, 9.8)	

* There were 13 subjects (5 on secukinumab and 8 on placebo) who were non-responders due to missing data and 10 subjects (5 on secukinumab and 5 on placebo) who were non-responders due to treatment/study discontinuation.
Source: Statistical Reviewer and Table 14.2-1.1 of Clinical Study Report CAIN457P12302

8.1.5. Integrated Assessment of Effectiveness

Efficacy of secukinumab SC for the treatment of AS, nr-axSpA, and PsA has already been established as reflected in the current label. The SC efficacy studies are briefly summarized as follows.

The applicant submitted the results from two phase 3 randomized, double- blind, placebo-controlled clinical trials, CAIN457F2306 and CAIN457F2312, to support the efficacy of secukinumab for the treatment of PsA. The two studies were similarly designed in nearly all study design features (eligibility criteria, study schedule, primary efficacy outcome variable and analysis, secondary and exploratory efficacy outcome measures and analyses), with the exception of the choice of subcutaneous (SC) or intravenous (IV) loading and the addition of 300 mg SC dosing regimen in F2312. The subjects in F2306 were randomized in 1:1:1 ratio to one of the three treatment groups: secukinumab IV (10mg/kg) loading at BSL, Weeks 2 and 4 followed by secukinumab 75 mg SC at Week 8 and Q4W , secukinumab IV (10 mg/kg) loading at BSL, Weeks 2 and 4 followed by 150 mg at Week 8 and Q4W, or placebo IV followed by placebo SC at the same intervals. The subjects in F2312 were randomized to one of four treatment groups: secukinumab SC loading at BSL, Weeks 1, 2, 3 and 4 followed by 75 mg SC Q4W , secukinumab SC loading at BSL, Weeks 1, 2, 3 and 4 followed by 150 mg Q4W,

secukinumab 300 mg loading at BSL, Weeks 1, 2, 3 and 4 followed by 300 mg SC dosing Q4W, or placebo SC loading followed by placebo SC, The primary efficacy endpoint was the American College of Rheumatology 20 (ACR20) response at Week 24 in both studies.

The efficacy data from Study F2306 provided statistical evidence of efficacy for the secukinumab 75 mg and 150 mg doses for treatment of PsA based on ACR20, the primary endpoint, and all the key secondary endpoints, including PASI75, PASI90, DAS28-CRP, SF-36 PCS, HAQ-DI, ACR50, mTSS, dactylitis, and enthesitis. The efficacy data from Study F2312 provided statistical evidence of efficacy for the secukinumab 150 mg and 300 mg doses based on the primary endpoint of ACR20 response and most of the key secondary endpoints.

The applicant submitted the results from two phase 3 randomized, double- blind, placebo-controlled clinical trials, CAIN457F2305 and CAIN457F2310, to support the efficacy of secukinumab for the treatment of AS. The two studies were similarly designed in nearly all study design features (eligibility criteria, study schedule, primary efficacy outcome variable and analysis, secondary and exploratory efficacy outcome measures and analyses), with the exception of choice of placebo escape and subcutaneous (SC) loading for study F2305 or intravenous (IV) loading for study F2310. Subject were randomized to one of three treatment groups in 1:1:1 ratio to one of the three treatment groups: secukinumab 75 mg, secukinumab 150 mg, or placebo. The primary efficacy endpoint was the American College of Rheumatology 20 (ACR20) response at Week 16 in both studies.

The efficacy data from Study F2305 provided statistical evidence of efficacy for the secukinumab 75 mg and 150 mg doses for treatment of AS based on ASAS20, the primary endpoint, and all the key secondary endpoints, including ASAS40, hsCRP, ASAS5/6, BASDAI, SF-36 PCS, ASQoL, and ASAS partial remission. The efficacy data from Study F2310 provided statistical evidence of efficacy for the secukinumab 150 mg dose based on the primary endpoint of ASAS20 response and most of the key secondary endpoints.

The applicant submitted the data from a single study, CAIN457H2315, to support the efficacy of secukinumab in treating patients with nr-axSpA. This was a phase 3, randomized multicenter, double-blind, placebo-controlled study with 555 patients with nr-axSpA. Patients were randomized equally to one of 3 treatment groups: secukinumab 150 mg Load, secukinumab 150 mg No Load, or placebo.

Based on the predefined primary endpoint, ASAS40 response at Week 52, secukinumab was statistically significantly superior over placebo. This analysis used a composite estimand where patients that discontinued treatment or switch over to OL rescue or SOC at Week 20 were considered non-responders. To address concerns of potential bias induced in the analyses at Week 52 that the observed trend could have been driven by the high proportion of patients who had initiated OL secukinumab by Week 52, efficacy findings comparing secukinumab 150

mg to placebo at Week 16 were conducted. At Week 16 use of OL secukinumab was not allowed and missing data was minimal. Results indicated that regardless of loading dose or not, there was a significant treatment effect in favor of secukinumab with respect to the primary endpoint, ASAS40 response rate, as well as the individual components that make up the ASAS instrument. This was also supported by the analysis of the key secondary endpoints.

In the current submission, the applicant submitted data from the Week 16 primary analyses of IV studies with 3 mg/kg maintenance dose, CAIN457P12301 and CAIN457P12302, to assess the consistency of results with the estimated exposure-response relationships, in order to support the validity of the PK-bridging approach. Study P12301 was a randomized, double-blind, placebo-controlled, parallel group, phase III multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Ankylosing Spondylitis or non-radiographic axial SpondyloArthritis. Study P12302 was a randomized, double-blind, placebo-controlled, parallel group, phase III multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Psoriatic Arthritis.

The ASAS Response Criteria (ASAS40) response was defined as the primary efficacy endpoint in study P12301. The study demonstrated statistically significantly higher ASAS40 response rate in the secukinumab IV group than the placebo group. The ACR response (ACR50) was defined as the primary efficacy endpoint in study P12302. The study demonstrated statistically significantly higher ACR50 response rate in the secukinumab IV group than the placebo group.

In both studies P12301 and P12302, secukinumab 6 mg/kg-3 mg/kg was shown to be superior to placebo at Week 16 for all endpoints in the pre-defined statistical testing hierarchy. Both studies met all secondary efficacy endpoints listed in the Study Endpoints section.

In summary, the efficacy analyses from Studies P12301 and P12302 have provided supportive evidence of effectiveness on better ASAS40 response for AS and nr-axSpA patients and better ACR50 response for PsA patients respectively in the secukinumab IV group compared with the placebo group.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary safety assessment for PsA, AS, and nr-axSpA are based on PK/Exposure-matched extrapolation from the approved maintenance SC doses of 150 and 300 mg Q4W as described in section 6. The safety of IV secukinumab in PsA, AS, and nr-axSpA is based on similar pharmacokinetic exposure and extrapolation of the established safety of SC secukinumab in PsA, AS, and nr-axSpA patients. As the only approved maintenance SC dose for nr-axSpA is 150 mg, additional safety data in nr-axSpA subjects for IV secukinumab (study P12301) and for a 300

mg SC maintenance dose (extension study H2315) are provided to support the proposed IV maintenance dose of 1.75 mg/kg Q4W in nr-axSpA.

Known safety risks of secukinumab, as communicated in Warnings and Precautions in the USPI, include Infections (including Serious infections), Hypersensitivity Reactions (including cases of Anaphylaxis and urticaria), Inflammatory Bowel Disease (including exacerbations and new cases), Eczematous Eruptions, and higher risk of Immunization with live vaccines. For Infections, higher rates of common infections, such as nasopharyngitis, upper respiratory infection, and mucocutaneous infections with candida were observed in clinical trials with secukinumab compared with placebo. The most common adverse reactions occurring in clinical trials of secukinumab have included nasopharyngitis, diarrhea, and upper respiratory infection.

8.2.2. Review of the Safety Database

Overall Exposure

The primary safety assessment for PsA, AS, and nr-axSpA are based on PK/Exposure-matched extrapolation from the approved maintenance SC doses of 150 and 300 mg Q4W. However, for nr-axSpA, the only approved SC dose is 150 mg. Therefore, additional data is provided to support the proposed IV maintenance dose of 1.75 mg/kg Q4W in nr-axSpA. The additional data supporting the safety of the proposed IV dosing regimen in nr-AxSpA is summarized below.

Additional sources of safety for nr-axSpA are being summarized to support the approval of the IV route of administration in nr-axSpA. First, safety data from studies P12301 and P12302, in which IV doses higher than the proposed IV dose were studied in patients with AS/nr-axSpA and PsA, respectively. Second, a placebo-controlled long-term extension of study H2315 provides comparative safety data for the 300 mg dose vs 150 mg dose of SC secukinumab in nr-axSpA.

Both P12301 and P12302 were randomized, double-blind, placebo-controlled, parallel group studies to compare efficacy and safety of secukinumab versus placebo (PBO) for an IV regimen of 6 mg/kg IV single loading dose followed by 3 mg/kg IV every 4 weeks (Q4W), i.e. a maintenance dose higher than the proposed maintenance dose of 1.75 mg/kg IV Q4W. Both studies included a 16 week placebo controlled period (Treatment Period 1; TP1), followed by a 36 week period during which all subjects received open label IV secukinumab 3 mg/kg Q4W (Treatment Period 2; TP2), followed by an 8 week safety Follow Up period (FUP). Safety data from studies P12301 and P12302 also is reviewed as additional supportive evidence for the proposed IV doses in AS and PsA, respectively.

H2315 was a randomized, double-blind, placebo-controlled, parallel group study of secukinumab 150 mg in active nr-axSpA up to two years with an optional extension phase of either 150 mg or 300 mg SC for up to another 2 years. At Week 104, subjects were given the option to enter an extension phase in which clinical responders were randomized to 150 mg or

300 mg SC SEC. This extension period provides active-comparator controlled safety data for the 300 mg SC SEC dose compared to the approved dose of 150 mg SC SEC for nr-axSpA.

Adequacy of the safety database:

The safety database to support the approval of the proposed IV regimen in PsA and AS is adequate and is primarily based on the registrational trials for approval of SC secukinumab in PsA and AS. The registrational trials provided safety data for SC secukinumab in a database of over 1,000 patients for PsA, over 800 patients for AS, and over 550 patients for nr-axSpA.

The safety database to support the approval of the proposed IV regimen in nr-axSpA is adequate and is based on both the registrational trial for approval of SC secukinumab in nr-axSpA as well as the data from the higher IV dose studied in nr-axSpA in study P12301 and the comparative data for 300 mg SC secukinumab studied in the long-term extension of study H2315.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no issues regarding data integrity and submission quality. Safety data are presented based on the final clinical study reports for studies P12301, P12301, and H2315. Safety data for secukinumab treated patients compared to PBO during the 16-week placebo-controlled period in studies P12301 and P12302 are presented as frequencies, while 52-week safety data, which includes open-label data beyond week 16 are presented as exposure-adjusted incidence rates (per 100 patient-years) to account for the different exposure periods for PBO and secukinumab. The 52-week safety data for subcutaneous secukinumab 300 mg Q4W compared to 150 mg Q4W is presented both as raw frequencies and also as exposure-adjusted incidence rates.

Categorization of Adverse Events

All safety evaluations were conducted and reported according to Good Clinical Practice guidelines with data collected for AEs, clinical laboratory test results, and vital signs. Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries and predefined lists of preferred terms (PTs) were developed by the Applicant and used to analyze the data for safety events.

Routine Clinical Tests

Routine clinical tests that were performed in studies P12301, P12302 and H2315. The tests performed were adequate to evaluate for secukinumab associated adverse events and were adequate to assess patients with nr-axSpA.

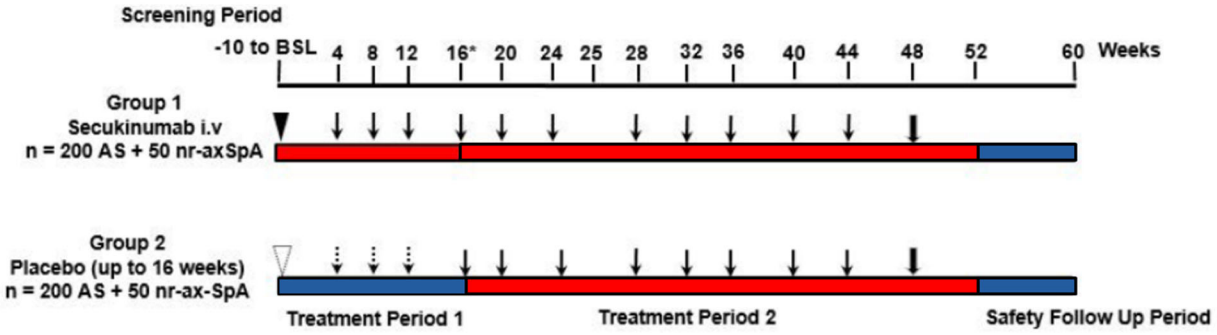
8.2.4. **Safety Results**

Studies of IV secukinumab—P12301 and P12302

Both P12301 and P12302 were randomized, double-blind, placebo-controlled, parallel group studies to compare efficacy and safety of secukinumab versus placebo (PBO) for an IV regimen of 6 mg/kg IV single loading dose followed by 3 mg/kg IV every 4 weeks (Q4W), i.e. a maintenance dose higher than the proposed maintenance dose of 1.75 mg/kg IV Q4W. Both studies included a 16 week placebo controlled period (Treatment Period 1; TP1), followed by a 36 week period during which all subjects received open label IV secukinumab 3 mg/kg Q4W (Treatment Period 2; TP2), followed by an 8 week safety Follow Up period to detect any adverse events due to exposure up to and including Week 52.

The following (Figure 20) is the overall schema for both studies P12301 and P12302:

Figure 20: Study Schema for studies P12301 and P12302



Source: P12301 and P12302 CSR Study Schemata

The database lock for study P12301 at Week 16 occurred on February 17, 2022; the 120 Day Safety Update included data up to Week 60 for serious adverse events (SAE) only. The DBL for study P12302 at Week 16 occurred on July 14, 2021; the 120 Day Safety Update included data through Week 52 for serious adverse events (SAE) only.

In study P12301, a total 526 adult subjects were randomized to receive either intravenous secukinumab (SEC IV) or intravenous placebo (PBO IV), of which the ratio of patients with AS to nr-axSpA was approximately 4:1. Specifically, 208 AS and 56 nr-axSpA patients were randomized to receive SEC IV; 205 AS and 56 nr-axSpA patients were randomized to receive PBO IV. The majority of subjects completed the 16-week placebo-controlled period (PCP)—82.6% of subjects randomized to IV secukinumab and 88.1% randomized to placebo.

In study P12302, a total of 381 adult subjects with active PsA were randomized to receive either SEC IV (191 patients) or PBO IV (190 patients). The majority of subjects completed the 16-week

placebo-controlled period (PCP)—74.3% of subjects randomized to IV secukinumab and 84.7% randomized to placebo.

The Following Safety Sections are focused specifically on the patients in Study P12301 with a diagnosis of nr-axSpA:

In study P12301 during the 16-week placebo-controlled period (PCP), a total of 112 subjects with active nr-axSpA were randomized to receive either IV placebo (PBO IV) or an IV regimen of secukinumab (SEC IV) or a single loading dose of 6mg/kg IV followed by a maintenance dose of 3 mg/kg IV every 4 weeks. A summary of all adverse events during the PCP are shown in Table 17.

Table 17: Summary of Adverse Events in nr-axSpA patients during the PCP of study P12301

Description	Secukinumab IV N=56 n (%)	PBO N=56 n (%)
Number with any AE	27 (48.2)	28 (50.0)
Number with Serious or Other Significant Events		
Death	0 (0.0)	0 (0.0)
SAE	3 (5.4)	0 (0.0)
Discontinuation due to AE	3 (5.4)	0 (0.0)

Source: Study P12301 CSR

After the 16-week PCP, all patients received the IV secukinumab maintenance dose of 3 mg/kg Q4W. A summary of the Entire Treatment Period (ETP) comprising the entire 52 weeks of treatment is shown in Table 18.

Table 18: Summary of Adverse Events in nr-axSpA patients during the ETP of study P12301

Description	Secukinumab IV N=109 n (EAIR)	PBO N=56 n (EAIR)
Number with any AE	73 (143.0)	28 (226.7)

Number with Serious or Other Significant Events		
Death	1	0
SAE	9 (9.6)	0 (0.0)
Discontinuation due to an AE	5 (4.3)	0 (0.0)

Source: Study P12301 CSR

Deaths nr-axSpA in Study P12301

There were no deaths during the 16-week PCP.

During the 52-week ETP, one death occurred in a nr-axSpA patient randomized to IV secukinumab during the PCP and who continued receiving Q4W maintenance IV secukinumab infusions through Week 32. The death was attributed to a myocardial infarction and occurred in a 69 yo woman with a known history of hypertension and tobacco use.

Serious Adverse Events nr-axSpA in Study P12301

The three SAEs that occurred during the PCP period in nr-axSpA patients receiving IV secukinumab were one case each of anemia, seminoma, and asthma. While no SAEs occurred in the PBO arm in nr-axSpA patients during the PCP, the results should be interpreted with caution due to the small sample sized. For comparison in AS patients in study P12301, there were 4 SAEs (1.9%) in 208 AS patients randomized to receive IV secukinumab and 3 SAEs (1.5%) in 205 AS patients randomized to receive placebo during the 16-week PCP.

6 additional SAEs occurred in nr-axSpA patients treated with IV secukinumab between weeks 16 and 52 (includes both patients originally randomized to IV secukinumab and originally randomized to PBO). The additional SAEs were one infection, 2 GI disorders (1 abdominal pain and 1 Colitis), one drug hypersensitivity, and two cardiac disorders (both Myocardial Infarctions). The EAIR for total SAEs over the entire treatment period for nr-axSpA patients in study P12301 was 9.6 per 100 PYs, however the total number of nr-axSpA patients was small and the results should be interpreted with caution. For comparison, for the ETP, in AS patients there were 23 SAEs (EAIR = 5.9) in IV secukinumab-treated patients and 3 SAEs (EAIR = 4.8) in PBO-treated patients.

Dropouts and/or Discontinuations Due to Adverse Effects nr-axSpA in Study P12301

Adverse events leading to discontinuation due to AE during the PCP in nr-axSpA patients treated with IV secukinumab were once case each of hypersensitivity, ALT increased, and

anemia. The two additional events leading to discontinuation due to AE beyond the 16-week PCP were atopic dermatitis and Crohn's disease.

Treatment Emergent Adverse Events and Adverse Reactions nr-axSpA in Study P12301

During the 16-week PCP, the overall rate of TEAEs was similar between nr-axSpA patients treated with IV secukinumab (27/56; 48.2%) and IV placebo (28/56; 50.0%). The most common TEAEs occurring in nr-axSpA subjects during the PCP in study P12301 are summarized in Table 19. Rates for SOC and preferred term were also balanced between the two arms, including GI disorders (8.9% vs 7.1%), Infections and Infestations (25.0% vs 23.2%), and lab abnormalities (3.6% vs 3.6%) for IV secukinumab and PBO arms, respectively. Review of each SOC by PT does not reveal major disparities (>2%) between AS and nr-axSpA, and placebo; the exception were 2 hypersensitivity events reported in the nr-axSpA subgroup though none of these events were reported as SAEs and were not a serious or anaphylactic allergic reaction.

Table 19: Common TEAEs (≥ 1%) by SOC and PT Occurring During the Placebo-Controlled Period (PCP) in Study P12301 in Subjects with nr-axSpA

SOC PT	SEC IV N=56 n (%)	PBO IV N=56 n (%)
Any TEAE	27 (48.2)	28 (50.0)
Gastrointestinal disorders	5 (8.9)	4 (7.1)
Immune system disorders Drug Hypersensitivity	2 (3.6)	0 (0.0)
Infections and infestations	14 (25.0)	13 (23.2)
COVID-19	2 (3.6)	2 (3.6)
Nasopharyngitis	1 (1.8)	3 (5.4)
Upper respiratory infection	1 (1.8)	2 (3.6)
Investigations (lab abnormalities)	2 (3.6)	2 (3.6)
Musculoskeletal and connective tissue disorders	1 (1.8)	3 (5.4)
Nervous system disorders	0 (0.0)	2 (3.6)

Respiratory, thoracic and mediastinal disorders	4 (7.1)	3 (5.4)
Skin and subcutaneous disorders	3 (5.4)	3 (5.4)

Source: Study P12301 CSR

For the entire treatment period, in the nr-axSpA population, the EAIR rates for secukinumab and placebo respectively were 143.0 (73 events in 109 subjects) vs 226.7 (28 events in 56 subjects). The most common TEAEs occurring in nr-axSpA subjects during the ETP in study P1301 are summarized in Table 20. For nr-axSpA, increased EAIRs compared placebo were observed for some infectious events like COVID-19 (19.2 per 100 PYs in nr-axSpA vs. 11.5 per 100 PYs in placebo) and UTI (5.3 per 100 PYs in nr-axSpA vs. 0 per 100 PYs in placebo). Similarly, for drug hypersensitivity, higher rates were observed in the nr-axSpA subgroup (4.2 per 100 PYs in nr-axSpA vs. 0 per 100 PYs in placebo). Inflammatory bowel disease (IBD) cases were infrequent (one Crohn's disease patient in secukinumab vs 0 in placebo).

Table 20: Common TEAEs (EAIR ≥4) by PT Occurring During the Entire Treatment Period (ETP) in Study P12301 in Subjects with nr-axSpA

PT	SEC IV N=109 n (EAIR) (95% CI)	PBO IV N=56 n (EAIR) (95% CI)
Any TEAE	73 (143.0) (112.1, 179.9)	28 (226.7) (150.6, 327.6)
COVID-19	17 (19.2) (11.2, 30.7)	2 (11.5) (1.4, 41.7)
Nasopharyngitis	9 (9.7) (4.4, 18.4)	3 (17.0) (3.5, 49.8)
Arthralgia	6 (6.4) (2.3, 13.9)	0 (0.0) (0.0, 20.8)
Diarrhea	5 (5.3) (1.7, 12.5)	1 (5.8) (0.1, 32.2)
Headache	5 (5.3) (1.7, 12.3)	1 (5.8) (0.1, 32.1)
Sinusitis	5 (5.3) (1.7, 12.3)	4 (23.0) (6.3, 58.9)
Urinary tract infection	5 (5.3) (1.7, 12.4)	0 (0.0) (0.0, 20.8)
Drug Hypersensitivity	4 (4.2) (1.1, 10.8)	0 (0.0) (0.0, 20.8)

Upper respiratory infection	4 (4.2) (1.2, 10.8)	2 (11.6) (1.4, 41.9)

Source: Study P12301 CSR

Comparison of 300 mg to 150 mg subcutaneous secukinumab in nr-axSpA—Study H2315

H2315 was a randomized, double-blind, placebo-controlled, parallel group study of secukinumab 150 mg in active nr-axSpA up to two years with an optional extension phase of either 150 mg or 300 mg SC for up to another 2 years. At Week 104, subjects were given the option to enter an extension phase in which clinical responders were randomized to 150 mg or 300 mg SC SEC. This extension period provides active-comparator controlled safety data for the 300 mg SC SEC dose compared to the approved dose of 150 mg SC SEC for nr-axSpA.

In the extension phase of study H2315, 294 subjects were rerandomized at a 1:1 ratio (147 in each arm) to either continue 150 mg SC SEC or 300 mg SC SEC every 4 weeks. Adverse events were recorded for this blinded, comparator-arm controlled extension phase for the period from Week 104 through Week 156.

The overall exposure to 150 mg or 300 mg was similar during the extension phase of study H2315, with ~75% of subjects receiving Q4W SC secukinumab for 44 weeks (11 injections) in both treatment arms and ~50% of subjects receiving Q4W SC secukinumab for 52 weeks (13 injections) in both treatment arms.

There were no deaths reported during the extension phase of study H2315. SAEs were numerically higher in the 150 mg arm (8, 5.5%) compared to the 300 mg arm (6, 4.1%). The most common SAEs in the 150 mg group were in the Infections and Infestations SOC (2, 1.4%) and Musculoskeletal and connective tissue disorders SOC (2, 1.4%) and the most common SAEs in the 300 mg group were in the Gastrointestinal disorders SOC (3, 2.0%).

A summary of TEAEs is provided in the following table (Table 21).Treatment-emergent AEs in the period from Week 104 up to Week 156 were generally balanced for both treatment groups—76 (52.1%) and 77 (52.4%) patients in the secukinumab 150 mg and 300 mg groups, respectively. In both groups, by SOC, the most commonly reported AEs were from the Infections and Infestations SOC, with a somewhat lower rate reported in the secukinumab 150 mg arm (38, 26.0%) than in the 300 mg arm (46, 31.3%). Nasopharyngitis and upper respiratory infections were the most commonly reported TEAEs by PT overall in both treatment groups—12 (8.2%) in the 150 mg arm and 17 (11.6%) in the 300 mg arm for nasopharyngitis; 6 (4.1%) in the 150 mg arm and 9 (6.1%) in the 300 mg arm. There was some variability in the dose-response for TEAEs as GI disorders, Investigations (lab abnormalities), Musculoskeletal and connective tissue disorders, Nervous system disorders, Psychiatric disorders, and Respiratory thoracic and mediastinal disorders all occurred at a higher rate in the lower dose 150 mg group than the higher dose 300 mg group, while Infections and Infestations, General disorders and

administration site conditions, and Skin and subcutaneous tissue disorders all occurred at a higher rate in the higher dose 300 mg group than the lower dose 150 mg group.

Table 21: Summary of TEAEs for 150 and 300 mg SC SEC for the Blinded Extension Phase of Study H2315

Description SOC	Secukinumab SC 150 mg N=147	Secukinumab SC 300 mg N=147
	n (%)	n (%)
Number with any AE	76 (52.1%)	77 (52.4%)
Infections & Infestations	38 (26.0%)	46 (31.3%)
Gastrointestinal disorders	17 (11.6%)	10 (6.8%)
General disorders and administration site conditions	4 (2.7%)	6 (4.1%)
Investigations (lab abnormalities)	7 (4.8%)	6 (4.1%)
Musculoskeletal and connective tissue disorders	15 (10.3%)	9 (6.1%)
Nervous system disorders	8 (5.5%)	6 (4.1%)
Psychiatric disorders	4 (2.7%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	7 (4.8%)	3 (2.0%)
Skin and subcutaneous tissue disorders	2 (1.4%)	6 (4.1%)

Source: Study H2315 CSR

8.2.5. **Analysis of Submission-Specific Safety Issues (focus on nr-axSpA in context)**

Certain adverse events of special interest observed during the placebo-controlled periods of registrational studies of secukinumab in PsA, AS and nr-axSpA all occurred at higher frequency in secukinumab-treated patients than placebo-treated patients. These are hypersensitivity, infections, neutropenia and inflammatory bowel disease. The rates of these secukinumab-associated adverse events in patients with nr-axSpA are compared between studies of IV and SC secukinumab and also compared to AS patients in study P12301 for additional context.

1. Hypersensitivity: There were similar incidences reported for Hypersensitivity (SMQ narrow search) in nr-axSpA subjects in the PCP of study P12301 (7.1%) and in the 300 mg group (3.4%) in the H2315 extension study. There were no recorded cases of hypersensitivity in the placebo arm for study P12301. One case of preferred term (PT) hypersensitivity in the nr-axSpA group in study P12301 was a mild event at the Week 16 infusion, which was considered related to study treatment by the investigator and resolved the same day with treatment. The subject remained in the study. There are 7 reported cases with PT of hypersensitivity in the Entire Treatment Period of Study P12301. Four cases of PT hypersensitivity occurred after Week 16; three cases were in nr-axSpA (2 moderate & 1 mild) and one case in AS (mild). There were no cases of anaphylactic reactions during the Entire Treatment Period.

2. Infections: During the Placebo-controlled Period, Infections and infestations (SOC) AEs were reported in 14 subjects (25.0%) in the secukinumab group and 13 subjects (23.2%) in the placebo group in the nr-axSpA population of Study P12301; 37 (17.8%) subjects in the secukinumab group and 31 (15.1%) subjects in the placebo group in the AS population of Study P12301. This is compared to 26.0% and 31.3% in 150 mg and 300 mg groups, respectively, in the extension phase of study H2315. During the Entire Treatment Period for the nr-axSpA population, there was no relevant difference in the EAIR for AEs in the SOC Infections and infestations for IV secukinumab in Study P12301 and SC secukinumab in Study H2315 (82.7 vs 76.1).

3. Neutropenia: During the Placebo-controlled Period in Study P12301, the majority of newly occurring or worsening from baseline laboratory abnormalities in hematology parameters were CTCAE Grade 1 or 2. Grade 1 and 2 abnormalities in neutrophils were more frequent in the secukinumab group: Grade 1, 22/258 (8.5%) and 6/261 (2.3%) respectively, compared to 3/254 (1.2%) and 4/258 (1.6%), respectively, in the placebo group. One subject (0.4%) in each treatment group developed Grade 3 abnormalities in neutrophils. The EAIR for AEs of Neutropenia (PT) was low and similar in secukinumab groups in Study P12301 and H2315 (2.1 and 0 in the AS and nr-axSpA populations respectively, compared to 0.5 in secukinumab in Study H2315) during the Entire Treatment Period.

4. Inflammatory Bowel Disease (IBD): During the Placebo-controlled Period, AEs of Crohn's disease, Ulcerative Colitis, or Inflammatory bowel disease (PT) were reported at low rates: Colitis ulcerative, 0.5 % (1 case) in the AS population in Study P12301; 0 cases in the nr-axSpA population in Study P12301. No IBD cases occurred in the placebo arms of studies P12301. During the Entire Treatment Period, EAIRs for AEs of Crohn's disease, Ulcerative colitis, or Inflammatory bowel disease (PT) were low and similar in the secukinumab groups in study P12301 and H2315. For Crohn's Disease, there was 1 case in the nr-axSpA group in study P12301 compared to 3 cases in the AS. For Ulcerative Colitis, there were 0 cases in the nr-axSpA group in study P12301 compared to 2 cases in the AS group. In the extension phase of study H2315, there were no cases of Ulcerative Colitis; there was one case each of Crohn's Colitis in the 150 mg and 300 mg arms.

Additional Supportive Safety Information from Studies P12301/P12302

In study P12301, a total 526 adult subjects were randomized to receive either intravenous secukinumab (SEC IV) or intravenous placebo (PBO IV), of which the ratio of patients with AS to nr-axSpA was approximately 4:1. Specifically, 208 AS and 56 nr-axSpA patients were randomized to receive SEC IV; 205 AS and 56 nr-axSpA patients were randomized to receive PBO IV. The IV secukinumab dosing regimen was a baseline loading dose of 6m/kg, followed by 3.0 mg/kg every four weeks. The maintenance IV dose in studies P12301 and P12302 is higher than the proposed maintenance IV dose of 1.75 mg/kg Q4W.

In study P12302, a total of 381 adult subjects with active PsA were randomized to receive either SEC IV (191 patients) or PBO IV (190 patients); the placebo-controlled period was 16 weeks, after which all patients received open-label IV secukinumab through Week 52.

Overall, in both studies, two deaths occurred—one at Week 34 in a nr-axSpA patient receiving IV secukinumab in study P12301; one on Day 10 in a PsA patient receiving IV placebo in study P12302.

No cases of Anaphylaxis were reported in either study P12301 or P12302.

P12301—AS and nr-axSpA combined

The following table (Table 22) is a summary of adverse events (AEs) occurring in combined AS and nr-axSpA patients during the placebo-controlled period (PCP) in study P12301. In general, the two arms were balanced for total treatment-emergent adverse events—102 (38.6%) in SEC IV compared to 102 (39.1%) in PBO IV. There were no deaths during the PCP. A greater number of serious adverse events (SAE), discontinuations due to any AE, and discontinuations due to SAE occurred in the SEC IV arm compared to the PBO IV arm—7 (2.7%) vs 3 (1.1%); 5 (1.9%) vs 1 (0.4%); and 2 (0.8%) vs 0 (0.0%), respectively.

Table 22: Summary of Adverse Events Occurring During the Placebo-Controlled Period in Study P12301

Description	SEC IV N=264 n (%)	PBO IV N=261 n (%)
Number with any AE	102 (38.6)	102 (39.1)
Number with Serious or Other Significant Events		
Death	0 (0.0)	0 (0.0)
SAE	7 (2.7)	3 (1.1)
Discontinued Due to any AE	5 (1.9)	1 (0.4)
Discontinued Due to any SAEs	2 (0.8)	0 (0.0)

Source: Study P12301 CSR

For the entire 52 week treatment period in study P12301, including the open-label IV secukinumab in all patients from Week 16 through Week 52, there was one death in study P12301. The cause of death is reported as myocardial infarction in a 69 yo female with a history of hypertension and tobacco use. The death occurred 16 days after the IV infusion of secukinumab at Week 32 (8 infusions) in a subject with nr-axSpA.

No SAE (by preferred term) occurred in more than one patient during PCP in study P12301 in either arm, as summarized in the table below (Table 23).

Table 23: SAEs by Preferred Term Occurring During the Placebo-Controlled Period (PCP) in Study P12301

Preferred Term	SEC IV N=264 n (%)	PBO IV N=261 n (%)
Any preferred term	7 (2.7)	3 (1.1)
Anemia	1 (0.4)	0 (0.0)

Asthma	1 (0.4)	0 (0.0)
Cellulitis	1 (0.4)	0 (0.0)
Chest pain	1 (0.4)	0 (0.0)
Colitis ulcerative	1 (0.4)	0 (0.0)
Seminoma	1 (0.4)	0 (0.0)
Sepsis	1 (0.4)	0 (0.0)
Cholecystitis	0 (0.0)	1 (0.4)
Ovarian cyst ruptured	0 (0.0)	1 (0.4)
Tonsillitis	0 (0.0)	1 (0.4)

Source: Study P12301 CSR

Serious adverse events were reported for the entire treatment period in study P12301, which includes open-label IV secukinumab in all patients from Week 16 through Week 52. Out of 517 patients exposed to secukinumab IV at any time during the study, there were a total of 32 (6.2%) SAEs in 516 SEC IV patients compared to 3 (1.1%) out of 261 patients receiving PBO IV. The exposure adjusted incidence rate (EAIR) of any SAE was 6.6 per 100 patient years (PY) for SEC IV and 3.7 per 100 PY for PBO IV. Most SAEs were rare. There was an imbalance for SAEs occurring higher in the SEC IV than PBO IV arms for the SOC of Infections and infestations (EAIR 1.8 vs 1.2), gastrointestinal disorders (EAIR 1.3 vs 0.0), and cardiac disorders (0.8 vs 0.0).

During the PCP in study P12301, treatment-emergent adverse events (TEAE) by System Organ Class (SOC) and preferred term (PT) were higher in the SEC IV arm than the PBO IV arm for gastrointestinal disorders, infections and infestations, lab abnormalities and respiratory, thoracic and mediastinal disorders; and higher in the PBO IV arm than SEC IV arm for musculoskeletal and connective tissue disorders, nervous system disorders and skin and subcutaneous disorders. The specific data are presented in the following table (Table 24).

Table 24: Common TEAEs by SOC and PT Occurring During the Placebo-Controlled Period (PCP) in Study P12301

SOC PT	SEC IV N=264	PBO IV N=261

	n (%)	n (%)
Any TEAE	102 (38.6)	102 (39.1)
Gastrointestinal disorders	22 (8.3)	15 (5.7)
Infections and infestations	51 (19.3)	43 (16.5)
COVID-19	11 (4.2)	9 (3.4)
Upper respiratory infection	6 (2.3)	7 (2.7)
Investigations (lab abnormalities)	13 (4.9)	8 (3.1)
Musculoskeletal and connective tissue disorders	7 (2.7)	9 (3.4)
Nervous system disorders	8 (3.0)	12 (4.6)
Respiratory, thoracic and mediastinal disorders	8 (3.0)	6 (2.3)
Skin and subcutaneous disorders	7 (2.7)	9 (3.4)

Source: Study P12301 CSR

P12302—PsA

The following table (Table 25) is a summary of adverse events (AEs) occurring in PsA patients during the placebo-controlled period (PCP) in study P12302. In general, the two arms were balanced for total treatment-emergent adverse events—72 (37.7%) in SEC IV compared to 73 (38.4%) in PBO IV. There was one death in the placebo group due to cerebrovascular accident before Week 16 (the subject had a past medical history of myocardial infarction, vascular disease, and associated cardiovascular risk factors). A fewer number of serious adverse events (SAE) and discontinuations due to AE occurred in the SEC IV arm compared to the PBO IV arm—3 (1.6%) vs 4 (2.1%) and 1 (0.5%) vs 3 (1.6%), respectively. The 3 SAEs in the SEC IV arm were one case each of COVID-19, hypertension and pyelonephritis; the 4 SAEs in the PBO IV arm were 2 cases of COVID-19 pneumonia and one case each of cerebrovascular accident and transient ischemic attack.

Table 25: Summary of Adverse Events Occurring During the Placebo-Controlled Period in Study P12302

Description	SEC IV N=191 n (%)	PBO IV N=190 n (%)
Number with any AE	72 (37.7)	73 (38.4)
Number with Serious or Other Significant Events		
Death	0 (0.0)	1 (0.5)
SAE	3 (1.6)	4 (2.1)
Discontinued Due to any AE	1 (0.5)	3 (1.6)

Source: Study P12302 CSR

No SAE (by preferred term) occurred in more than one patient during PCP in study P12302 in either arm with the exception of 2 cases of COVID-19 pneumonia in the PBO arm, as summarized in the table below (Table 26).

Table 26: SAEs by Preferred Term Occurring During the Placebo-Controlled Period (PCP) in Study P12302

Preferred Term	SEC IV N=191 n (%)	PBO IV N=190 n (%)
Any preferred term	3 (1.6)	4 (2.1)
COVID-19	1 (0.5)	0 (0.0)
COVID-19 pneumonia	0 (0.0)	2 (1.1)
Pyelonephritis	1 (0.5)	0 (0.0)
DM inadequate control	1 (0.5)	0 (0.0)
Hypertension	1 (0.5)	0 (0.0)

Cerebrovascular accident	0 (0.0)	1 (0.5)
Transient ischemic attack	0 (0.0)	1 (0.5)

Source: Study P12302 CSR

A number of SAEs (by preferred term) were imbalanced between SEC IV and PBO IV for the entire treatment period (ETP) in study P12302, as summarized in the table below (Table 27), however most SAEs occurred in only one subject. While more serious COVID-19 infections occurred in the SEC IV arm, the two arms were balanced for COVID-19 pneumonia. Overall COVID-19 infections were balanced between treatment groups (Table 28).

Table 27: SAEs by Preferred Term Occurring During the Entire Treatment Period (ETP) in Study P12302

Preferred Term	SEC IV N=374 n (EAIR)	PBO IV N=190 n (EAIR)
Any preferred term	14 (6.9)	4 (6.9)
COVID-19	3 (1.4)	0 (0.0)
COVID-19 pneumonia	2 (1.0)	2 (3.5)
Angina unstable	1 (0.5)	0 (0.0)
Basal cell carcinoma	1 (0.5)	0 (0.0)
DM inadequate control	1 (0.5)	0 (0.0)
Gastroenteritis	1 (0.5)	0 (0.0)
Hypertension	1 (0.5)	0 (0.0)
Pyelonephritis	1 (0.5)	0 (0.0)
Urinary tract infection	1 (0.5)	0 (0.0)

Cerebrovascular accident	0 (0.0)	1 (1.2)
Transient ischemic attack	0 (0.0)	1 (1.2)

Source: Study P12302 CSR

During the PCP in study P12302, treatment-emergent adverse events (TEAE) by System Organ Class (SOC) and preferred term (PT) were generally balanced between the SEC IV arm than the PBO IV arms, with the exception of gastrointestinal disorders, infections and infestations, and lab abnormalities and respiratory, which were somewhat higher in the SEC IV than PBO IV arm. The specific data are presented in the following table (Table 28).

Table 28: Common TEAEs by SOC and PT Occurring During the Placebo-Controlled Period (PCP) in Study P12302

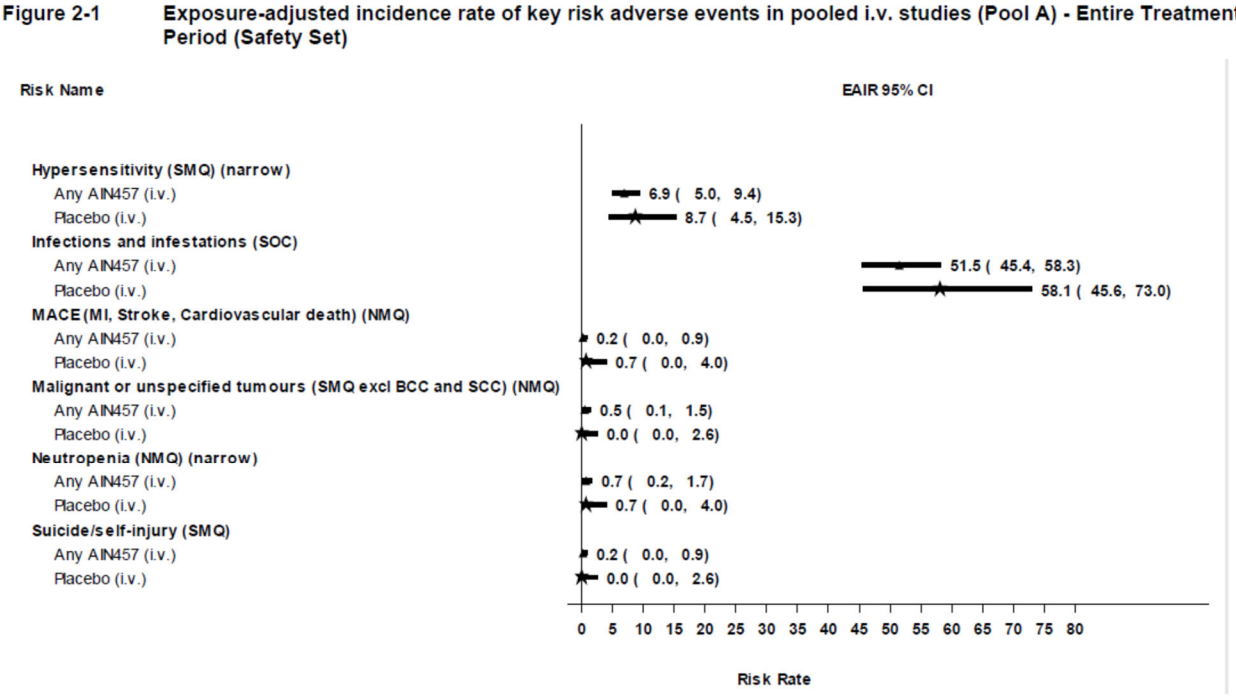
SOC PT	SEC IV N=191 n (%)	PBO IV N=190 n (%)
Any TEAE	72 (37.7)	73 (38.4)
Gastrointestinal disorders	12 (6.3)	6 (3.2)
Infections and infestations	31 (16.2)	30 (15.8)
COVID-19	6 (3.1)	7 (3.7)
Upper respiratory infection	1 (0.5)	6 (3.2)
Investigations (lab abnormalities)	16 (8.4)	15 (7.9)
Musculoskeletal and connective tissue disorders	9 (4.7)	9 (4.7)
Nervous system disorders	6 (3.1)	9 (4.7)
Respiratory, thoracic and mediastinal disorders	2 (1.0)	3 (1.6)
Skin and subcutaneous disorders	8 (4.2)	8 (4.2)

Source: Study P12302 CSR

8.2.5.1. AESI summary for IV Secukinumab Studies P12301/P12301

The Applicant provided a summary of exposure-adjusted incidence rates for key adverse events of special interest (AESI) previously identified for subcutaneous secukinumab observed during treatment with long-term IV secukinumab in studies P12301 and P12302 using a higher maintenance dose than the proposed IV maintenance dose for approval (Figure 21).

Figure 21: Applicant Summary of Key AESI during long-term study of IV secukinumab in AS/nr-axSpA and Ps



Source: Secukinumab Summary of Clinical Safety for BLA 761349 Figure 2-1

The EAIRs for the key risk AEs in the pooled IV studies (Study P12301 and Study P12302) during the Entire Treatment Period indicate that the EAIRs were generally low and balanced between IV secukinumab ("Any AIN457" in the figure) and IV placebo for the key risks of MACE (MI, stroke, cardiovascular death), malignant and unspecified tumors, neutropenia, and suicide and self-injury. The EAIRs for hypersensitivity AEs and the Infections and infestations SOC were higher than for the other key risks and slightly higher in the placebo IV groups compared to the Any secukinumab IV treatment group.

Reviewer's Comment: It is reassuring that exposure to long-term IV secukinumab in AS, nr-axSpA and PsA patients during studies P12301 and P12302 did not result in an increased risk of identified AESI for secukinumab and that no new safety concerns were observed with IV

secukinumab. It is additionally reassuring that that the maintenance IV regimen used in these studies was higher (3.0 mg/kg Q4W) than the proposed IV maintenance dose of 1.75 mg/kg IV Q4W.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not Applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Not Applicable.

8.2.8. Specific Safety Studies/Clinical Trials

Not Applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not Applicable.

Human Reproduction and Pregnancy

Not Applicable.

Pediatrics and Assessment of Effects on Growth

Not Applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Postmarketing Safety issues described in the USPI Section 6.3:

The following adverse reactions have been reported during post-approval use of COSENTYX. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: Eczematous eruptions (atopic dermatitis-like eruptions,

dyshidrotic eczema, and erythroderma) [see Warnings and Precautions (5.5)].

Expectations on Safety in the Postmarket Setting

A PREA PMR study is planned (see below in Sections 10 and 13).

8.2.11. Integrated Assessment of Safety

There was no pooling of safety data, however the overall safety in AS and PsA was consistent between previously completed registrational trials of SC secukinumab both with and without an initial IV load and studies P12301 and P12302, respectively, of an IV maintenance dosing regimen higher than the proposed IV dose for approval.

The overall safety in nr-axSpA was consistent across studies H2315 (150 mg subcutaneous secukinumab in the core study), the P12301 study of intravenous secukinumab in nr-axSpA subjects, and the extension phase of H2315 in which subjects were treated with subcutaneous secukinumab at both 150 and 300 mg doses.

8.3. Statistical Issues

There are no statistical issues as the two efficacy studies P12301 and P12302 were only considered supportive.

8.4. Conclusions and Recommendations

There is adequate safety data to support the proposed IV secukinumab maintenance dose of 1.75 mg/kg Q4W with or without a loading IV dose of 6 mg/kg in PsA, AS, and nr-axSpA. The primary safety assessment for PsA, AS, and nr-axSpA are based on PK/Exposure-matched extrapolation from the approved maintenance SC doses of 150 and 300 mg Q4W as described above. The safety of IV secukinumab in PsA, AS, and nr-axSpA is based on similar pharmacokinetic exposure and leveraging of the established safety of SC secukinumab in PsA, AS, and nr-axSpA patients**.**

The overall safety findings with an IV regimen higher than the proposed 1.75 mg/kg IV maintenance dose and also resulting in exposure that is estimated to be higher than the approved subcutaneous dose of 150 mg in nr-axSpA in study P12301 are consistent with the known safety profile in registrational studies and post-marketing evaluation of 150 mg subcutaneous secukinumab in nr-axSpA.

The overall safety findings with 300 mg subcutaneous secukinumab in nr-axSpA in study H2315 are consistent with the known safety profile in registrational studies and post-marketing evaluation of 150 mg subcutaneous secukinumab in nr-axSpA. No dose-related safety findings or new safety findings were identified. As the proposed IV dosing regimen of secukinumab may

approximate a dose of subcutaneous secukinumab that is higher than the approved dose of 150 mg for nr-axSpA, the safety findings for 300 mg subcutaneous secukinumab from study H2315 provide additional support for the approval of the proposed IV secukinumab dosing regimen for nr-axSpA.

APPEARS THIS WAY ON ORIGINAL

9 Advisory Committee Meeting and Other External Consultations

There were no scientific or regulatory questions that warranted input from an Advisory Committee.

10 Pediatrics

AS/nr-axSpA

The Applicant requests a waiver of the pediatric study requirement for the intravenous use of secukinumab in AS and nr-axSpA for patients 0 to 17 years of age because the necessary studies are impossible or highly impracticable as the disease is not typically diagnosed in pediatric patients this young, and there are too few children with the disease to study.

The Division accepts the Applicant's plan for a full waiver of pediatric studies (0 to <18) for AS/nr-axSpA and a partial waiver (age < 2) for PsA, based on the fact that these conditions are extremely rare in those age groups, respectively.

PsA

The Applicant requests a waiver of the pediatric study requirement for the intravenous use of secukinumab in PsA for pediatric patients younger than 2 years of age (i.e., 0 – 1 year old) as studies are impossible or highly impractical as the disease is not typically diagnosed in pediatric patients this young, and there are too few children with the disease to study.

(b) (4)

For JPsA patients, secukinumab is currently approved in the SC formulation down to 2 years of age.

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The response to the IR was received on 7/21/2023, summarized:

(b) (4)

Based on the above considerations, the Division has concluded that there is inadequate data an information to support the (b) (4) (b) (4) (b) (4) in pediatric PsA patients. (b) (4) the approved SC regimen in pediatric patients. Further, there is no pediatric safety data for the proposed loading dose of (b) (4) mg/kg in pediatric patients.

Therefore, a dedicated PK/Safety study of the IV formulation in pediatric PsA patients age 2 to < 18 is requested as a PREA PMR study.

PeRC agrees with the Division's plan (PeRC meeting took place on August 8th, 2023).

The need for a PK/safety study of the IV formulation in pediatric PsA patients was communicated to the Applicant on 9/15/2023.

The PREA PMR, agreed with the Applicant is as follows:

> Conduct an open-label study to evaluate the pharmacokinetics and safety of IV secukinumab plus background standard therapy in pediatric subjects ages 2 years to 17 years of age with PsA.

The Applicant accepted this PREA PMR, as communicated on 9/28/2023. The proposed milestones at the time of this review are as follows:

(b) (4)	(b) (4)
Final Protocol Submission:	October 2024
Study Completion:	October 2029
Final Report Submission:	April 2030

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The following is a high-level summary of major changes to the originally submitted Prescribing Information based on review of the data submitted in support of this application:

1) The IV secukinumab dosage for Adult PsA, AS and nr-axSpA indications should be listed as both with and without loading dose, corresponding to the approved subcutaneous dosage that includes both With and Without a loading dose. Also, the maximum IV secukinumab maintenance dose must be capped at 300 mg per infusion. The Applicant agreed with these recommendations. For Intravenous Dosage under the indications for Adult Patients with Psoriatic Arthritis, Ankylosing Spondylitis, and Non-Radiographic Axial Spondyloarthritis, the instructions are as follows:
    a. With a loading dosage: 6 mg/kg given at Week 0 as a loading dose, followed by 1.75 mg/kg every 4 weeks thereafter (max. maintenance

dose 300 mg per infusion).

b. Without a loading dosage: 1.75 mg/kg every 4 weeks (max. maintenance dose 300 mg per infusion).

2) It was recommended that information for psoriatic arthritis in adults and juvenile psoriatic arthritis be provided under separate subject sections to improve accessibility. The Applicant agreed with this recommendation. Section 2 has a subsection (2.4) for Recommended Dosage in Adults with Psoriatic Arthritis, which has separate subsections for Recommended Subcutaneous Dosage and Recommended Intravenous Dosage. There is a separate section (2.5) in Section 2 for Recommended Dosage in Pediatric Patients 2 Years of Age and Older with Juvenile Psoriatic Arthritis.
3) Under Dosage and Administration and under all sections for Recommended Intravenous Dosage, the wording for the time of infusion was recommended to be consistent and not to include the term (b) (4) The applicant agreed with this recommendation and also provided additional documentation of instructions for pharmacists for administration of intravenous secukinumab in studies P12301 and P12302. The consistent wording in the label for recommended intravenous dosage is to "Administer as an intravenous infusion over a period of 30 minutes."
4) It was recommended to remove wording proposed by the Applicant that stated (b) (4) (b) (4) The Applicant agreed and removed this from the label.
5) It was recommended to remove a statement on (b) (4) (b) (4) because (b) (4) The Applicant agreed and removed the statement.
6) In the section describing Pharmacokinetics Following Intravenous Administration, it was recommended that PK information be provided for an IV dose both with and without a loading dose. The Applicant agreed and proposed the following: "Following an intravenous administration of 1.75 mg/kg maintenance dose every four weeks, with or without a loading dose of 6 mg/kg at Day 0, the secukinumab concentrations [steady state trough secukinumab concentrations (Cmin,ss), mean secukinumab concentrations (Cavg,ss), and maximum secukinumab concentrations (Cmax,ss)] are estimated to be within the range of the steady state concentrations following subcutaneous administration of 150 mg and 300 mg doses of COSENTYX administered every four weeks."
7) The Applicant proposed language regarding the effectiveness of IV secukinumab in PsA, AS, and nr-axSpA was accepted as follows:
    a. <u>Treatment of Adult Patients with Active Psoriatic Arthritis with Intravenous COSENTYX</u>
        - The effectiveness of intravenous COSENTYX in the treatment of adult patients with active PsA was extrapolated from the established effectiveness of subcutaneous COSENTYX in adult patients with active PsA based on pharmacokinetic exposure [see Clinical Pharmacology

(12.3)].

b. Treatment of Adult Patients with Active Ankylosing Spondylitis with Intravenous COSENTYX
    - The effectiveness of intravenous COSENTYX in the treatment of adult patients with active AS was extrapolated from the established effectiveness of subcutaneous COSENTYX in adult patients with active AS based on pharmacokinetic exposure [see Clinical Pharmacology (12.3)].

c. Treatment of Adult Patients with Active Non-radiographic Axial Spondyloarthritis with Intravenous COSENTYX
    - The effectiveness of intravenous COSENTYX in the treatment of adult patients with active nr-axSpA was extrapolated from the established effectiveness of subcutaneous COSENTYX in adult patients with active nr-axSpA based on pharmacokinetic exposure [see Clinical Pharmacology (12.3)].

8) The Applicant proposed language for intravenous secukinumab in the Medication Guide and agreed to all formatting changes that were recommended to reduce redundancy and to make patient information more consistent and concise. The accepted description for IV administration is as follows:
    a. When administered intravenously (by vein)
        - You will be given COSENTYX by a healthcare provider through a needle placed in a vein (infusion). It takes about 30 minutes to give you the full dose of COSENTYX.
        - Your healthcare provider will tell you how often you should receive COSENTYX.
        - If you miss an appointment to receive COSENTYX, make another appointment as soon as possible.

Other Prescription Drug Labeling

Not Applicable.

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is warranted based on the data in this submission.

13 Postmarketing Requirements and Commitment

The only PMR study is required under PREA. See Section 10. Pediatrics.

> Conduct an open-label study to evaluate the pharmacokinetics and safety of IV secukinumab plus background standard therapy in pediatric subjects ages 2 years to 17 years of age with PsA.

The Applicant accepted this PREA PMR, as communicated on 9/28/2023. The proposed milestones at the time of this review are as follows:

(b) (4)	(b) (4)
Final Protocol Submission:	October 2024
Study Completion:	October 2029
Final Report Submission:	April 2030

14 Cross Discipline Team Leader Comments

The Applicant, Novartis Pharmaceutical Corporation, submitted this Biologics License Application, 761349, to include an IV formulation of secukinumab (Cosentyx®) for the treatment of psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis. On December 7, 2022, the Applicant submitted the sBLA for IV dosing of 1.75 mg/kg every 4 weeks with an initial loading dose of 6 mg/kg IV. As secukinumab is approved for treatment of psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis, the review division sent an information request to the Applicant to provide an IV dosing regimen without loading to which the Applicant agreed. Secukinumab was originally approved on January 21, 2015 as a subcutaneous formulation for the treatment of moderate to severe plaque psoriasis. Subsequently, the subcutaneous formulation of secukinumab for the treatment of psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis for which the Applicant is seeking approval of an IV formulation. Secukinumab is also approved for pediatric indications including pediatric plaque psoriasis (6 years of age and older), pediatric psoriatic arthritis (2 years of age and older) and enthesitis related arthritis (4 years of age and older).

The Applicant and the FDA had multiple interactions under the Model-Informed Drug Development (MIDD) program to determine what data would be needed to support approval of the IV formulation. During these discussion, it was determined that given the linear PK of secukinumab, given the proposed identical dosing interval, and given extensive clinical experience and PK data with both the to be marketed IV formulation and the approved SC formulation (see Table 29), a dedicated confirmatory PK study would not be needed in this specific case. To support approval of the IV formulation of secukinumab 125 mg/5 mL solution in vial, the Applicant proposed pharmacokinetic bridging to the efficacy of the previously conducted secukinumab studies in psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis that were used to support the currently licensed subcutaneous doses.

Table 29. Studies used to support MIDD approach

Study number	Secukinumab exposed patients*	Loading dose	Maintenance dose	Duration of study
Psoriatic Arthritis				
F2306	591	10 mg/kg IV at Weeks 0,2, and 4	75 or 150 mg every 4 weeks	104 weeks
F2312	397	75, 150, or 300 mg SC every week until Week 4	75, 150, or 300 mg SC every 4 weeks	268 weeks
P12302	190	6 mg/kg IV at baseline	3 mg/kg IV every 4 weeks	52 weeks
Ankylosing Spondylitis				

F2305	361	10 mg/kg IV at Weeks 0,2, and 4	75 or 150 mg SC every 4 weeks	104 weeks
F2310	211	75 or 150 mg SC every week until Week 4	75 or 150 mg SC every 4 weeks	268 weeks
F2314	223	10 mg/kg IV at Weeks 0,2, and 4	150 or 300 mg SC every 4 weeks	164 weeks
P12301	208	6 mg/kg IV at baseline	3 mg/kg IV every 4 weeks	52 weeks
Non-radiographic axial spondyloarthritis				
H2315	543	150 mg SC every week until Week 4	150 mg SC every 4 weeks	120 weeks
H2315 (extension phase)	294	NA	150 or 300 mg SC every 4 weeks	52 weeks
P12301	56	6 mg/kg IV at baseline	3 mg/kg IV every 4 weeks	52 weeks

Reviewer generated; *The numbers reflect the number of subjects for whom PK data was available

Population PK modeling was used to predict the IV dosing regimens (with load and without load) that would best approximate the exposures for which efficacy and safety have been established with subcutaneous secukinumab. Based on the modeling and simulation approach, the 1.75 mg/kg secukinumab IV every 4-week dosing regimen was predicted to achieve steady state exposures that were comparable to the known exposures of the approved 150 mg every 4 week dosing for psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis. The Applicant has proposed a 6 mg/kg IV loading dose as an option for treatment. The 6 mg/kg dose is expected to achieve similar concentrations as those achieved with the approved 150 mg SC dosing with SC loading. With the 6 mg/kg IV loading dose, steady state is expected to be reached in 4 weeks whereas without a loading dose, steady state is expected to be reached in approximately 16 weeks.

Due to expected Cmax exposures to be increased in patients weighing more than 170 kg, the maximum IV maintenance dose to be administered is 300 mg to ensure that patients with higher body weights ensure steady state trough and average concentrations similar to approved SC dosing.

To ensure safety of the maintenance IV dosing regimen, exposure-response analyses were conducted to estimate the safety of the 1.75 mg/kg IV dosing in the psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis populations. The analyses showed that the safety of the maintenance IV dosing regimen would be comparable to the safety of the 150 mg SC dosing regimen.

The safety of the single 6 mg/kg IV loading dose is supported by previous conducted studies P12301, P12302, F2306, F2305, and F2314 which used identical or higher than proposed loading doses than currently proposed by the Applicant for this BLA. IV loading doses as high as 10 mg/kg IV at Weeks 0, 2, and 4 have been studied in the relevant study population and did

not show dose dependent side effects as compared to approved SC loading dose regiments. The one time 6 mg/kg IV loading dose regimen is expected to approximate the approved 150 mg SC loading regimen.

Additional safety analyses were reviewed to provide additional support for the proposed IV dosing regimen for non-radiographic axial spondyloarthritis due to the exposures of the proposed dosing regimen (1.75 mg/kg IV every 4 weeks with or without a 6mg/kg IV loading dose) expected to approximate exposures in between the 150 mg SC and 300 mg SC dosing regimens approved. For non-radiographic axial spondyloarthritis, the only approved SC dosing regimen is 150 mg SC dosing as opposed to ankylosing spondylitis and psoriatic arthritis where both 150 mg SC and 300 mg SC dosing regimens are approved. Therefore, the review team considered 52 week safety collected in the extension phase of study H2315 which randomized 294 patients with non-radiographic axial spondyloarthritis to either 150 mg SC every 4 weeks or 300 mg SC every 4 weeks. In the 52 week safety extension period, no dose depend adverse events were noted. The review team also considered 56 non-radiographic axial spondyloarthritis patients in study P12301 who received IV doses higher than what is proposed in this BLA. No new safety findings were noted in this study and adverse events were in line with the adverse events noted in the 208 ankylosing spondylitis patients also studied in P12301. After reviewing this additional safety information from two studies, the review team concluded that the safety for the proposed IV dosing regimen was reasonable and expected to be consistent with the safety profile of secukinumab, as described in the FDA-approved labeling.

In summary, the Applicant proposed a MIDD approach to support the approval of a new IV formulation and dosing regimen for the treatment of adults with active psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis. Population PK modeling was used to predict the IV dosing regimens (with load and without load) that would approximate the exposures for which efficacy and safety have been established with subcutaneous secukinumab. To assess safety of the maintenance IV dosing regimen, exposure-response analyses were conducted to predict the safety of the 1.75 mg/kg IV dosing in the psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis populations. The analyses showed that the safety of the maintenance IV dosing regimen would be comparable to the safety of the 150 mg SC dosing regimen. Additional safety analyses were reviewed to support the proposed IV dosing regimen for non-radiographic axial spondyloarthritis due to the exposures of the proposed dosing regimen (1.75 mg/kg IV every 4 weeks with or without a 6mg/kg IV loading dose) expected to approximate exposures in between the 150 mg SC and 300 mg SC dosing regimens approved, thus supporting the overall favorable benefit-risk of the proposed secukinumab IV dosing regimen for the indications sought.

The recommended regulatory action is Approval for secukinumab IV for the treatment of psoriatic arthritis (PsA), ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) in adults.

15 Designated Signatory Authority Comments

I concur with the review team's assessment of the application and the recommendation to approve BLA 761349, secukinumab, intravenous (IV) formulation and dosing regimen for the treatment of adults with:

- Active psoriatic arthritis (PsA)
- Active ankylosing spondylitis (AS)
- Active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

Intravenous Dosage (for each of the tree indications sought):

- With a loading dosage: 6 mg/kg given at Week 0 as a loading dose, followed by 1.75 mg/kg every 4 weeks thereafter (maximum maintenance dose 300 mg per infusion).
- Without a loading dosage: 1.75 mg/kg every 4 weeks (max. maintenance dose 300 mg per infusion).

The IV formulation is provided as solution in a single-dose 125 mg/5 mL vial.

The applicant submitted new BLA 761349 relying on data from BLA 125504, secukinumab for subcutaneous (SC) administration approved for the indications sought under BLA 761349.

The substantial evidence of effectiveness of the proposed IV dosing regimen for each indication sought is established based upon PK bridging to the efficacy of SC secukinumab established in adequate and well-controlled clinical trials in adults with PsA, AS, and nr-axial SpA.

Clinical PK, safety, and efficacy data were available using the to-be-marketed IV formulation in two clinical studies (P12301 and P12302); however, the proposed IV dosing regimen is lower than that studied. The proposed IV dosing regimen better approximates the exposures for which efficacy and safety have been established for SC secukinumab for the indications sought for licensure with the IV dosing regimen. It is supported by a modeling and extrapolation approach in discussed presubmission with the FDA. Considering that secukinumab has linear PK, the dosing interval of the proposed IV dosing regimen is the same as the approved SC dosing regimen, and the extensive clinical experience with secukinumab, including clinical safety, efficacy, and PK data available with the to-be-marketed IV formulation in two of the indications sought, the FDA concluded that a dedicated PK validation study with the proposed IV secukinumab dosing regimen is not necessary in this case. Based on modeling and simulation, the 1.75 mg/kg secukinumab IV Q4W dosing regimen is predicted to achieve steady-state exposures that were either comparable (Ctrough) or higher (Cave, Cmax) than the

exposure established in PsA, AS and nr-axSpA patients with the approved 150 mg Q4W dosing regimens. The simulated time-concentration profile shows that the 1.75 mg/kg IV Q4W dosing regimen achieved comparable or higher secukinumab concentrations compared to the approved 150 mg Q4W SC dosing regimens throughout the dosing interval at steady state. Therefore, the PK data support the bridging of efficacy from secukinumab SC to secukinumab IV for the treatment of PsA, AS and nr-axSpA.

The safety data are leveraged from the safety established with secukinumab SC in the indications sought, at comparable exposures to those proposed for IV secukinumab, as well as supportive safety data from the Study P12301 and Study P12302 at higher exposures. No new safety concerns have been identified.

Thus, the overall benefit-risk of IV secukinumab at the dosing regimen to be described in labeling is favorable.

The review team emphasizes that this approach was considered applicable in this unique case based on the totality of data available from the secukinumab extensive development program and may not be generalizable to other SC to IV conversion programs.

The regulatory action for BLA 761349 is Approval for secukinumab IV for the treatment of adults with:

- Active psoriatic arthritis (PsA),
- Active ankylosing spondylitis (AS),
- Active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

Both routes of administration and dosing regimens, IV and SC, will be in a single labeling, clearly described in the dosage and administration section.

A PREA PMR study will be required to assess the PK and safety of the IV dosing regimen in pediatric patients with PsA 2 to 17 years of age.

16 Appendices

16.1. References

N/A

16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): CAIN457P12301/12302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 313/442		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3. OCP Appendices (Technical documents supporting OCP recommendations).

16.3.1. Bioanalytical Method Validation.

A well validated ELISA assays were used for the bioanalytical analysis of secukinumab in serum, with a lower limit of quantification (LLOQ) of 80 ng/mL at (b) (4) and 160 ng/mL at (b) (4) (b) (4) The same ELISA method was used for the measurement of secukinumab serum concentrations as in previous submissions.

Briefly, A purified anti-idiotypic antibody against AIN457 was coated on the microtiter plate. Serum samples (Calibration, Quality Control or unknown samples) and biotin-labeled AIN457 were mixed and added to the plate to compete for binding on the coating antibody. Nonbound material was removed by washing. Bound biotinylated-AIN457 was detected by incubating horseradish peroxidase-conjugated to streptavidin with O-phenylenediamine dihydrochloride (OPD) as enzyme substrate.

Table 30. Summary method performance of ELISA methods ((b) (4)) to measure secukinumab in serum.

Bioanalytical method validation report name, amendments, and hyperlinks	Quantitative determination of AIN457 in human serum by a competitive ELISA [BxSD RS686053-pk] [BxSD RS686053-pk-01] [DMPK RS686053-pk-02] [DMPK RS686053-pk-03] [DMPK RS686053-pk-04] [DMPK RS686053-pk-05]
Method description	A purified anti-idiotypic antibody against AIN457 was coated on the microtiter plate. Serum samples (Calibration, Quality Control or unknown samples) and biotin-labeled AIN457 were mixed and added to the plate to compete for binding on the coating antibody. Non-bound material was removed by washing. Bound biotinylated-AIN457 was detected by incubating horseradish peroxidase-conjugated to streptavidin with O-phenylenediamine dihydrochloride (OPD) as enzyme substrate.

Materials used for calibration curve & concentration	The calibration curve consisted of 7 calibration standard samples and 3 anchor points (AP) of AIN457 prepared in pooled normal human serum. Calibrators had the following concentrations: 10000 ng/mL (AP), 2500 ng/mL, 1500 ng/mL, 1000 ng/mL, 640 ng/mL, 320 ng/mL, 160 ng/mL, 80 ng/mL, 40 ng/mL (AP), 10 ng/mL (AP)			
Validated assay range	LLOQ = 80 ng/mL ULOQ = 2500 ng/mL			
Material used for QCs & concentration	The quality controls (QCs) were prepared with AIN457 in pooled normal human serum at the following concentrations: 2500 ng/mL (validation only), 2000 ng/mL, 500 ng/mL, 200 ng/mL, 80 ng/mL (validation only).			
Minimum required dilutions (MRDs)	1:8			
Source & lot of reagents (LBA)	AIN457 (Novartis Pharma)	batch Y105 0509 Amendment 01: lot no. Y105 0509, Y0690509 Amendment 02: lot no. Y105 0509, Y0690509, S0008 Amendment 03: S0017, S0024 Amendment 05: S2004, SYC34		
	Anti-AIN457 antibody (Novartis Pharma)	Batch no. 02/290605 Amendment 01: batch no. A312020149, PR120511A		
Regression model & weighting	4-Parameter Logistic (4PL) fit: y = ((A-D)/(1+((x/C)^B))+D; weighting factor=1			
Validation parameters	**Method validation summary**			**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ		7	[BxSD RS686053-pk Table 7-3]
	Cumulative accuracy (%bias) from LLOQ to ULOQ	AIN457	-6.6% to 8.1%	[BxSD RS686053-pk Table 7-3]
	Cumulative precision (%CV) from LLOQ to ULOQ	AIN457	≤ 8.3%	[BxSD RS686053-pk Table 7-3]
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs:	AIN457	Intra-assay bias: -12% to 13.0% Inter-assay bias: -3.0% to 3.6%	[BxSD RS686053-pk Table 7-4]
	Inter-batch %CV QCs:	AIN457	≤ 11.5%	[BxSD RS686053-pk Table 7-4]
	Total error QCs:	AIN457	N/A	N/A
Selectivity & matrix effect	Total 15 individual healthy population serum samples were tested for selectivity and matrix effect. 12 out of 15 healthy population serum sample met the acceptance criteria. Range of observed bias was -26.8% to 37.5%.			[DMPK RS686053-pk-05 Table 7-60]
Interference & specificity	Interference of Ustekinumab (Stelara), Adalimumab (Humira), Etanercept (Enbrel) and Infliximab (Remicade) were tested at below given concentrations for AIN457 at HQC (2000 ng/mL), MQC (500 ng/mL) and LQC (200 ng/mL). Ustekinumab (Stelara): 1000, 300, 100, 30.0, 10.0 and 0.00 ng/mL Adalimumab (Humira): 10000, 3000, 1000, 300, 100 and 0.00 ng/mL Etanercept (Enbrel): 2000, 600, 200, 60.0, 20.0 and 0.00 ng/mL Infliximab (Remicade): 100, 30.0, 10.0, 3.00, 1.00 and 0.00 µg/mL Interference results showed no interference on any QC performance.			[DMPK RS686053-pk-02 Table 7-26], [Table 7-27], [Table 7-28], and [Table 7-29]
	IL-17A interference with AIN457 at LLOQ (80 ng/mL) and ULOQ (2500 ng/mL). Results showed no interference with AIN457 up to 3000 pg/mL concentration levels of IL-17A.			[DMPK RS686053-pk-05 Table 7-68]

Hemolysis effect	Total 3 hemolyzed serum samples were tested for hemolysis effect. 3 out of 3 hemolyzed serum samples met the acceptance criteria. Range of observed bias was -17.0% to 8.2%.	[DMPK RS686053-pk-05 Table 7-61]
Lipemic effect	Total 3 lipemic serum samples were tested for lipemic effect. 3 out of 3 lipemic serum samples met the acceptance criteria. Range of observed bias was -16.0% to 19.1%.	[DMPK RS686053-pk-05 Table 7-62]
Dilution linearity & hook effect	Dilution linearity and hook effect were determined in BMD R0450380. No apparent dilution effect up to a dilution 1:2000	[BMD R0450380 Table 8-6]
Bench-top/process stability	Stability of AIN457 was demonstrated at room temperature for up to 96 hours AIN457	[DMPK RS686053-pk-03 Table 7--51] and [Table 7-52]
Freeze-Thaw stability	Freeze and thaw stability of AIN457 was demonstrated in -20°C and in -70°C. AIN457	[DMPK RS686053-pk-05 Table 7-58] and [Table 7-59]
Long-term storage	Long-term stability of AIN457 in human serum at or below -15°C was demonstrated for at least 12 months. Long-term stability of AIN457 in human serum at or below -70°C was demonstrated for at least 52 months. AIN457	[BxSD RS686053-pk-01 Table 7-7] [DMPK RS686053-pk-03 Table 7-53]
Parallelism	Parallelism has been successfully demonstrated for Active PsO, Palmoplantar psoriasis, Severe nail population, Moderate to severe chronic plaque-type psoriasis with or without PsA comorbidity, Japanese patients with active Ankylosing Spondylitis, Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis, Scalp psoriasis, Severe chronic plaque psoriasis and active-Ankylosing Spondylitis populations.	[DMPK RS686053-pk-03 Table 7-40], [Table 7-41], [Table 7-42], [Table 7-43], [Table 7-44], [Table 7-45], [Table 7-46], [Table 7-47], and [Table 7-48] [DMPK RS686053-pk-05 Table 7-69], [Table 7-70], and
	Parallelism has also been successfully demonstrated for moderate to severe plaque psoriasis, active psoriatic arthritis populations.	[Table 7-71]
Carry over	N/A	N/A
Method performance in study P12302 (Interim Bioanalytical data report: Determination of AIN457 in human serum. A randomized, double-blind, placebo-controlled, parallel group, phase III multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Psoriatic Arthritis, [DMPK RCAIN457P12302-pk-int])		
Assay passing rate	79.7% (As this is interim bioanalytical data report, the final data will be reported in final bioanalytical data report)	[DMPK RCAIN457P12302-pk-int Table 5-1]
Standard curve performance	• Cumulative bias range: -1.3% to 3.8% • Cumulative precision: ≤ 8.1% CV	[DMPK RCAIN457P12302-pk-int Table 5-3]
QC performance	• Cumulative bias range: 3.0% to 7.0% • Cumulative precision: ≤ 15.3% CV • TE: N/A (LBA only)	[DMPK RCAIN457P12302-pk-int Table 5-4]
Method reproducibility	Incurred sample reanalysis was performed in (226) 8.8% of study samples and (205) 7.9 % of samples met the pre-specified criteria (i.e. 90.7% of ISR samples met the acceptance criteria)	[DMPK RS686053-pk-05 Table 7-65]
Study sample analysis/ stability	The stability period covers the maximum length of time from specimen collection (19 Feb-2020) to analysis (11-Sep-2021) which is within 570 days in study CAIN457P12302.	

Table 31. Summary method performance of a bioanalytical method (b) (4) to measure secukinumab in serum.

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a method for the determination of AIN457 in human serum samples by competitive ELISA [DMPK R2000248-pk] [DMPK R2000248-pk-01] [DMPK R2000248-pk-02] [DMPK R2000248-pk-03] [DMPK R2000248-pk-04]
Method description	A purified anti-idiotypic antibody against AIN457 was coated on the microtiter plate. Serum samples (Calibration, Quality Control or unknown samples) and biotin-labeled AIN457 were mixed and added to the plate to compete for binding on the coating antibody. Non-bound material was removed by washing. Bound biotinylated-AIN457 was detected by incubating horseradish peroxidase-conjugated to streptavidin with O-phenylenediamine dihydrochloride (OPD) as enzyme substrate.
Materials used for calibration curve & concentration	The calibration curve consisted of 6 calibration standard samples and 4 anchor points (AP) of AIN457 prepared in pooled normal human serum. Calibrators had the following concentrations: 10000 ng/mL (AP), 2500 ng/mL, 1500 ng/mL, 1000 ng/mL, 640 ng/mL, 320 ng/mL, 160 ng/mL, 80 ng/mL (AP), 40 ng/mL (AP), 10 ng/mL (AP)
Validated assay range	LLOQ = 160 ng/mL ULOQ = 2500 ng/mL
Material used for QCs & concentration	The quality controls (QCs) were prepared with AIN457 in pooled normal human serum at the following concentrations: 2500 ng/mL (validation only), 2000 ng/mL, 500 ng/mL, 200 ng/mL, 80 ng/mL (validation only).
Minimum required dilutions (MRDs)	1:8

Source & lot of reagents (LBA)	AIN457 (Novartis Pharma) Anti-AIN457 antibody (b) (4)	AIN457, batch no. S2004 Amendment 1: SYC34 Batch no. PR120515I	
Regression model & weighting	4-Parameter Logistic (4PL) fit: y = ((A-D)/(1+((x/C)^B))+D; weighting factor = 1		
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	7	[DMPK R2000248-pk Table 7-3]
	Cumulative accuracy (%bias) from LLOQ to ULOQ AIN457	-3.2% to 3.8%	[DMPK R2000248-pk Table 7-3]
	Cumulative precision (%CV) from LLOQ to ULOQ AIN457	≤ 5.8%	[DMPK R2000248-pk Table 7-3]
QCs performance during accuracy & precision	**Cummulative accuracy (%bias) in 5 QCs** QCs: AIN457	Intra-assay bias: -13.8% to 14.4% Inter-assay bias: -9.4% to 6.8%	[DMPK R2000248-pk Table 7-5]
	Inter-batch %CV QCs: AIN457	≤ 10.8%	[DMPK R2000248-pk Table 7-5]
	Total error QCs: AIN457	≤ 14.4%	[DMPK R2000248-pk Table 7-5]
Selectivity & matrix effect	In total 15 lots were tested, 80.0% of the matrix sources spiked at 80.0 ng/mL and 100% of the matrix sources spiked at 2000 ng/mL and the spike control sample result had a bias within		[DMPK R2000248-pk Table 7-8]

	acceptance criteria and responses for all 15 unspiked samples (100.0%) were below the validated LLOQ. Range of observed bias was -29.7% to 28.5%.	
Interference & specificity	IL-17A interference with AIN457 at 160 ng/mL and 2500 ng/mL was tested. Results showed no interference with AIN457 up to 3000 pg/mL concentration levels of IL-17A.	[DMPK R2000248-pk-01 Table 4-6]
Hemolysis effect	Total 3 hemolyzed serum samples were tested for hemolysis effect. 100% of the analyzed samples passed the acceptance criteria. Range of observed bias was -6.4% to 20.0%.	[DMPK R2000248-pk Table 7-9]
Lipemic effect	Total 10 lipemic serum samples were tested for hemolysis effect. 100% of the analyzed samples passed the acceptance criteria. Range of observed bias was -16.9% to 39.2%.	[DMPK R2000248-pk Table 7-10], [Table 7-11]
Dilution linearity & hook effect	Dilution linearity and hook effect were determined.	[DMPK R2000248-pk Table 7-6] and [Table 7-7]
Bench-top/process stability	Stability of AIN457 was demonstrated at room temperature for at least 24 hours and up to 96 hours. AIN457	[DMPK R2000248-pk Table 7-13] and [DMPK RS686053-pk-03 Table 7-51] and [Table 7-52]
Freeze-Thaw stability	Freeze and thaw stability of AIN457 was demonstrated for at least 5 cycles. AIN457	[DMPK R2000248-pk Table 7-12]
Long-term storage	Long-term stability of AIN457 in human serum at or below -15°C was demonstrated for up to 12 months. Long-term stability of AIN457 in human serum at or below -70°C was demonstrated for at least 52 months. AIN457	[BxSD RS686053-pk-01 Table 7-7] [DMPK RS686053-pk-03 Table 7-53]
Parallelism	Parallelism has been successfully demonstrated for active ankylosing spondylitis, lichen planus, moderate to severe hidradenitis suppurativa populations.	[DMPK R2000248-pk-02 Table 3-10], [DMPK R2000248-pk-03 Table 3-7], [DMPK R2000248-pk-04 Table 3-7]
Carry over	N/A	N/A
Method performance in study P12301		
(Interim bioanalytical data report: Determination of AIN457 in human serum samples of adult patients with ankylosing spondylitis or non-radiographic axial spondylitis by competitive ELISA for clinical trial CAIN457P12301. A randomized, double-blind, placebo-controlled, parallel group, phase III multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Ankylosing Spondylitis or non-radiographic axial SpondyloArthritis, [DMPK RCAIN457P12301-pk-int])		
Assay passing rate	69.0 % (As the sample analysis is ongoing, the final data will be reported in final bioanalytical data report)	[DMPK RCAIN457P12301-pk-int Table 8-1]
Standard curve performance	• Cumulative bias range: -3.2% to 2.2% • Cumulative precision: ≤ 10.0% CV	[DMPK RCAIN457P12301-pk-int Table 8-2]
QC performance	• Cumulative bias range: 0.0% to 7.0% • Cumulative precision: ≤ 13.1% CV • TE: N/A (LBA only)	[DMPK RCAIN457P12301-pk-int Table 8-4]
Method reproducibility	Incurred sample reanalysis was performed in (123) 5.8% of study samples and (119) 5.7 % of samples met the pre-specified criteria (i.e. 96.7 % of ISR samples met the acceptance criteria)	[DMPK RCAIN457P12301-pk-int Table 8-6]
Study sample analysis/ stability	The stability period covers the maximum length of time from specimen collection (11-Mar-2020) to analysis (17-Mar-2022) which is within 736 days in study CAIN457P12301.	

16.3.2. **Population PK-PD Analysis**

Executive Summary:

Population PK, exposure response (E-R) analysis for efficacy and safety were conducted by the Applicant in patients with AS, PsA or nr-axSpA received different doses of secukinumab administered via the IV or SC route. Modeling and simulation were applied to support the approval of the secukinumab IV regimen for the treatment of PsA, AS, or nr-axSpA.

The population PK model was developed for secukinumab in patients with AS, PsA and nr-axSpA and used to predict the exposures achieved at the proposed IV dosing regimen (1.75 mg/kg, up to 300 mg Q4W) and the approved SC dosing regimen (150 and 300 mg Q4W). The results of the population PK modeling and simulation were generally acceptable due to the agreement of prediction and observation and abundant PK data in both IV and SC dosing regimen. Simulation of 1.75 mg/kg (up to 300 mg) IV regimen results in comparable $C_{min,ss}$ to 150 mg Q4W SC regimen, comparable $C_{max,ss}$ to 300 mg Q4W SC regimen and $C_{avg,ss}$ between 150 mg and 300 mg SC regimens in maintenance treatment. Patients with higher bodyweight tends to have higher exposure under proposed IV regimen than SC regimen, while the exposure is still within the range of all patients. Applicant's E-R efficacy analysis showed similar efficacy between the proposed IV regimen and approved 150 mg SC regimen due to the similar exposures. Applicant's E-R safety analysis showed the predicted incidence rates of most AEs are similar between the proposed IV regimen and approved SC regimens. While the incidence rates of Candida infections and hypersensitivity reactions were predicted to be slightly higher under proposed IV regimen than 150 mg SC regimen, the difference was small.

16.3.3. **Population PK Analysis**

Population PK Summary Table

General Information	
Objectives of PPK Analysis	To develop a popPK model that describes the PK of secukinumab administered via the IV or SC route in PsA, AS, and nr-axSpA subjects. To support approval of the secukinumab IV regimen in PsA, AS, and nr-axSpA determined using modeling and simulation, that results in drug exposures that approximate the exposures achieved at the approved SC dosing regimen (150 and 300 mg Q4W).
Study Included (Table 32)	CAIN457A2206, CAIN457A2209, CAIN457F2305, CAIN457F2306, CAIN457F2308, CAIN457F2310, CAIN457F2312, CAIN457F2314, CAIN457F2318, CAIN457F2320, CAIN457F2336, CAIN457F2342, CAIN457H2315, CAIN457P12301, CAIN457P12302
Dose(s) Included (Table 32)	IV: 0.1, 1.0, 3, 6, 10 mg/kg SC: 75, 150, 300 mg
Population Included	2055 subjects with AS 3080 subjects with PsA 651 subjects with nr-axSpA

Population Characteristics (Table 33)	General	Age median: 45 (range: 18-84) years Weight median: 79.8 (range: 32 - 183) kg Sex: 3214 (56%) males Race: 4595 (79%) Caucasian 868 (15%) Asian 40 (1%) Black or African American 283 (5%) Other or Missing	
	Pediatrics (if any)	NA	
No. of Patients, PK Samples, and BLQ		All subjects in final population PK model: No. of subjects: 5786 No. of PK samples: 25931 (6178 under IV & 19753 under SC) No. of BLQ samples: 2120 (7.6%)	
Covariates Evaluated	Static	Population effect	
	Time-varying	NA	
Final Model		Summary	Acceptability [FDA's comments]
Software and Version		Population PK modeling employed nonlinear mixed effects modeling using the computer program NONMEM version 7.5.0. For data manipulation, data presentation and construction of plots related to Population PK modeling, R version 4.1.2 (the R Foundation for Statistical Computing) was used. For the exposure-response analyses, PK simulation were obtained using NONMEM version 7.4.3., and data manipulation, data analyses, data presentation and construction of plots were obtained using R version 4.1.0.	Acceptable
Model Structure		Those models described the pharmacokinetics of secukinumab by means of a two compartment disposition model with first-order elimination and first-order absorption for the SC administration, and constant rate	Acceptable

	infusion for the IV administration. The models included covariate effects of body weight on clearance (CL), central volume (Vc), peripheral volume (Vp), and race (Asian vs. others) on CL.	
Model Parameter Estimates	Table 34	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Table 34 Source: Sponsor's Pharmacometrics Report, Page 28-29, Table 5-1.	Acceptable
BLQ for Parameter Accuracy	All BLQ observations were excluded from population PK analysis	Acceptable
GOF, VPC	The goodness-of-fit plots of the final population PK model are shown in Figure 22. VPCs for secukinumab concentrations in patients and external validation with Study P12301 data (Figure 23 - Figure 24) show good agreement between simulated and observed data.	Acceptable
Significant Covariates and Clinical Relevance	NA	NA
Simulation and dose selection	Three secukinumab IV maintenance regimens, i.e., 1.5, 1.75, or 2 mg/kg administered Q4W were simulated to compare with the PK of the approved secukinumab 150 and 300 mg SC regimens in PsA and axSpA patients, and the results were shown in Figure 25 - Figure 27 and Table 35. Secukinumab concentration time-profiles and PK exposures of patients treated with the 1.75 mg/kg Q4W IV regimen with loading (3.5, 6, or 10 mg/kg administered at Week 0) or without loading were simulated to compare with the approved secukinumab 150 and 300 mg SC regimens in PsA and axSpA patients. The results were shown in	Acceptable

	Figure 28, Table 36, Figure 29, Table 37 and Table 38. To limit the total maintenance dose administered to heavy patients, it is proposed to cap the maximum IV dose at 300 mg. Comparison of secukinumab exposures at steady-state (1.75 mg/kg IV, 1.75 mg/kg capped at 300 mg IV and 300 mg SC) for bodyweight effect were shown in Figure 30.	

Table 32. Clinical Studies Included in Population PK Analysis.

Study	Description	Regimens	Time-point cut-offs or data base locks
CAIN457 A2206	PoC PD study of efficacy of AIN457	2 x 10 mg/kg i.v. q3w Placebo	Complete study / PsA
CAIN457 A2209	PoC PD study of efficacy of AIN457	2 x 0.1, 1.0 or 10 mg/kg i.v. q3w Placebo	Complete study / AS
CAIN457 F2305	Phase III efficacy safety and tolerability	3 x 10 mg/kg i.v. q2w + 150 mg s.c. q4w from wk8 3 x 10 mg/kg i.v. q2w + 75 mg s.c. q4w from wk8 Placebo	Complete study / AS
CAIN457 F2306	Phase III efficacy safety and tolerability	3 x 10 mg/kg i.v. q2w + 150 mg s.c. q4w from wk8 3 x 10 mg/kg i.v. q2w + 75 mg s.c. q4w from wk8 placebo + 150 mg s.c. q4w from wk24 placebo + 75 mg s.c. q4w from wk24 placebo 150 mg s.c. q4w from wk16 placebo + 75 mg s.c. q4w from wk16 placebo	Complete study / PsA
CAIN457 F2308	Phase III efficacy safety and tolerability	5 x 300 mg s.c. q1w + 300 mg s.c. q4w from wk8 5 x placebo s.c. q1w + 2 x placebo s.c. q4w from wk8 and 150 mg s.c. q4w from wk16	Complete study / AS
CAIN457 F2310	Phase III efficacy, safety and tolerability	5 x 150 mg s.c. q1w and 150 mg s.c. q4w from wk8 5 x 75 mg s.c. q1w and 75 mg s.c. q4w from wk8 Placebo	Complete study / AS
CAIN457 F2312	Phase III efficacy, safety and tolerability	5 x 300 mg s.c. q1w + 300 mg s.c. q4w from wk8 5 x 150 mg s.c. q1w + 150 mg s.c. q4w from wk8 5 x 75 mg s.c. q1w + 75 mg s.c. q4w from wk8 placebo + 300 mg s.c. q4w from wk24 placebo + 150 mg s.c. q4w from wk24 placebo + 300 mg s.c. q4w from wk16 placebo + 150 mg s.c. q4w from wk16 placebo	Complete study / PsA
CAIN457 F2314	Phase III efficacy, safety and tolerability	3 x 10 mg/kg i.v. q2w + 150 mg s.c. q4w from wk8 3 x 10 mg/kg i.v. q2w + 300 mg s.c. q4w from wk8 Placebo	Complete study / AS
CAIN457 F2318	Phase III efficacy, safety and tolerability. Auto-injector	5 x 300 mg s.c. q1w + 300 mg s.c. q4w from wk8 5 x 150 mg s.c. q1w + 150 mg s.c. q4w from wk8 placebo + 300 mg s.c. q4w from wk24 placebo + 150 mg s.c. q4w from wk24 placebo + 300 mg s.c. q4w from wk16 placebo + 150 mg s.c. q4w from wk16 placebo	Complete study / PsA

Study	Description	Regimens	Time-point cut-offs or data base locks
CAIN457 F2320	Phase III efficacy, safety and tolerability	5 x 150 mg s.c. q1w + 150 mg s.c. q4w from wk8 150 mg s.c. q4w (no-load) placebo + 150 mg s.c. q4w from wk16	Complete study / AS
CAIN457 F2336	Phase III efficacy, safety and tolerability	150 mg s.c. q4w (no-load) 5 x 150 mg s.c. q1w + 150 mg s.c. q4w from wk8 placebo + 150 mg s.c. q4w from wk24 placebo + 150 mg s.c. q4w from wk16 placebo	Complete study / PsA
CAIN457 F2342	Phase III efficacy, safety and tolerability	150 mg s.c. q4w (no-load) 5 x 150 mg s.c. q1w + 150 mg s.c. q4w from wk8 5 x 300 mg s.c. q1w + 300 mg s.c. q4w from wk8 placebo + 150 mg s.c. q4w from wk24	Complete study /
		placebo + 300 mg s.c. q4w from wk24 placebo + 150 mg s.c. q4w from wk16 placebo + 300 mg s.c. q4w from wk16 placebo	PsA
CAIN457 H2315	Phase III efficacy, safety and tolerability	5 x 150 mg s.c. q1w + 150 mg s.c. q4w from wk8 150 mg s.c. q4w (no-load) placebo	Complete study / nr-axSpA
CAIN457 P12301	Phase III efficacy, safety and tolerability	6 mg/kg i.v. at wk0 + 3 mg/kg i.v. q4w from wk4 Placebo + 3 mg/kg i.v. q4w from wk16	Week 16 / AS or nr-axSpA
CAIN457 P12302	Phase III efficacy, safety and tolerability	6 mg/kg i.v. at wk0 + 3 mg/kg i.v. q4w from wk4 Placebo + 3 mg/kg i.v. q4w from wk16. APPEARS THIS WAY ON ORIGINAL	Week 16 / PsA

Source: Sponsor's Pharmacometrics Report, Page 17-19, Table 3-1.

Table 33. Summary of Subject Demographics – PopPK analysis dataset.

		Study							
Covariate	Statistic	A2206	A2209	F2305	F2306	F2308	F2310	F2312	F2314
	Number of Subjects (%)	28 (0)	54 (1)	360 (6)	587 (10)	453 (8)	211 (4)	387 (7)	223 (4)
Age (yrs)	Mean (SD)	46.7 (11.3)	42.6 (9.93)	41.7 (12.5)	48.9 (11.8)	34.5 (10.3)	43.2 (12.9)	47.9 (12.0)	42.7 (11.4)
	Median	49.0	42.5	40.5	50.0	32.0	44.0	49.0	42.0
	(Min-Max)	(21.0-61.0)	(23.0-65.0)	(18.0-76.0)	(20.0-77.0)	(18.0-66.0)	(19.0-77.0)	(20.0-77.0)	(20.0-73.0)
Body Weight (kg)	Mean (SD)	94.9 (25.3)	80.6 (15.1)	76.5 (17.1)	82.9 (20.6)	71.2 (16.9)	81.3 (17.0)	87.2 (19.6)	80.5 (17.3)
	Median	91.5	80.2	74.4	81.4	68.5	79.6	86.4	79.0
	(Min-Max)	(65.0-178)	(50.0-117)	(40.0-142)	(32.0-163)	(43.4-159)	(47.5-134)	(47.3-161)	(45.8-138)
Gender N (%)	Female	19 (68)	21 (39)	110 (31)	319 (54)	73 (16)	66 (31)	199 (51)	89 (40)
	Male	9 (32)	33 (61)	250 (69)	268 (46)	380 (84)	145 (69)	188 (49)	134 (60)
Race N (%)	Asian	.	1 (2)	61 (17)	114 (19)	364 (80)	9 (4)	14 (4)	3 (1)
	Black	.	1 (2)	.	5 (1)	.	.	1 (0)	5 (2)
	Caucasian	28 (100)	49 (91)	229 (64)	463 (79)	87 (19)	201 (95)	361 (93)	182 (82)
	Native American	.	.	15 (4)	.	.	1 (0)	2 (1)	15 (7)
	Other	.	3 (6)	54 (15)	3 (1)	2 (0)	.	6 (2)	17 (8)
	Pacific Islander	.	.	1 (0)	1 (0)	.	.	2 (1)	.
	Unknown	.	.	.	1 (0)	.	.	1 (0)	1 (0)
Population	AS	.	54 (100)	360 (100)	.	453 (100)	211 (100)	.	223 (100)
	nr-axSpAnr-Ax-SpA	.	.	.	.	.	.	.	.
	PsA	28 (100)	.	.	587 (100)	.	.	387 (100)	.

Covariate	Statistic	Study							
		F2318	F2320	F2336	F2342	H2315	P12301	P12302	Overall
	Number of Subjects (%)	406 (7)	346 (6)	334 (6)	964 (17)	543 (9)	516 (9)	374 (6)	5786
Age (yrs)	Mean (SD)	49.7 (12.3)	43.2 (11.7)	49.0 (12.0)	48.7 (12.3)	39.4 (11.5)	39.5 (12.1)	47.8 (13.6)	44.6 (12.9)
	Median	50.0	42.0	50.0	49.0	39.0	39.0	47.5	45.0
	(Min-Max)	(20.0-84.0)	(19.0-79.0)	(19.0-81.0)	(19.0-81.0)	(18.0-80.0)	(18.0-79.0)	(19.0-81.0)	(18.0-84.0)
Body Weight (kg)	Mean (SD)	85.4 (18.3)	81.6 (18.6)	85.0 (20.4)	83.3 (19.2)	77.9 (16.6)	78.0 (18.2)	84.7 (22.7)	81.3 (19.3)
	Median	84.2	79.8	82.2	82.2	77.0	76.0	82.3	79.8
	(Min-Max)	(42.0-147)	(46.0-161)	(49.5-172)	(36.2-174)	(42.1-151)	(42.0-157)	(37.0-183)	(32.0-183)
Gender N (%)	Female	224 (55)	108 (31)	193 (58)	475 (49)	293 (54)	178 (34)	205 (55)	2572 (44)
	Male	182 (45)	238 (69)	141 (42)	489 (51)	250 (46)	338 (66)	169 (45)	3214 (56)
Race N (%)	Asian	9 (2)	3 (1)	1 (0)	113 (12)	22 (4)	103 (20)	51 (14)	868 (15)
	Black	.	2 (1)	.	5 (1)	3 (1)	12 (2)	6 (2)	40 (1)
	Caucasian	388 (96)	340 (98)	333 (100)	789 (82)	497 (92)	354 (69)	294 (79)	4595 (79)
	Native American	2 (0)	1 (0)	.	9 (1)	.	.	.	45 (1)
	Other	7 (2)	.	.	44 (5)	19 (3)	6 (1)	4 (1)	165 (3)
	Pacific Islander	.	.	.	.	2 (0)	41 (8)	19 (5)	66 (1)
	Unknown	.	.	.	4 (0)	.	.	.	7 (0)
Population	AS	.	346 (100)	.	.	.	408 (79)	.	2055 (36)
	nr-axSpA	.	.	.	.	543 (100)	108 (21)	.	651 (11)
	PsA	406 (100)	.	334 (100)	964 (100)	.	.	374 (100)	3080 (53)

PsA = Psoriatic Arthritis, AS = Ankylosing Spondylitis, nr-axSpA = Non-Radiographic Axial Spondyloarthritis

Source: Sponsor's Pharmacometrics Report, Page 28-29, Table 5-1.

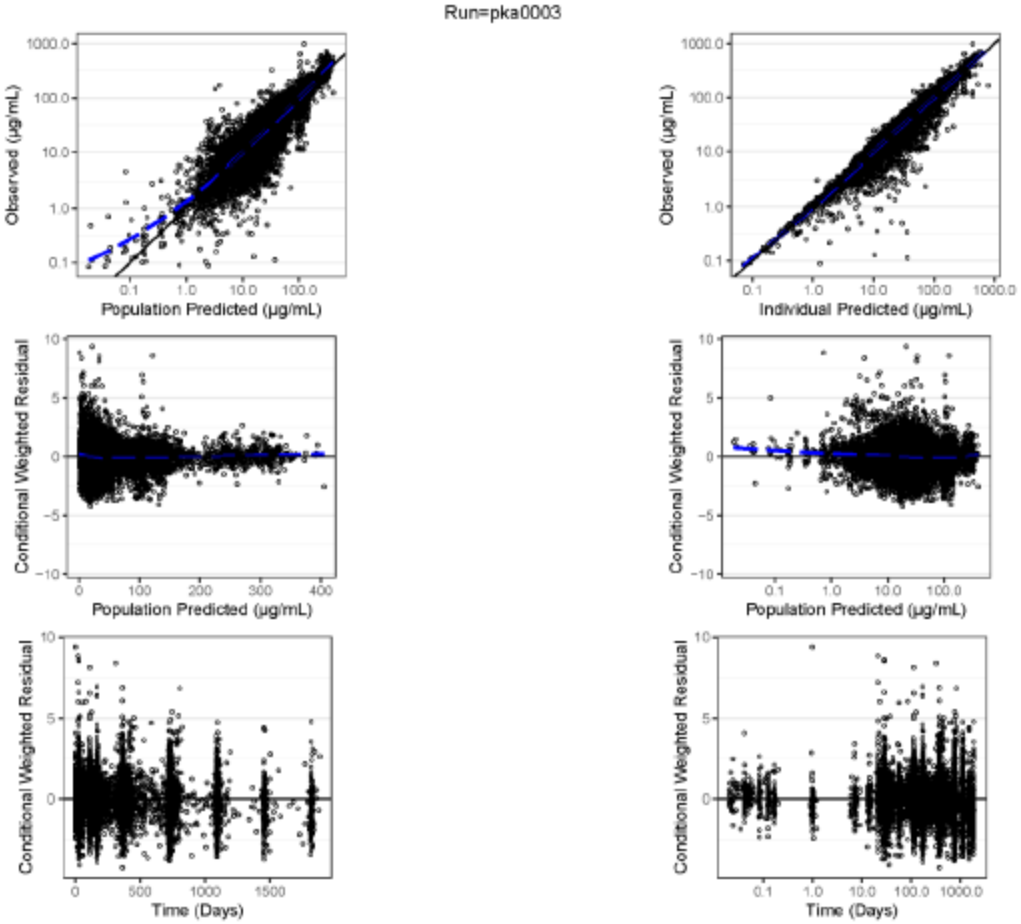
Table 34. Parameter Estimates and Variability for Secukinumab in Final Population PK Models

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	
CL [L/day]	0.171	0.836	0.168-0.174	
V_c [L]	3.32	1.44	3.23-3.41	
Q [L/day]	0.350	4.37	0.320-0.380	
V_p [L]	2.63	1.81	2.54-2.72	
KA [1/day]	0.180 fixed	-	-	
F1 (bioavailability)	0.783	0.789	0.771-0.795	
CL~Weight	0.892	2.32	0.851-0.933	
V_c~Weight	0.651	7.51	0.555-0.747	
V_p~Weight	0.712	8.02	0.600-0.824	
CL~Asian	1.13	1.18	1.10-1.16	
Inter-individual				**CV%* or R**
ω^2_{CL}	0.0912	2.47	0.0868-0.0956	30.2
Covar η_{CL}, η_{Vc}	0.0489	7.03	0.0422-0.0556	0.62
ω^2_{Vc}	0.0691	6.95	0.0597-0.0785	26.3
ω^2_{Vp}	0.113	8.23	0.0948-0.131	33.6
Residual variability				**CV%**
σ^2_{prop}	0.0544	1.15	0.0532-0.0556	23.3

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = clearance, V_c = volume of central compartment, Q = inter-compartmental exchange flow rate, V_p = volume of peripheral compartment, KA= absorption rate constant, F1=bioavailability, σ_{prop} = proportional component of the residual error model, 95% CI= 95% confidence interval on the parameter; CV% = coefficient of variation (in %); R= correlation coefficient; ω^2_{CL}, ω^2_{Vc}, ω^2_{Q}, ω^2_{Vp} and ω^2_{KA} = variance of random effect of CL, V_c, Q, V_p and KA, respectively; Covar η_{CL}, η_{Vc} = covariance of random effect of CL and V_c; σ^2_{prop} is the variance of the proportional residual error; the variance of the additive residual error was fixed to 0 as included 0 in the 95% CI when estimated; CV% = coefficient of variation (in %) calculated as the square root of the variance times 100; The reference population is a 84 kg non-Asian patient.

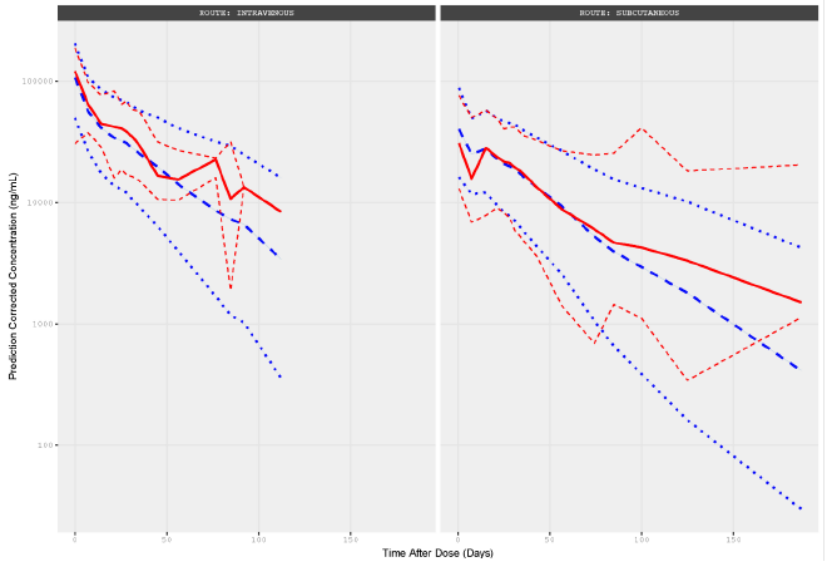
Source: Sponsor's Pharmacometrics Report, Page 35, Table 5-4.

Figure 22. Goodness-of-Fit plots for the final popPK model (pka0003) – Overall.



Source: Sponsor's Pharmacometrics Report, Page 36, Figure 5-1.

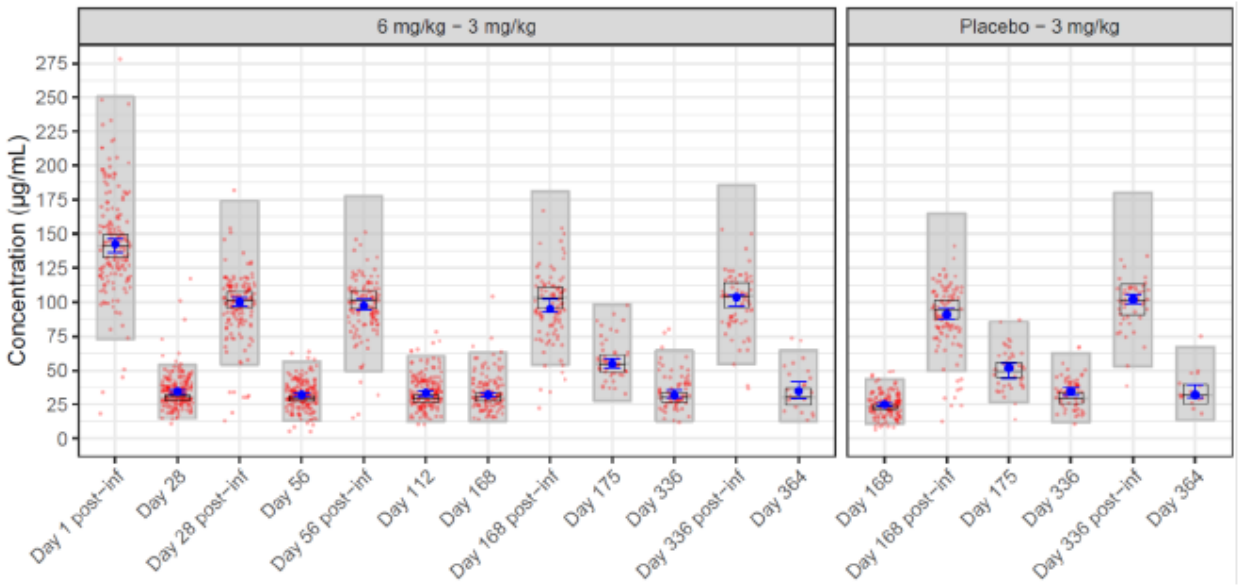
Figure 23. Prediction-Corrected VPC for the final popPK model (pka0003) based on time from secukinumab dose.



Red solid line: Median of observed concentrations; red dashed lines: 2.5th and 97.5th percentiles of observed concentrations. Blue solid line: Median of predicted concentrations; blue dashed lines: 2.5th and 97.5th percentiles of predicted concentrations.

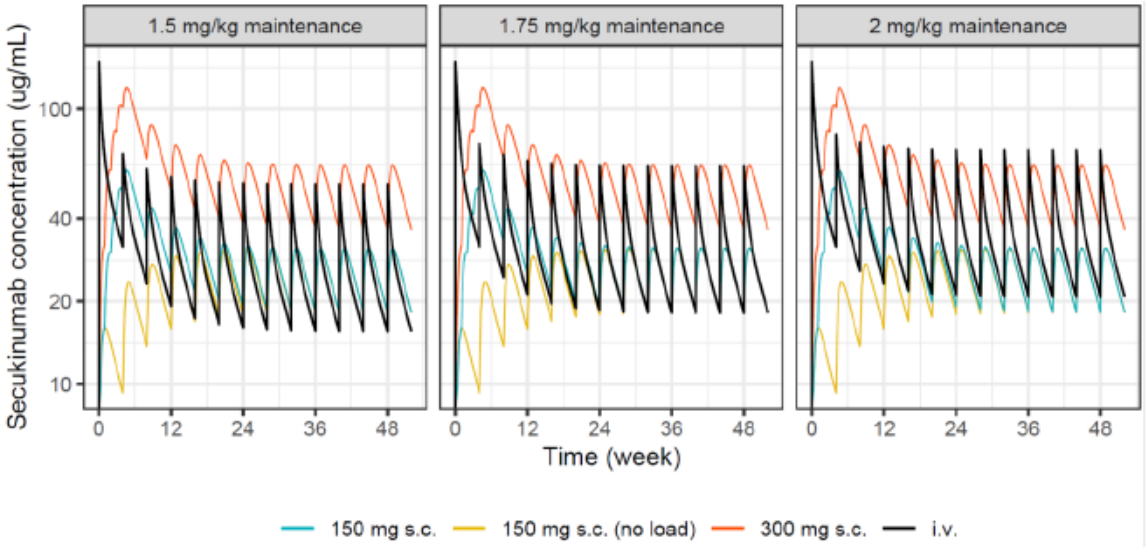
Source: Sponsor's Pharmacometrics Report, Page 52, Figure 5-13.

Figure 24. External validation of the final popPK model using Study P12301 data –VPC by treatment group and scheduled time points.



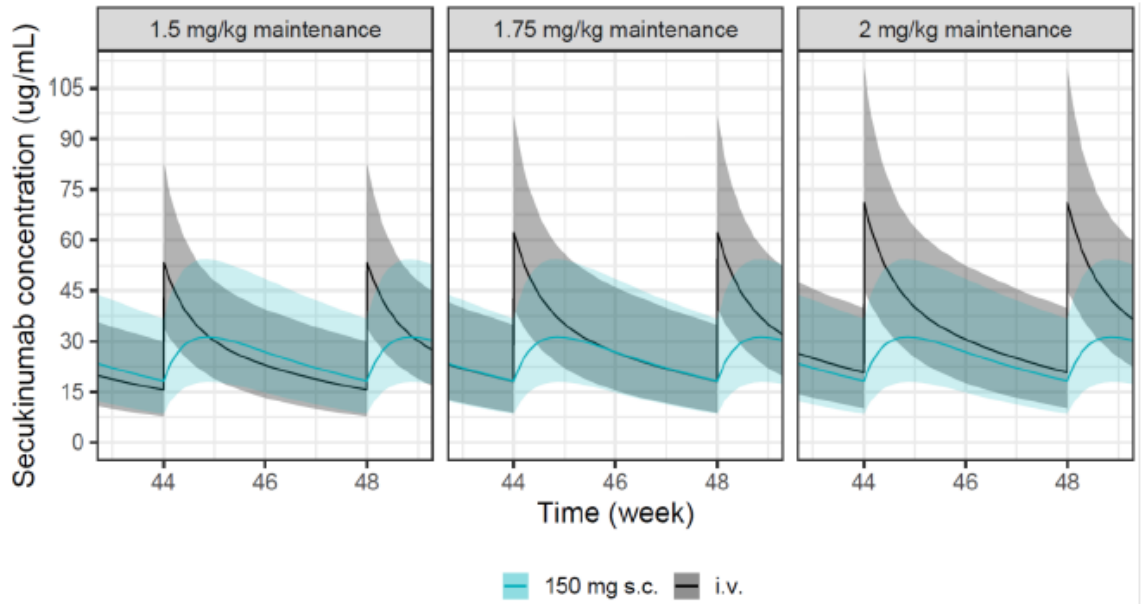
Source: Sponsor's Pharmacometrics Report, Page 63, Figure 5-22.

Figure 25. Median predicted concentration-time profiles of three IV maintenance regimens that approximate the 150 mg and the 300 mg SC regimens.



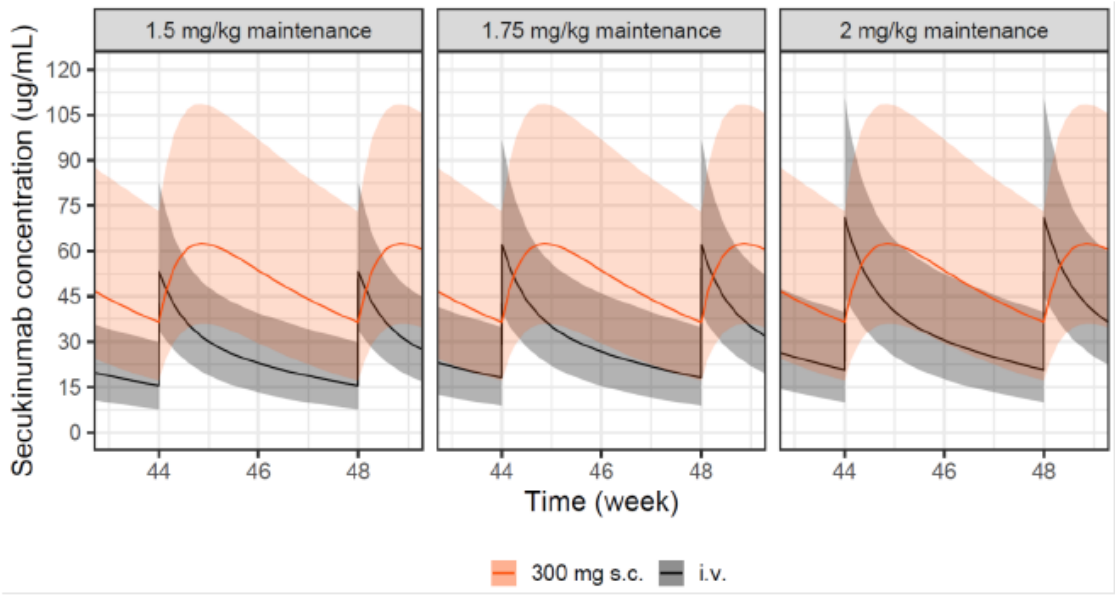
Source: Sponsor's Pharmacometrics Report, Page 67, Figure 5-24.

Figure 26. Distribution of predicted PK profiles at steady-state for the three IV regimens and the 150 mg SC Q4W regimen.



Source: Sponsor's Pharmacometrics Report, Page 68, Figure 5-25.

Figure 27. Distribution of predicted PK profiles at steady-state for the three IV regimens and the 300 mg and SC Q4W regimen



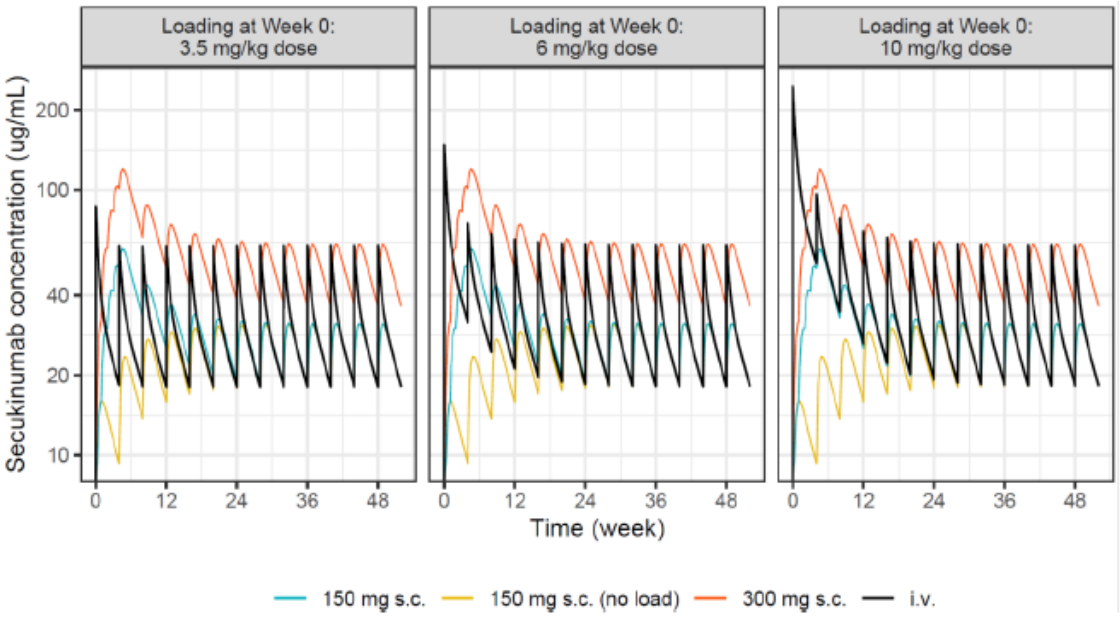
Source: Sponsor's Pharmacometrics Report, Page 69, Figure 5-26.

Table 35. Summary of predicted steady-state PK parameters of the IV and SC secukinumab regimens.

Maintenance regimen	Median (90% PI)		
	Cmin,ss	Cavg,ss	Cmax,ss
1.5 mg/kg i.v. q4w	15.6 (7.6, 29.9)	25.1 (13.7, 45.7)	53.3 (34.0, 83.0)
1.75 mg/kg i.v. q4w	18.1 (8.9, 34.8)	29.2 (16, 53.4)	62.1 (39.6, 96.9)
2 mg/kg i.v. q4w	20.7 (10.2, 39.7)	33.4 (18.2, 61.0)	71.0 (45.3, 110.7)
150 mg s.c. q4w	18.2 (8.6, 36.5)	25.1 (12.3, 50.6)	31.3 (18.0, 54.3)
300 mg s.c. q4w	36.4 (17.2, 73.2)	50.1 (24.6, 101.2)	62.6 (36.1, 108.7)

Source: Sponsor's Pharmacometrics Report, Page 69, Table 5-6.

Figure 28. Impact of three different loading doses at Week 0 on the median predicted concentration-time profiles of the 1.75 mg/kg IV maintenance regimen.



Source: Sponsor's Pharmacometrics Report, Page 71, Figure 5-27.

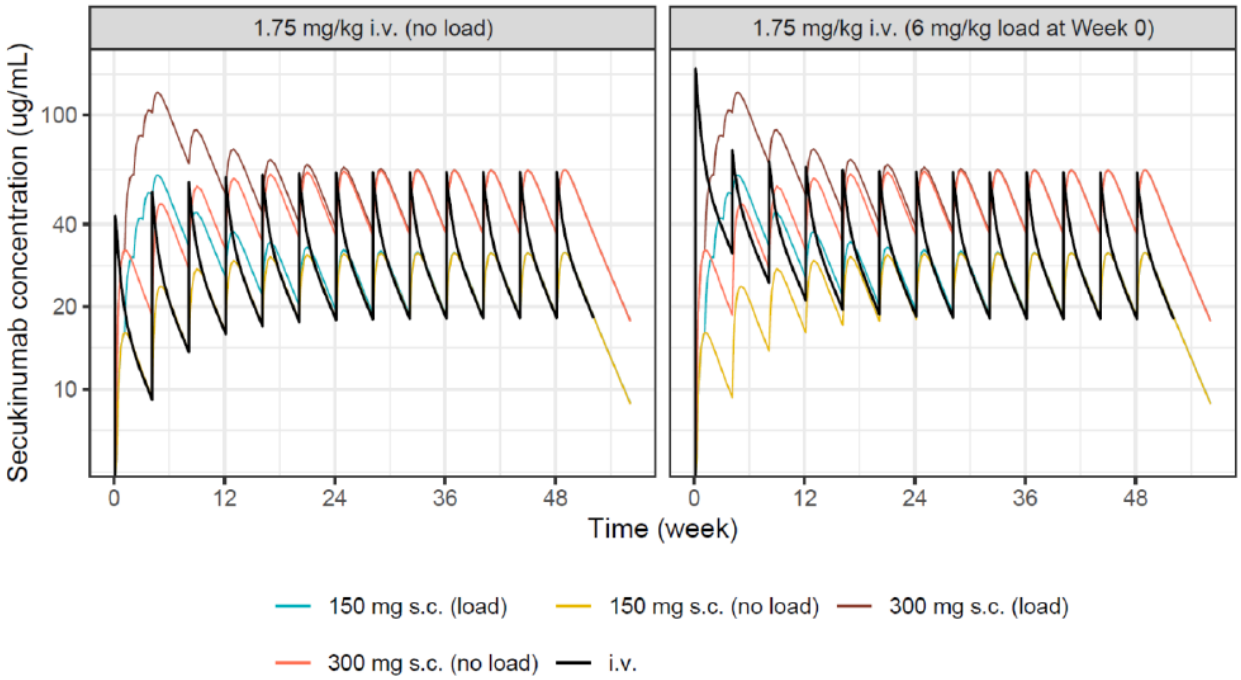
Table 36. Summary of predicted Cmin at Week 16 for various IV and SC loading regimens

	Cmin,16W
	Median (90% PI)
Loading regimens (at Week 0) with 1.75 mg/kg as maintenance	
3.5 mg/kg#	18.0 (9.1, 32.4)
6 mg/kg	19.6 (9.3, 37.3)
10 mg/kg	22.1 (10.0, 44.5)
For comparison purpose: s.c. regimens	
150 mg without loading	16.9 (8.3, 31.9)
150 mg with loading	21.6 (9.8, 43.7)
300 mg with loading	43.1 (19.7, 87.4)
Additional i.v. regimen:	
Loading regimens (at Week 0) with 1.5 mg/kg as maintenance	
3 mg/kg#	15.5 (7.8, 27.8)
6 mg/kg	17.3 (8.1, 33.4)
10 mg/kg	19.9 (8.8, 40.6)
Loading regimens (at Week 0) with 2 mg/kg as maintenance	
4 mg/kg#	20.6 (10.3, 37.0)
6 mg/kg	21.9 (10.5, 41.2)
10 mg/kg	24.5 (11.3, 48.2)

Cmin,16W = predose concentration at Week 16. The statistics (median and 90% PI) have been obtained by simulation for 3000 PsA and 3000 axSpA patients from the final popPK model pka0003. The 90% PI is the 5th and 95th percentiles of the simulations. The simulated patients' weights were obtained by bootstrapping from Studies P12301 and P12302.

Source: Sponsor's Pharmacometrics Report, Page 69, Table 5-7.

Figure 29. Median predicted concentration time-profiles (Week 0 to 52) for the 1.75 mg/kg IV maintenance regimen with and without loading, along with the 150 and 300 mg SC regimens with and without loading.



Source: Information Request – FDA on August 11, 2023, Page 8, Figure 1-3.

Table 37. Summary of predicted C_{min} of the IV and SC with or without loading secukinumab regimens

Treatment	Week 4	Week 8	Week 12	Week 16	Steady-state
	Median (90% PI)	Median (90% PI)	Median (90% PI)	Median (90% PI)	Median (90% PI)
1.75 mg/kg i.v. (load)	31.2 (18.8, 48.7)	24.4 (12.6, 41.6)	21.1 (10.3, 38.5)	19.5 (9.4, 36.7)	18 (8.9, 34.5)
1.75 mg/kg i.v. (no load)	9.2 (5.5, 14.3)	13.7 (7.6, 22.3)	15.9 (8.4, 27.1)	17 (8.7, 30)	18.1 (8.8, 34.9)
150 mg s.c. (load)	51 (32.6, 78.6)	33.3 (17.2, 59.3)	25.5 (11.8, 49.2)	21.8 (9.9, 44)	18.4 (8.7, 37)
150 mg s.c. (no load)	9.3 (5.2, 15.7)	13.8 (7.3, 24.3)	16 (8.2, 29.2)	17.1 (8.5, 32.1)	18.3 (8.8, 36.6)
300 mg s.c. (load)	101.9 (65.2, 157.2)	66.5 (34.5, 118.6)	51 (23.7, 98.4)	43.7 (19.7, 88.1)	36.8 (17.4, 74)
300 mg s.c. (no load)	18.6 (10.4, 31.4)	27.6 (14.6, 48.6)	32.1 (16.3, 58.4)	34.3 (17, 64.2)	36.7 (17.5, 73.2)

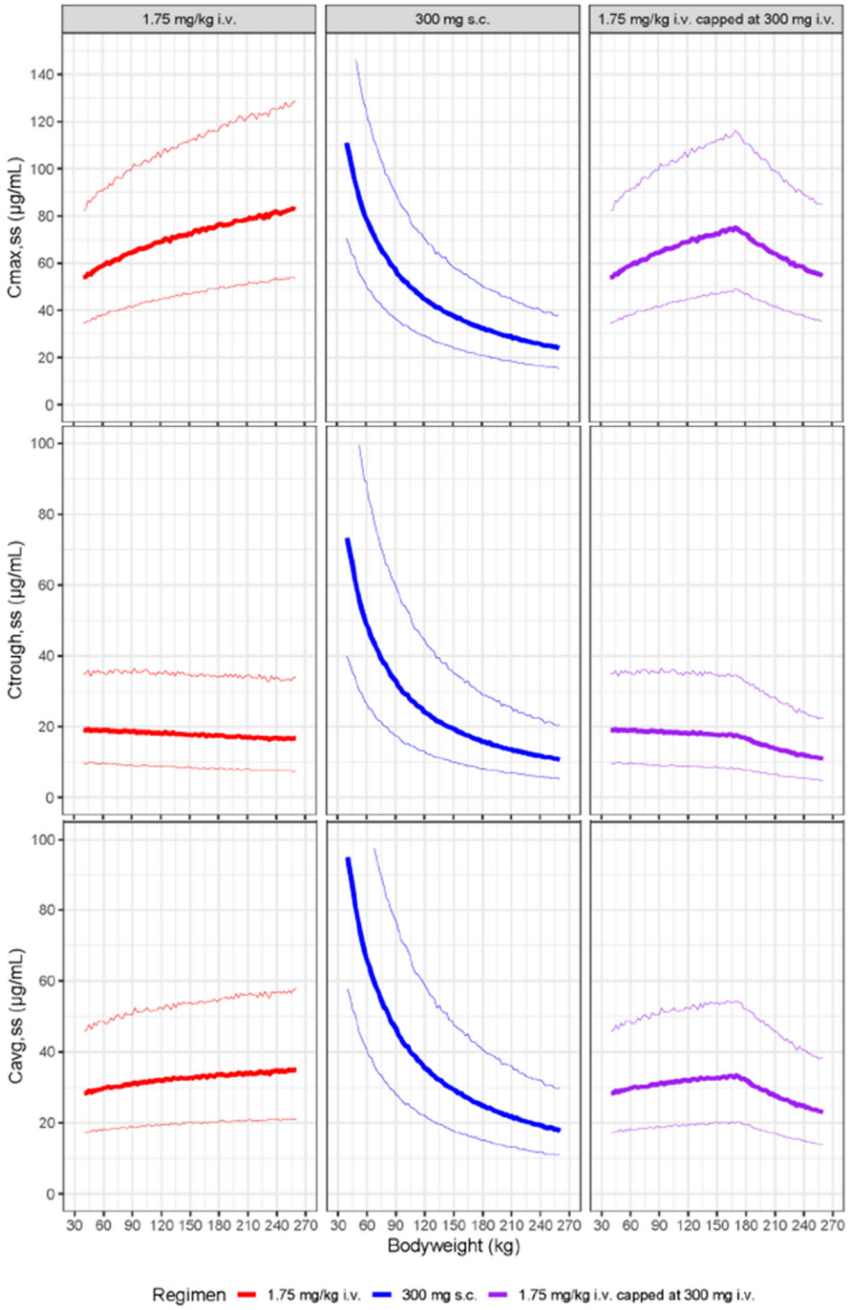
Source: Information Request – FDA on August 11, 2023, Page 9, Table 1-1.

Table 38. Summary of predicted C_{max} of the IV and SC with or without loading secukinumab regimens

Treatment	Week 0-3	Week 4-7	Week 8-11	Week 12-15	Steady-state
	Median (90% PI)	Median (90% PI)	Median (90% PI)	Median (90% PI)	Median (90% PI)
1.75 mg/kg i.v. (load)	148.1 (94, 232.5)	74.7 (49.3, 111.7)	67.8 (43.7, 104.1)	64.7 (41.3, 100.6)	61.8 (39.6, 96.4)
1.75 mg/kg i.v. (no load)	43.1 (27.5, 68.5)	52.4 (34.3, 80.8)	57.2 (37.2, 87.3)	59.5 (38.5, 91.3)	62.1 (39.6, 97.4)
150 mg s.c. (load)	52.2 (33.7, 79.8)	60.6 (38.4, 93.8)	44.2 (25.1, 74.7)	37.6 (21, 65.6)	31.6 (18.3, 54.9)
150 mg s.c. (no load)	16.2 (10.8, 23.6)	23.8 (15.1, 36.5)	27.6 (16.9, 43.8)	29.5 (17.7, 48.1)	31.5 (18.3, 54.8)
300 mg s.c. (load)	104.4 (67.5, 159.5)	121.1 (76.8, 187.7)	88.5 (50.2, 149.5)	75.2 (42, 131.2)	63.2 (36.6, 109.8)
300 mg s.c. (no load)	32.3 (21.7, 47.1)	47.6 (30.2, 73)	55.1 (33.9, 87.7)	58.9 (35.4, 96.3)	63 (36.6, 109.5)

Source: Information Request – FDA on August 11, 2023, Page 10, Table 1-2.

Figure 30. Effect of body weight on secukinumab C_{max}, C_{trough} and C_{avg} at steady-state.



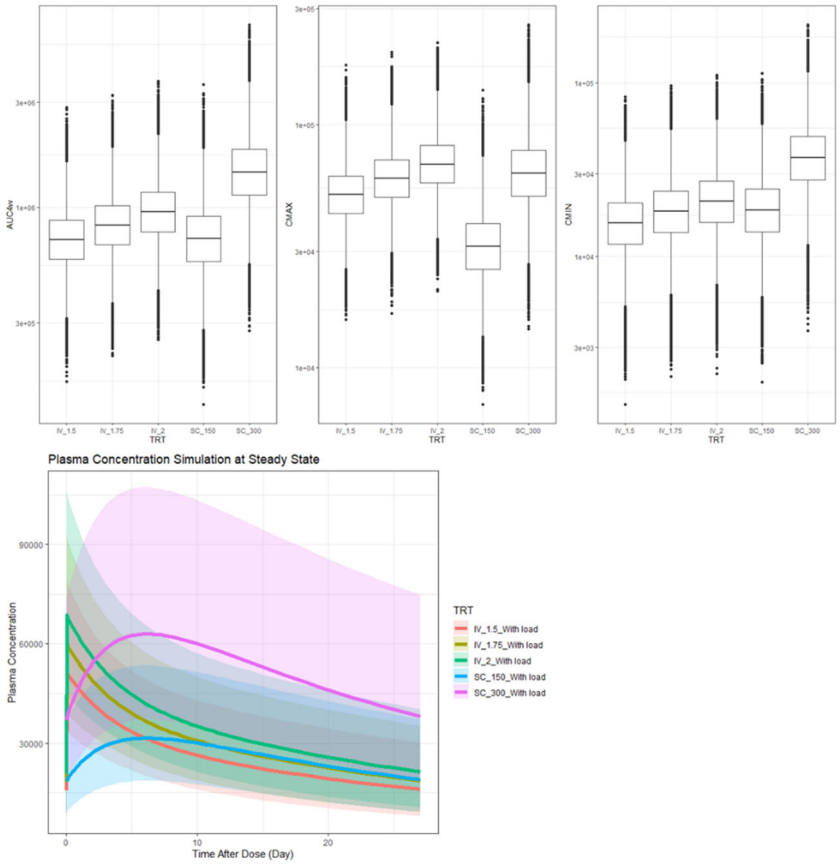
Source: Sponsor's Pharmacometrics Report, Page 73-75, Figure 5-28 to Figure 5-30.

The FDA's Assessment:

The result of population PK analysis for secukinumab in patients with AS, PsA and nr-axSpA were checked by the reviewer. The results of the population PK modeling and simulation were generally acceptable due to the agreement of prediction and observation. No PK difference was observed across different patient populations. Simulation of 1.75 mg/kg (up to 300 mg) IV

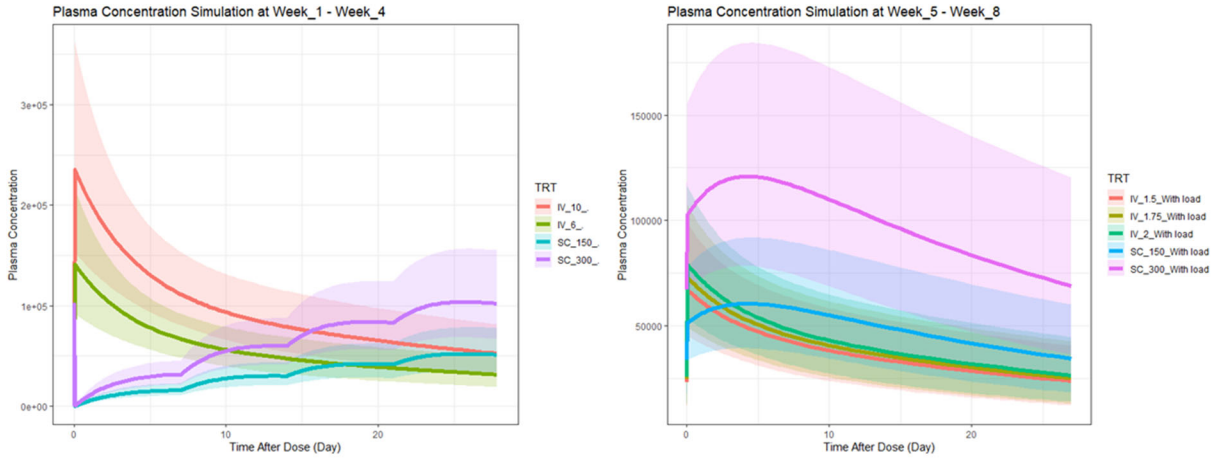
regimen results in comparable $C_{min,ss}$ to 150 mg Q4W SC regimen, comparable $C_{max,ss}$ to 300 mg Q4W SC regimen and $C_{avg,ss}$ between 150 mg and 300 mg SC regimens in maintenance treatment (Figure 31). Simulation of 6 mg/kg IV regimen with loading dose results in comparable initial concentration levels to the approved SC regimen with loading dose, except for C_{min} at day 28 (39% lower than 150 mg SC regimen with loading, higher than SC regimen without loading) (Figure 32). Simulation IV regimen of 1.75 mg/kg without loading results in comparable C_{min} to approved 150 mg SC regimen without loading dose, and slightly higher C_{max} than 300 mg SC regimen without loading dose in the first 4 weeks (Figure 29, Table 37 and Table 38). Body weight effects on secukinumab exposures under IV and SC dosing regimen were shown in Figure 33. Subjects with higher bodyweight tend to have higher exposure under proposed IV regimen than SC regimen, while the exposure is still within the range of all patients. The exposure differences across different bodyweight groups under IV regimen are similar as that under SC regimen. In summary, the population PK modeling and simulation suggest the proposed IV dosing regimen of 1.75 mg/kg with or without loading dose provides similar exposure to the approved SC dosing regimen and is therefore acceptable.

Figure 31. Comparison of secukinumab exposures under different maintenance doses at steady state.



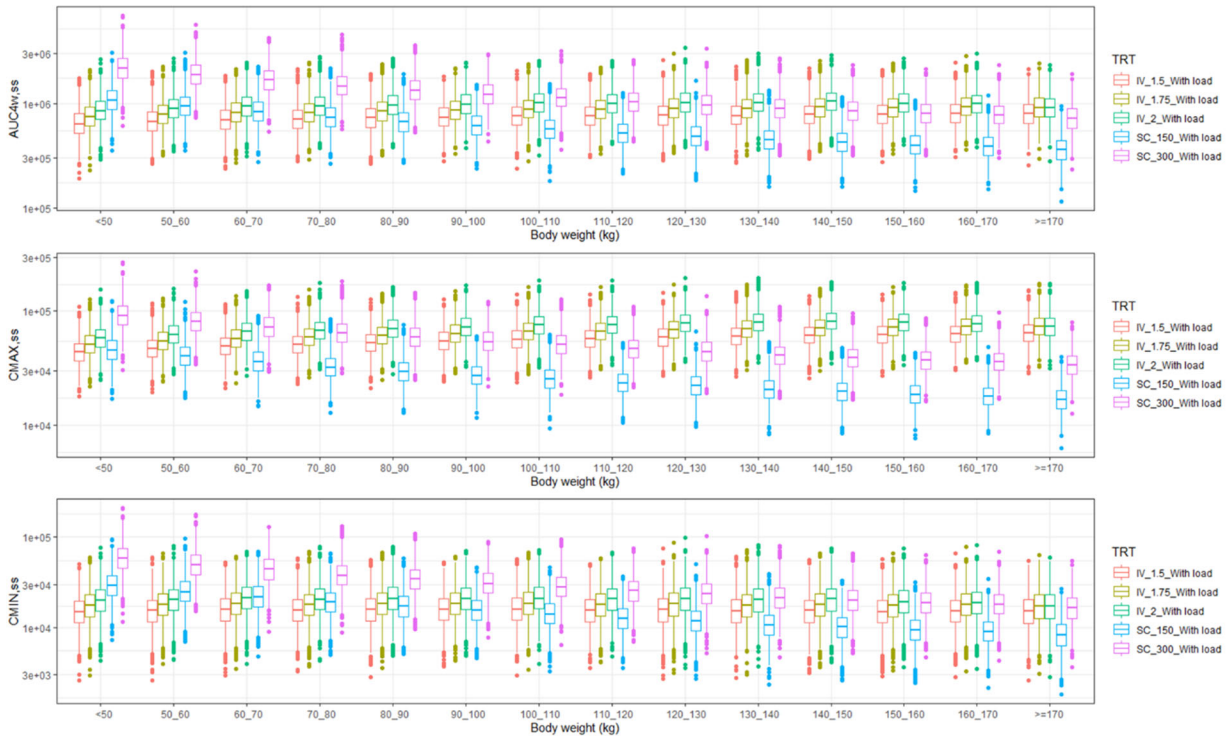
Source: Reviewer's analysis.

Figure 32. Comparison of secukinumab exposures under different loading doses at Week 1 to Week 8.



Source: Reviewer's analysis.

Figure 33. Comparison of secukinumab steady-state exposures under different doses in bodyweight groups.



Source: Reviewer's analysis.

16.3.4. **E-R Analysis for Efficacy**

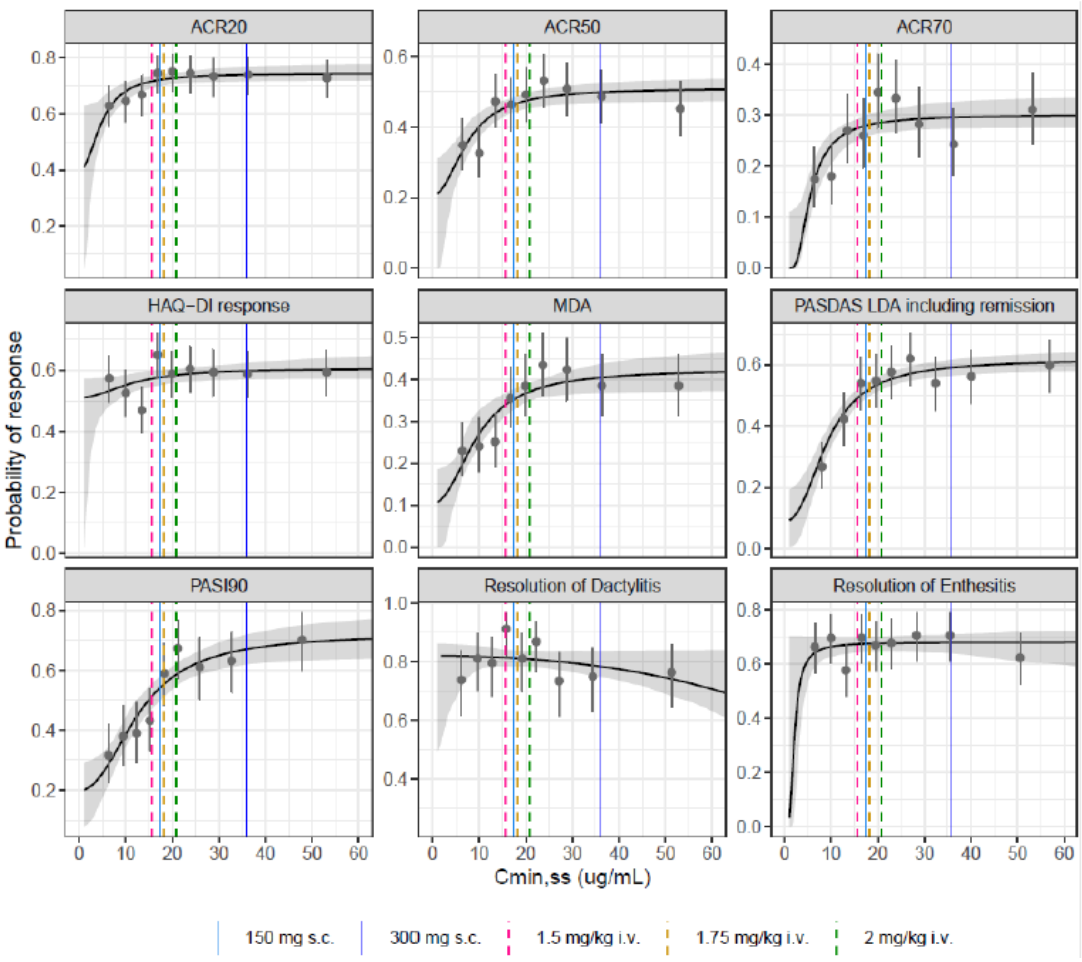
E-R Efficacy Summary

General Information		
Goal of E-R analysis		To predict the safety and efficacy of the proposed secukinumab IV regimen by exposure-response analysis.
Study Included		CAIN457F2305, CAIN457F2306, CAIN457F2308, CAIN457F2310, CAIN457F2312, CAIN457F2314, CAIN457F2318, CAIN457F2320, CAIN457F2336, CAIN457F2342, CAIN457P12301, CAIN457P12302
Endpoint		Patients with AS (Week 16 and Week 52) ASAS20, ASAS40, ASAS 5/6, ASAS PR, ASDAS-CRP MI, ASDAS-CRP ID, BASDAI50 Patients with PsA (Week and Week 52) ACR20, ACR50, ACR70, MDA, PASDAS LDA IR, HAQ-DI R, PASI90, R Dactylitis, R Enthesitis.
No. of Patients (total, and with individual PK)		Patients with AS: Approximate 1236 at Week 16, 1066 at Week 52 in treatment group Approximate 694 at Week 16, 578 at Week 52 in placebo group Patients with PsA: Approximate 1955 at Week 16, 1620 at Week 52 in treatment group Approximate 976 at Week 16, 724 at Week 52 in treatment group
Population Characteristics	General	Patients with AS at Week 52: Age median: 39 (range: 18-77) years Weight median: 76 (range: 40 - 161) kg Sex: 1198 (73%) males Race: 1085 (66%) White 443 (17%) Asian 116 (7%) Other or missing Patients with PsA at Week 52: Age median: 50 (range: 19-84) years Weight median: 83 (range: 32 - 174) kg Sex: 1129 (48%) males

		Race: 2036 (87%) White 227 (10%) Asian 81 (3%) Other or missing	
	Pediatrics (if any)	NA	
Dose(s) Included		Patients with AS at week 16 IV: 6mg/kg - 3mg/kg SC: 75 mg, 150 mg (no load), 150 mg (load) Patients with PsA at week 16 IV: 6mg/kg - 3mg/kg SC: 75 mg, 150 mg (no load), 150 mg (load), 300 mg Patients with AS at week 52 IV: 6mg/kg - 3mg/kg SC: 75 mg, 150 mg, 300mg, Patients with PsA at week 52 SC: 75 mg, 150 mg, 300mg	
Exposure Metrics Explored (range)		Patients with AS at week 16 C_{min}: 0.1 – 134 µg/mL Patients with PsA at week 16 C_{min}: 2.4 – 141 µg/mL Patients with AS at week 52 C_{min}: 0.3 – 71 µg/mL Patients with PsA at week 52 C_{min}: 1 -110 µg/mL	
Covariates Evaluated		NA	
Final Model Parameters		Summary	Acceptability [FDA's comments]
Model Structure		Logistic regression with a sigmoidal Emax function of $C_{min,ss}$	Acceptable
Visualization of E-R relationships		The relationship between secukinumab $C_{min,ss}$ and the efficacy response at Week 16 or Week 52 was estimated for each efficacy endpoint separately by means of a logistic regression analysis and shown in Figure 34 - Figure 37. The median $C_{min,ss}$ of the proposed IV regimen and two approved SC regimens were also shown in the plots. Model predicted efficacy endpoints were shown in Table 39-	Acceptable

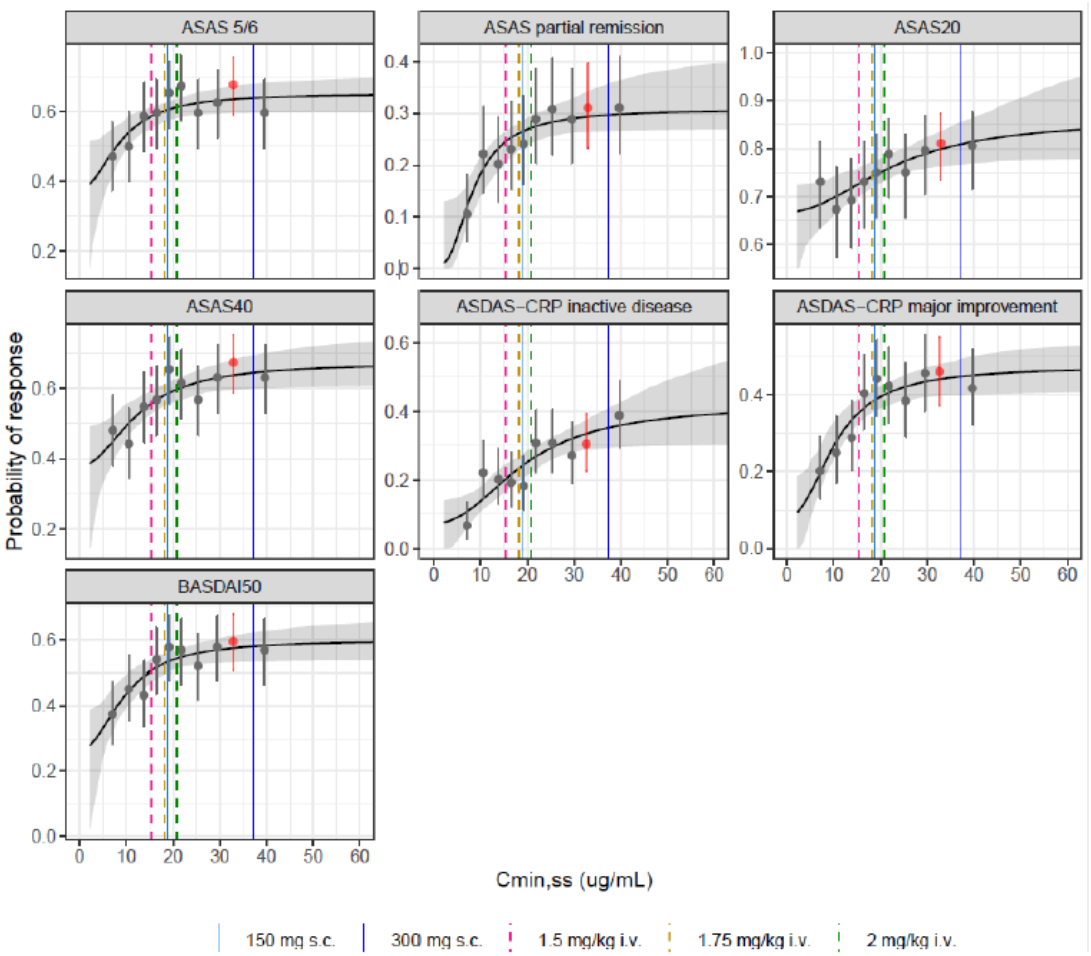
	Table 42. The predicted efficacy at the median $C_{min,ss}$ of proposed IV regimen (1.75 mg/kg) are similar as the approved 150 mg SC regimen due to the similar exposures. Slight improvements were observed with the 2 mg/kg compared with 1.75 mg/kg IV regimen.	

Figure 34. Exposure-response relationship at Week 52 – PsA efficacy endpoints.



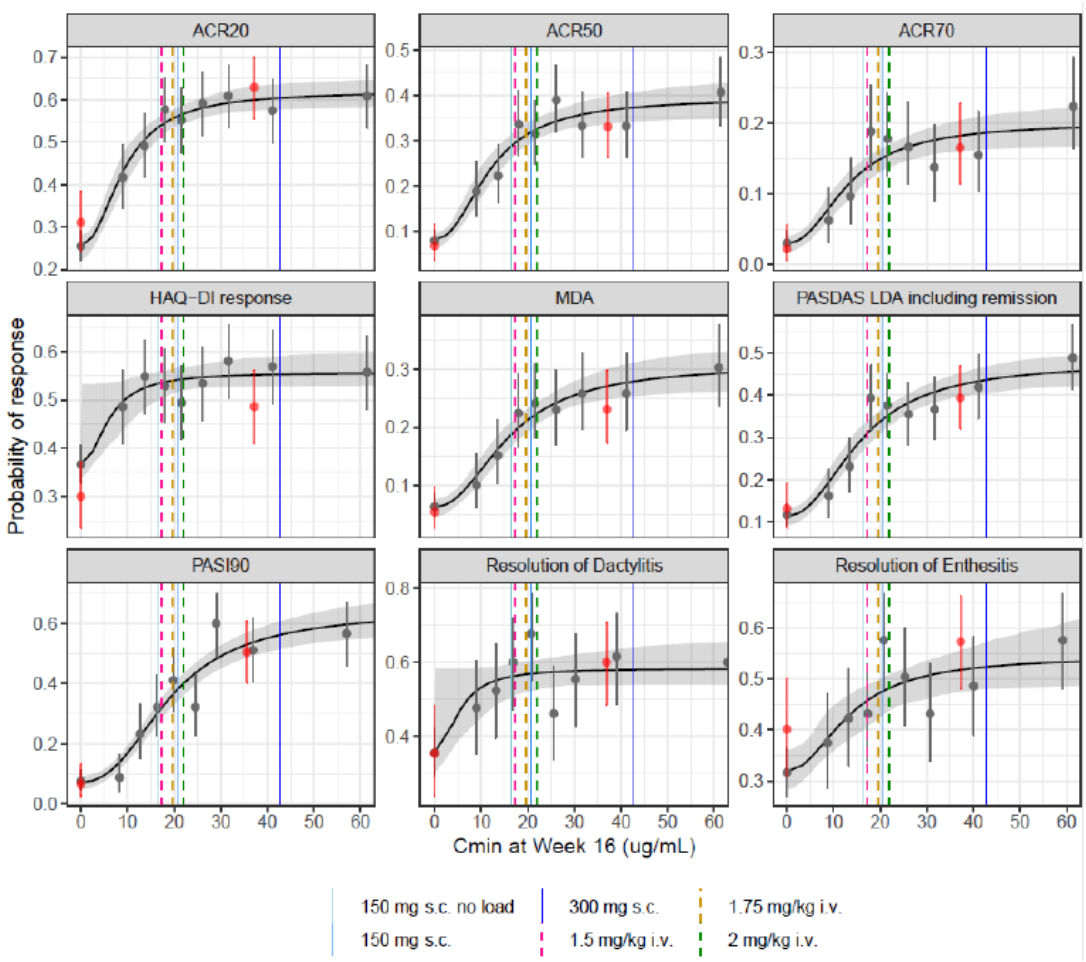
Source: Sponsor's Pharmacometrics Report, Page 79, Figure 5-31.

Figure 35. Exposure-response relationship at Week 52 – AS efficacy endpoints



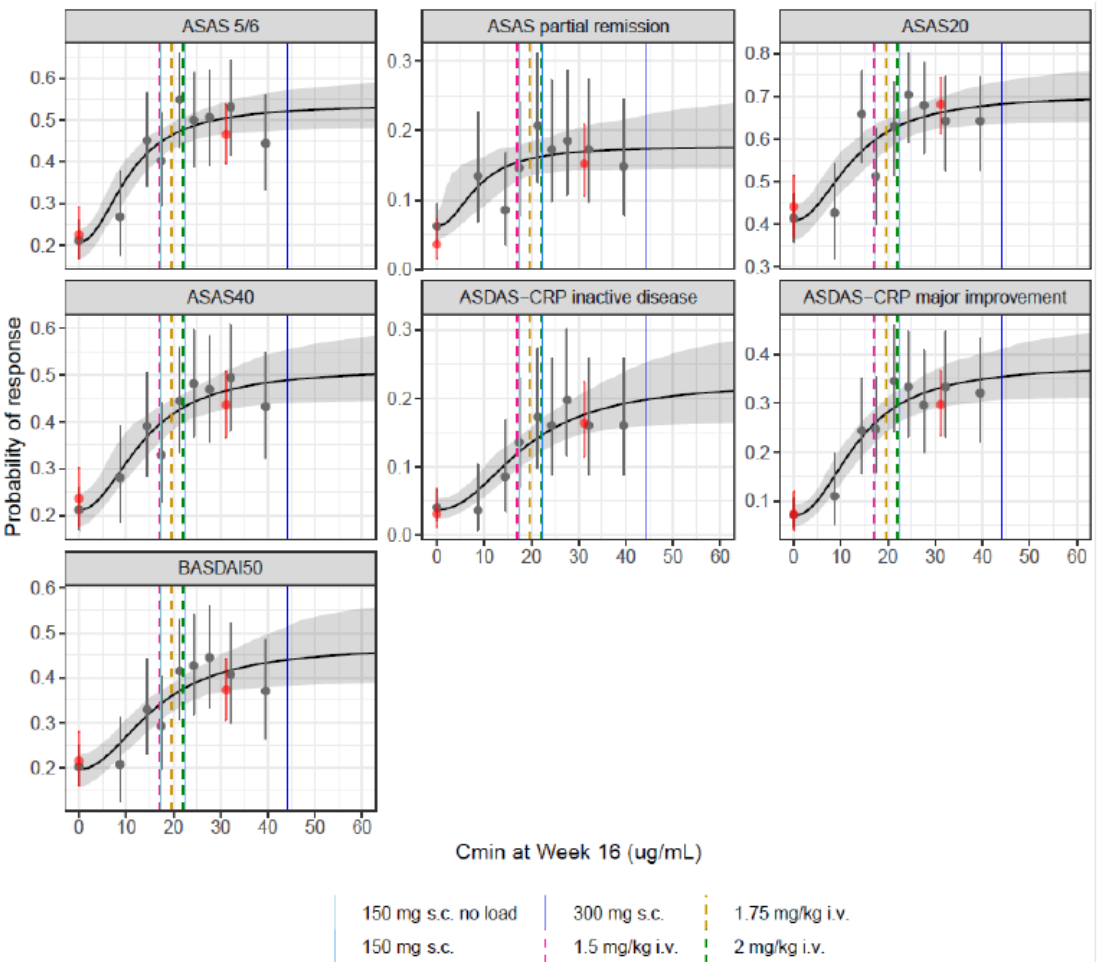
Source: Sponsor's Pharmacometrics Report, Page 80, Figure 5-32.

Figure 36. Exposure-response relationships at Week 16 – PsA efficacy endpoints.



Source: Sponsor's Pharmacometrics Report, Page 84, Figure 5-33.

Figure 37. Exposure-response relationship at Week 16 – AS efficacy endpoints.



Source: Sponsor's Pharmacometrics Report, Page 80, Figure 5-34.

Table 39. Treatment effect estimates at Week 52 – PsA efficacy endpoints.

		Probability of response	
Efficacy endpoint	Treatment group	Mean predicted	90% CI
ACR20	150 mg s.c.	0.71	(0.69; 0.73)
	300 mg s.c.	0.74	(0.71; 0.76)
	1.5 mg/kg i.v.	0.71	(0.68; 0.72)
	1.75 mg/kg i.v.	0.72	(0.69; 0.73)
	2 mg/kg i.v.	0.72	(0.7; 0.74)
ACR50	150 mg s.c.	0.45	(0.43; 0.48)
	300 mg s.c.	0.49	(0.46; 0.52)
	1.5 mg/kg i.v.	0.44	(0.42; 0.47)
	1.75 mg/kg i.v.	0.46	(0.44; 0.48)
	2 mg/kg i.v.	0.47	(0.45; 0.49)
ACR70	150 mg s.c.	0.27	(0.25; 0.29)
	300 mg s.c.	0.29	(0.28; 0.32)
	1.5 mg/kg i.v.	0.27	(0.24; 0.28)
	1.75 mg/kg i.v.	0.27	(0.26; 0.29)
	2 mg/kg i.v.	0.28	(0.26; 0.3)
MDA	150 mg s.c.	0.34	(0.32; 0.37)
	300 mg s.c.	0.4	(0.36; 0.42)
	1.5 mg/kg i.v.	0.33	(0.31; 0.36)
	1.75 mg/kg i.v.	0.35	(0.33; 0.37)
	2 mg/kg i.v.	0.36	(0.34; 0.38)
PASDAS LDA including remission	150 mg s.c.	0.49	(0.47; 0.52)
	300 mg s.c.	0.58	(0.55; 0.61)
	1.5 mg/kg i.v.	0.47	(0.45; 0.5)
	1.75 mg/kg i.v.	0.5	(0.48; 0.52)
	2 mg/kg i.v.	0.52	(0.5; 0.54)
HAQ-DI response	150 mg s.c.	0.57	(0.55; 0.6)
	300 mg s.c.	0.59	(0.56; 0.62)
	1.5 mg/kg i.v.	0.57	(0.55; 0.59)
	1.75 mg/kg i.v.	0.58	(0.55; 0.6)
	2 mg/kg i.v.	0.58	(0.56; 0.6)
PASI90	150 mg s.c.	0.53	(0.49; 0.56)
	300 mg s.c.	0.65	(0.61; 0.7)
	1.5 mg/kg i.v.	0.5	(0.46; 0.54)
	1.75 mg/kg i.v.	0.54	(0.5; 0.57)
	2 mg/kg i.v.	0.57	(0.53; 0.6)
Resolution of Dactylitis	150 mg s.c.	0.81	(0.78; 0.84)
	300 mg s.c.	0.76	(0.73; 0.83)
	1.5 mg/kg i.v.	0.81	(0.78; 0.84)
	1.75 mg/kg i.v.	0.81	(0.78; 0.84)
	2 mg/kg i.v.	0.8	(0.78; 0.84)
Resolution of Enthesitis	150 mg s.c.	0.67	(0.65; 0.7)
	300 mg s.c.	0.68	(0.63; 0.71)
	1.5 mg/kg i.v.	0.67	(0.65; 0.7)
	1.75 mg/kg i.v.	0.67	(0.65; 0.7)
	2 mg/kg i.v.	0.68	(0.65; 0.7)

Source: Sponsor's Pharmacometrics Report, Page 81, Table 5-10.

Table 40. Treatment effect estimates at Week 52 – AS efficacy endpoints.

		Probability of response	
Efficacy endpoint	Treatment group	Mean predicted	90% CI
ASAS20	150 mg s.c.	0.75	(0.72; 0.77)
	300 mg s.c.	0.8	(0.77; 0.85)
	1.5 mg/kg i.v.	0.73	(0.7; 0.75)
	1.75 mg/kg i.v.	0.74	(0.72; 0.77)
	2 mg/kg i.v.	0.75	(0.73; 0.78)
ASAS40	150 mg s.c.	0.58	(0.55; 0.6)
	300 mg s.c.	0.64	(0.59; 0.68)
	1.5 mg/kg i.v.	0.55	(0.52; 0.58)
	1.75 mg/kg i.v.	0.57	(0.54; 0.59)
	2 mg/kg i.v.	0.59	(0.56; 0.61)
ASAS 5/6	150 mg s.c.	0.59	(0.57; 0.62)
	300 mg s.c.	0.63	(0.59; 0.67)
	1.5 mg/kg i.v.	0.58	(0.55; 0.61)
	1.75 mg/kg i.v.	0.59	(0.56; 0.62)
	2 mg/kg i.v.	0.6	(0.58; 0.63)
ASAS partial remission	150 mg s.c.	0.25	(0.23; 0.28)
	300 mg s.c.	0.29	(0.26; 0.36)
	1.5 mg/kg i.v.	0.23	(0.2; 0.26)
	1.75 mg/kg i.v.	0.25	(0.22; 0.27)
	2 mg/kg i.v.	0.26	(0.24; 0.29)
ASDAS-CRP major improvement	150 mg s.c.	0.37	(0.34; 0.39)
	300 mg s.c.	0.44	(0.4; 0.49)
	1.5 mg/kg i.v.	0.34	(0.31; 0.37)
	1.75 mg/kg i.v.	0.37	(0.33; 0.39)
	2 mg/kg i.v.	0.39	(0.36; 0.41)
ASDAS-CRP inactive disease	150 mg s.c.	0.24	(0.22; 0.26)
	300 mg s.c.	0.34	(0.29; 0.4)
	1.5 mg/kg i.v.	0.21	(0.18; 0.23)
	1.75 mg/kg i.v.	0.23	(0.21; 0.25)
	2 mg/kg i.v.	0.26	(0.23; 0.28)
BASDAI50	150 mg s.c.	0.52	(0.49; 0.55)
	300 mg s.c.	0.57	(0.53; 0.62)
	1.5 mg/kg i.v.	0.5	(0.46; 0.53)
	1.75 mg/kg i.v.	0.51	(0.48; 0.55)
	2 mg/kg i.v.	0.53	(0.5; 0.56)

Source: Sponsor's Pharmacometrics Report, Page 82, Table 5-11.

Table 41. Treatment effects estimates at Week 16 – PsA efficacy endpoints.

		Probability of response	
Efficacy endpoint	Treatment group	Mean predicted	90% CI
ACR20	150 mg s.c. no load	0.52	(0.5; 0.55)
	150 mg s.c.	0.55	(0.53; 0.57)
	300 mg s.c.	0.6	(0.57; 0.63)
	1.5 mg/kg i.v.	0.53	(0.5; 0.55)
	1.75 mg/kg i.v.	0.54	(0.52; 0.56)
	2 mg/kg i.v.	0.55	(0.53; 0.58)
ACR50	150 mg s.c. no load	0.28	(0.26; 0.3)
	150 mg s.c.	0.31	(0.29; 0.33)
	300 mg s.c.	0.37	(0.33; 0.39)
	1.5 mg/kg i.v.	0.29	(0.26; 0.31)
	1.75 mg/kg i.v.	0.3	(0.28; 0.32)
	2 mg/kg i.v.	0.31	(0.29; 0.33)
ACR70	150 mg s.c. no load	0.13	(0.11; 0.15)
	150 mg s.c.	0.15	(0.13; 0.16)
	300 mg s.c.	0.18	(0.16; 0.21)
	1.5 mg/kg i.v.	0.13	(0.12; 0.15)
	1.75 mg/kg i.v.	0.14	(0.13; 0.16)
	2 mg/kg i.v.	0.15	(0.13; 0.17)
MDA	150 mg s.c. no load	0.19	(0.17; 0.21)
	150 mg s.c.	0.21	(0.19; 0.23)
	300 mg s.c.	0.27	(0.24; 0.3)
	1.5 mg/kg i.v.	0.19	(0.17; 0.21)
	1.75 mg/kg i.v.	0.21	(0.19; 0.22)
	2 mg/kg i.v.	0.22	(0.2; 0.23)
PASDAS LDA including remission	150 mg s.c. no load	0.3	(0.27; 0.32)
	150 mg s.c.	0.34	(0.31; 0.36)
	300 mg s.c.	0.42	(0.39; 0.45)
	1.5 mg/kg i.v.	0.31	(0.28; 0.33)
	1.75 mg/kg i.v.	0.33	(0.3; 0.35)
	2 mg/kg i.v.	0.34	(0.32; 0.37)
HAQ-DI response	150 mg s.c. no load	0.53	(0.5; 0.55)
	150 mg s.c.	0.54	(0.51; 0.56)
	300 mg s.c.	0.55	(0.53; 0.59)
	1.5 mg/kg i.v.	0.53	(0.5; 0.55)
	1.75 mg/kg i.v.	0.53	(0.51; 0.56)
	2 mg/kg i.v.	0.54	(0.52; 0.56)
PASI90	150 mg s.c.	0.31	(0.28; 0.34)
	150 mg s.c.	0.37	(0.34; 0.4)
	300 mg s.c.	0.54	(0.49; 0.59)
	1.5 mg/kg i.v.	0.32	(0.29; 0.35)
	1.75 mg/kg i.v.	0.36	(0.33; 0.39)
	2 mg/kg i.v.	0.39	(0.36; 0.42)
Resolution of Dactylitis	150 mg s.c. no load	0.56	(0.51; 0.59)
	150 mg s.c.	0.56	(0.53; 0.6)
	300 mg s.c.	0.58	(0.54; 0.63)
	1.5 mg/kg i.v.	0.56	(0.51; 0.59)
	1.75 mg/kg i.v.	0.56	(0.52; 0.6)
	2 mg/kg i.v.	0.57	(0.53; 0.6)
Resolution of Enthesitis	150 mg s.c. no load	0.45	(0.42; 0.48)
	150 mg s.c.	0.47	(0.44; 0.5)
	300 mg s.c.	0.52	(0.48; 0.56)
	1.5 mg/kg i.v.	0.45	(0.42; 0.49)
	1.75 mg/kg i.v.	0.47	(0.44; 0.5)
	2 mg/kg i.v.	0.48	(0.45; 0.51)

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Source: Sponsor's Pharmacometrics Report, Page 86-87, Table 5-12.

Table 42. Treatment effects estimates at Week 16 – AS efficacy endpoints.

		Probability of response	
Efficacy endpoint	Treatment group	Mean predicted	90% CI
ASAS20	150 mg s.c. no load	0.59	(0.56; 0.62)
	150 mg s.c.	0.62	(0.59; 0.64)
	300 mg s.c.	0.67	(0.63; 0.72)
	1.5 mg/kg i.v.	0.59	(0.55; 0.62)
	1.75 mg/kg i.v.	0.6	(0.57; 0.63)
	2 mg/kg i.v.	0.62	(0.59; 0.64)
ASAS40	150 mg s.c. no load	0.39	(0.36; 0.43)
	150 mg s.c.	0.42	(0.38; 0.45)
	300 mg s.c.	0.48	(0.43; 0.56)
	1.5 mg/kg i.v.	0.39	(0.35; 0.42)
	1.75 mg/kg i.v.	0.4	(0.37; 0.44)
	2 mg/kg i.v.	0.42	(0.38; 0.45)
ASAS 5/6	150 mg s.c. no load	0.44	(0.4; 0.48)
	150 mg s.c.	0.46	(0.43; 0.5)
	300 mg s.c.	0.51	(0.47; 0.56)
	1.5 mg/kg i.v.	0.43	(0.4; 0.47)
	1.75 mg/kg i.v.	0.45	(0.41; 0.49)
	2 mg/kg i.v.	0.46	(0.43; 0.5)
ASAS partial remission	150 mg s.c. no load	0.15	(0.13; 0.17)
	150 mg s.c.	0.16	(0.14; 0.18)
	300 mg s.c.	0.17	(0.14; 0.22)
	1.5 mg/kg i.v.	0.15	(0.12; 0.17)
	1.75 mg/kg i.v.	0.15	(0.13; 0.18)
	2 mg/kg i.v.	0.16	(0.14; 0.18)
ASDAS-CRP major improvement	150 mg s.c. no load	0.26	(0.22; 0.29)
	150 mg s.c.	0.28	(0.25; 0.31)
	300 mg s.c.	0.35	(0.3; 0.4)
	1.5 mg/kg i.v.	0.25	(0.22; 0.28)
	1.75 mg/kg i.v.	0.27	(0.24; 0.3)
	2 mg/kg i.v.	0.28	(0.25; 0.31)
ASDAS-CRP inactive disease	150 mg s.c. no load	0.12	(0.1; 0.15)
	150 mg s.c.	0.14	(0.12; 0.16)
	300 mg s.c.	0.19	(0.15; 0.25)
	1.5 mg/kg i.v.	0.12	(0.1; 0.14)
	1.75 mg/kg i.v.	0.13	(0.11; 0.15)
	2 mg/kg i.v.	0.14	(0.12; 0.16)
BASDAI50	150 mg s.c. no load	0.34	(0.31; 0.37)
	150 mg s.c.	0.37	(0.34; 0.4)
	300 mg s.c.	0.43	(0.38; 0.48)
	1.5 mg/kg i.v.	0.34	(0.3; 0.37)
	1.75 mg/kg i.v.	0.35	(0.32; 0.38)
	2 mg/kg i.v.	0.37	(0.33; 0.4)

Source: Sponsor's Pharmacometrics Report, Page 87-88, Table 5-13.

The FDA's Assessment:

E-R efficacy simulation for patients with AS and PsA were checked by the reviewer. The results are generally acceptable. Due to the similar predicted $C_{min,ss}$ of secukinumab under proposed IV regimen and approved 150 mg SC regimen, similar efficacy was expected as 150 mg SC. Simulation for patients with AS and PsA under 2 mg/kg IV regimen shows slightly better efficacy than 1.75 mg/kg. E-R efficacy analysis was not conducted for nr-axSpA because of narrow exposure range from a single 150 mg dose level in study H2315.

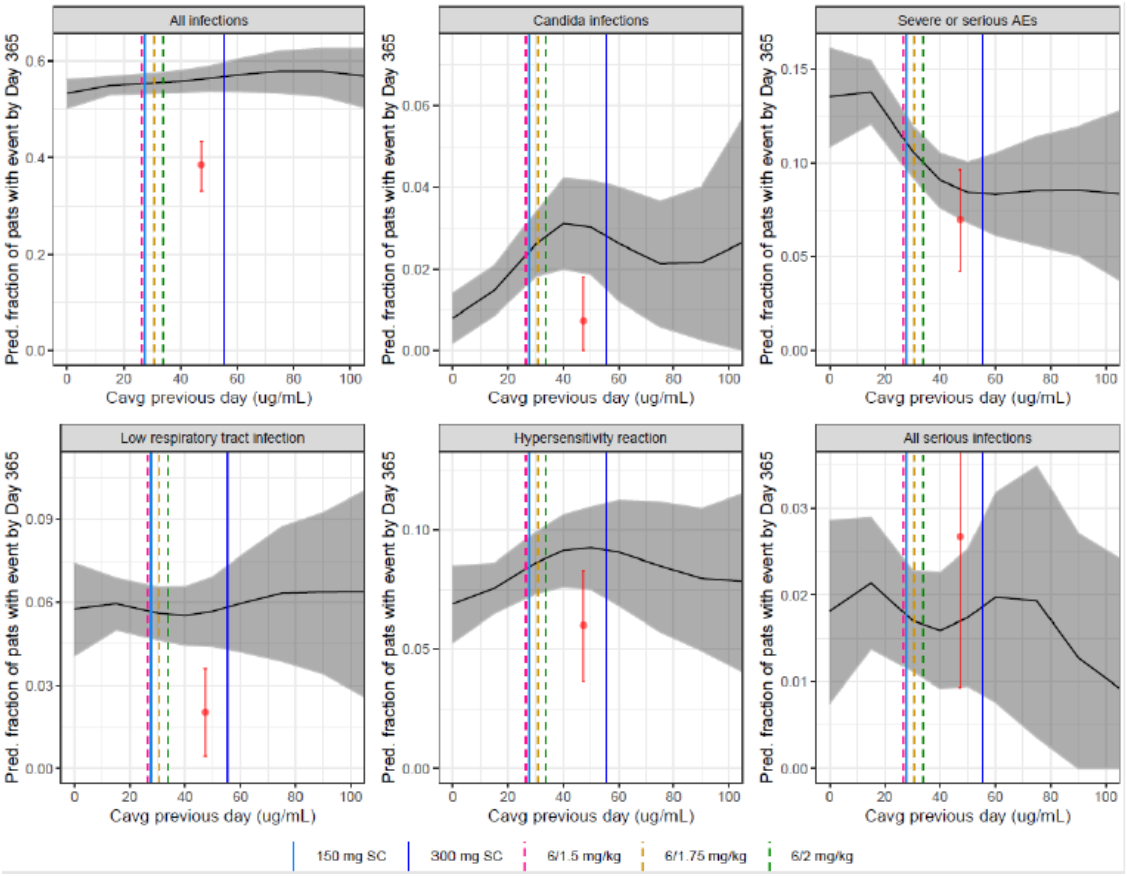
16.3.5. E-R Analysis for Safety

E-R Safety Summary Table

General Information			
Goal of E-R analysis		To predict the safety of the proposed secukinumab IV regimen by exposure-response analysis.	
Study Included		CAIN457F2305, CAIN457F2306, CAIN457F2308, CAIN457F2310, CAIN457F2312, CAIN457F2314, CAIN457F2318, CAIN457F2320, CAIN457F2336, CAIN457F2342, CAIN457P12301, CAIN457P12302	
Population Included		Patients with AS, PsA and nr-axSpA	
Endpoint		All infections Candida infections Severe or serious AEs Low respiratory tract infection Hypersensitivity reaction All serious infections	
No. of Patients (total, and with individual PK)		2095 Patients with AS 3177 Patients with PsA 667 Patients with nr-axSpA	
Population Characteristics	General	Age median: 45 (range: 18-84) years Weight median: 79.8 (range: 32 - 183) kg Sex: 3288 (55.3%) males Race: 4724 (79.5%) White 43 (0.7%) Black 879 (14.8%) Asian 293 (4.9%) Other or unknown	
	Pediatrics (if any)	NA	
Dose(s) Included		IV: 0.1 -10 mg/kg SC: 75 – 300 mg	
Exposure Metrics Explored		C_{avg} of last day. C_{avg} across the previous 7 days. C_{avg} across the previous 14 days. C_{avg} across the previous 28 days. C_{avg} across the previous 56 days.	
Covariates Evaluated		NA	
Final Model Parameters		Summary	Acceptability [FDA's comments]

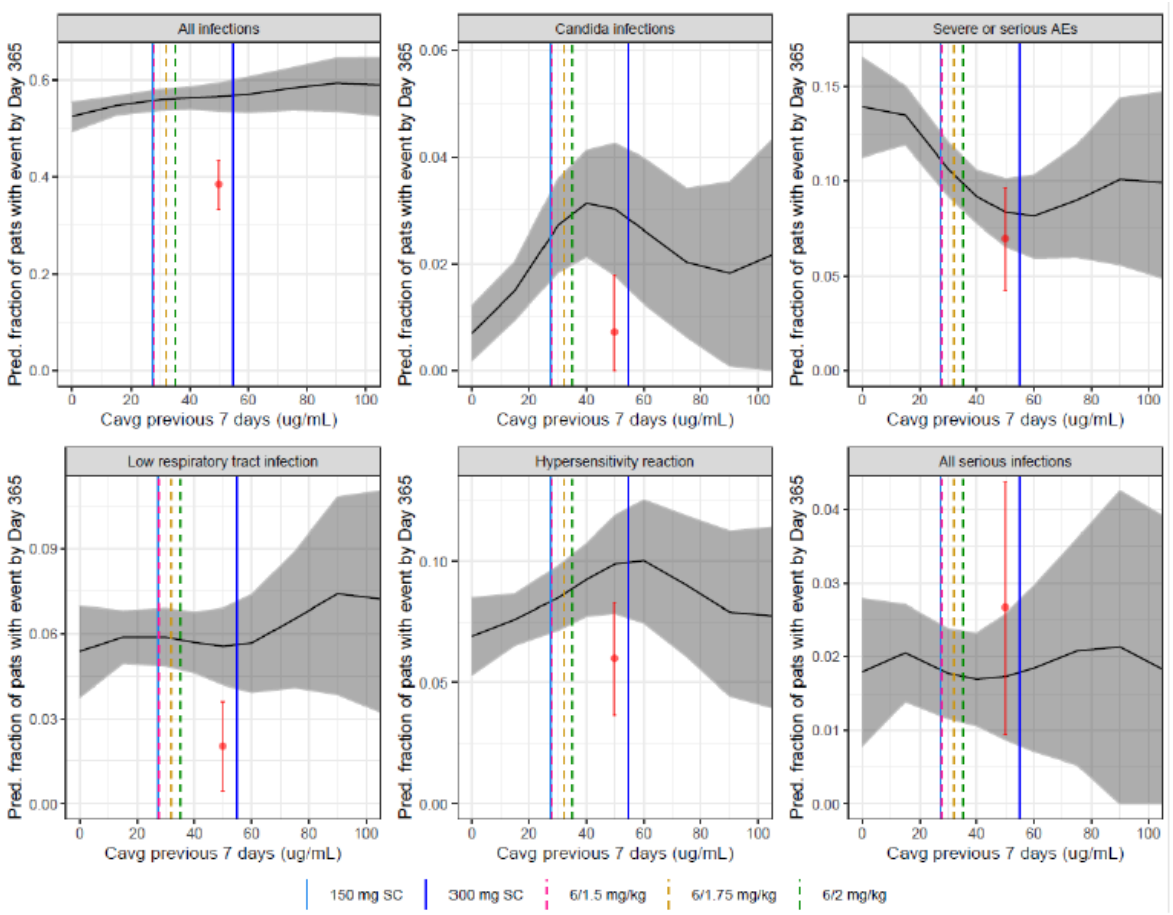
Model Structure	Model 1 Hazard models for a spline transformation of the time-varying concentration metric Model 2: Hazard models for a linear effect of the time-varying concentration metric Model 3: Hazard models for discretized time-varying concentration metric	Acceptable
Model Parameter Estimates	NA	
Covariates and Clinical Relevance	NA	
Visualization of E-R relationships	Figure 38 - Figure 52	Acceptable
Overall Clinical Relevance for E-R	The proposed 1.75 mg/kg IV regimen is expected to be similar to that of the 150 mg SC regimen, consistently across all efficacy endpoints in E-R efficacy analysis. For E-R safety analyses, the predicted incidences of most AEs are similar between the proposed IV regimen and approved SC regimens. Small increase in AE rate was predicted for Candida infections and hypersensitivity reactions for the proposed IV regimens over 150 mg SC regimen.	Acceptable

Figure 38. Estimated E-R relationships between AE and C_{avg} of previous day in model 1.



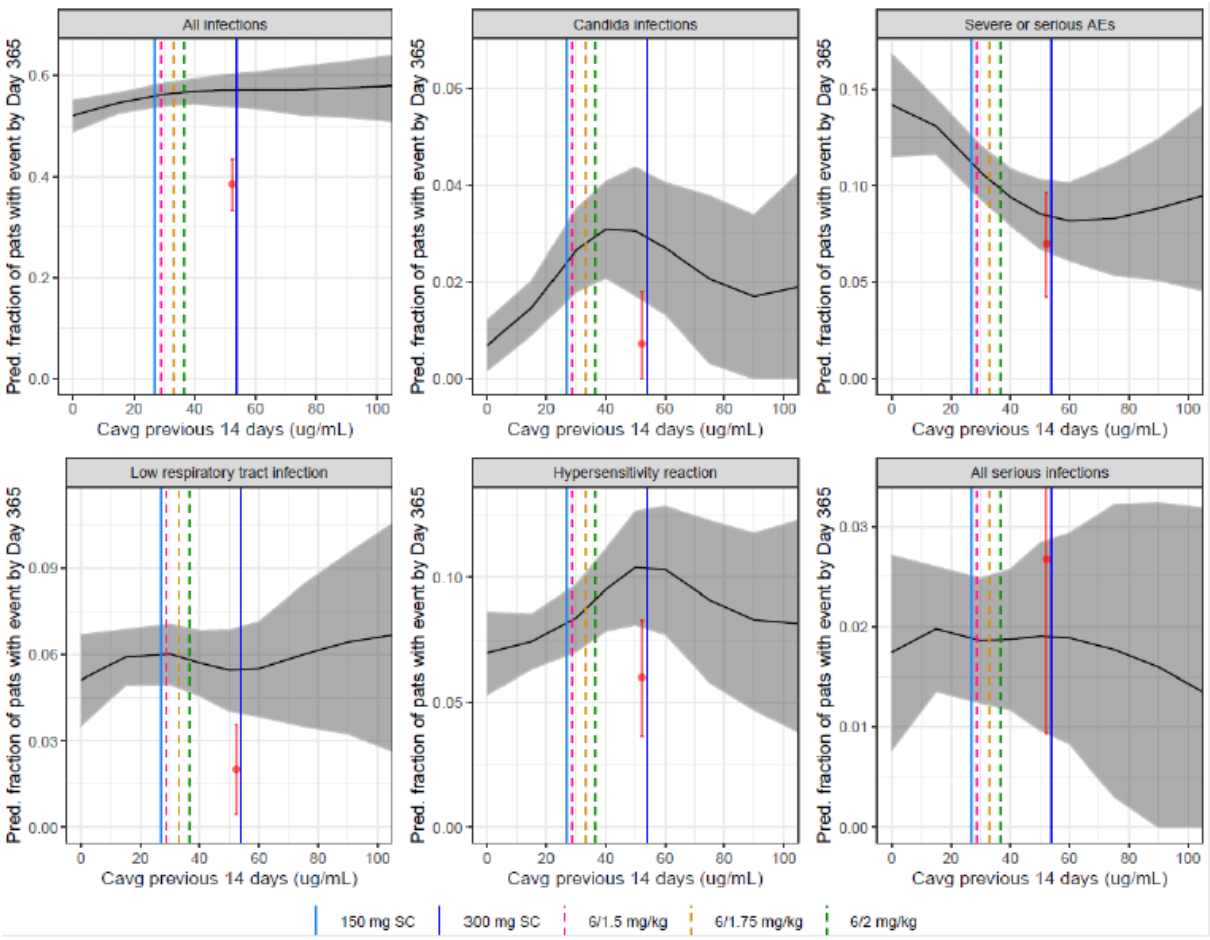
Source: Sponsor's Pharmacometrics Report, Page 103, Figure 5-46.

Figure 39. Estimated E-R relationships between AE and C_{avg} of previous 7 days in model 1



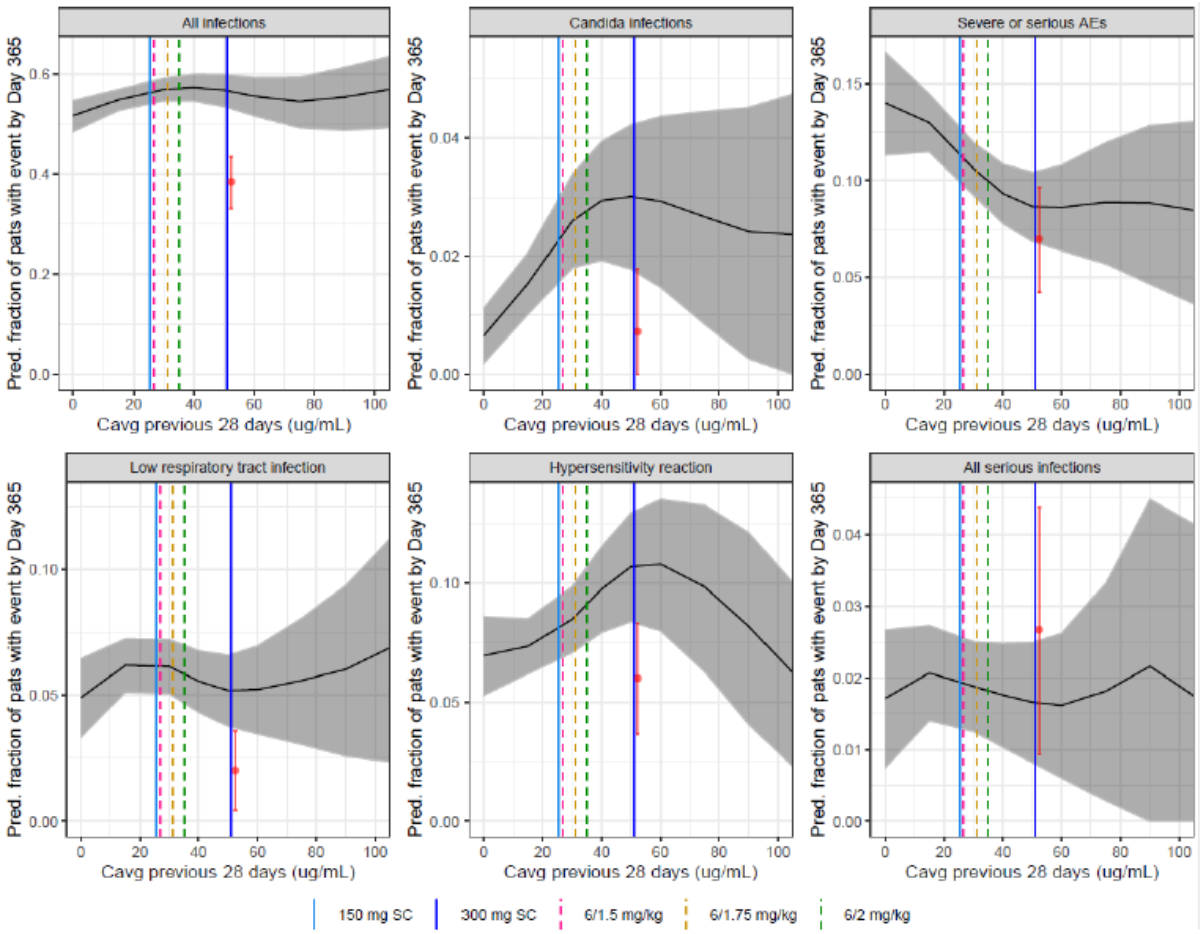
Source: Sponsor's Pharmacometrics Report, Page 104, Figure 5-47.

Figure 40. Estimated E-R relationships between AE and C_{avg} of previous 14 days in model 1.



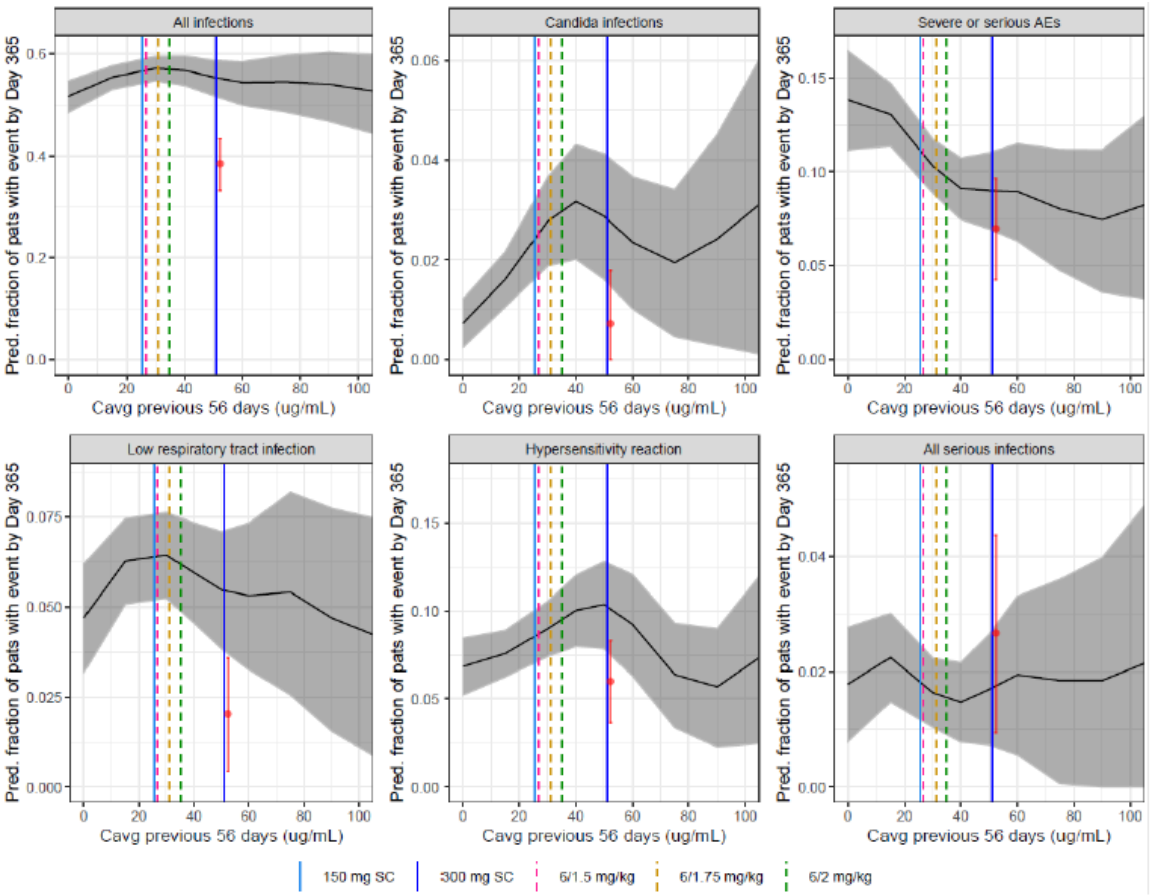
Source: Sponsor's Pharmacometrics Report, Page 105, Figure 5-48.

Figure 41. Estimated E-R relationships between AE and C_{avg} of previous 28 days in model 1.



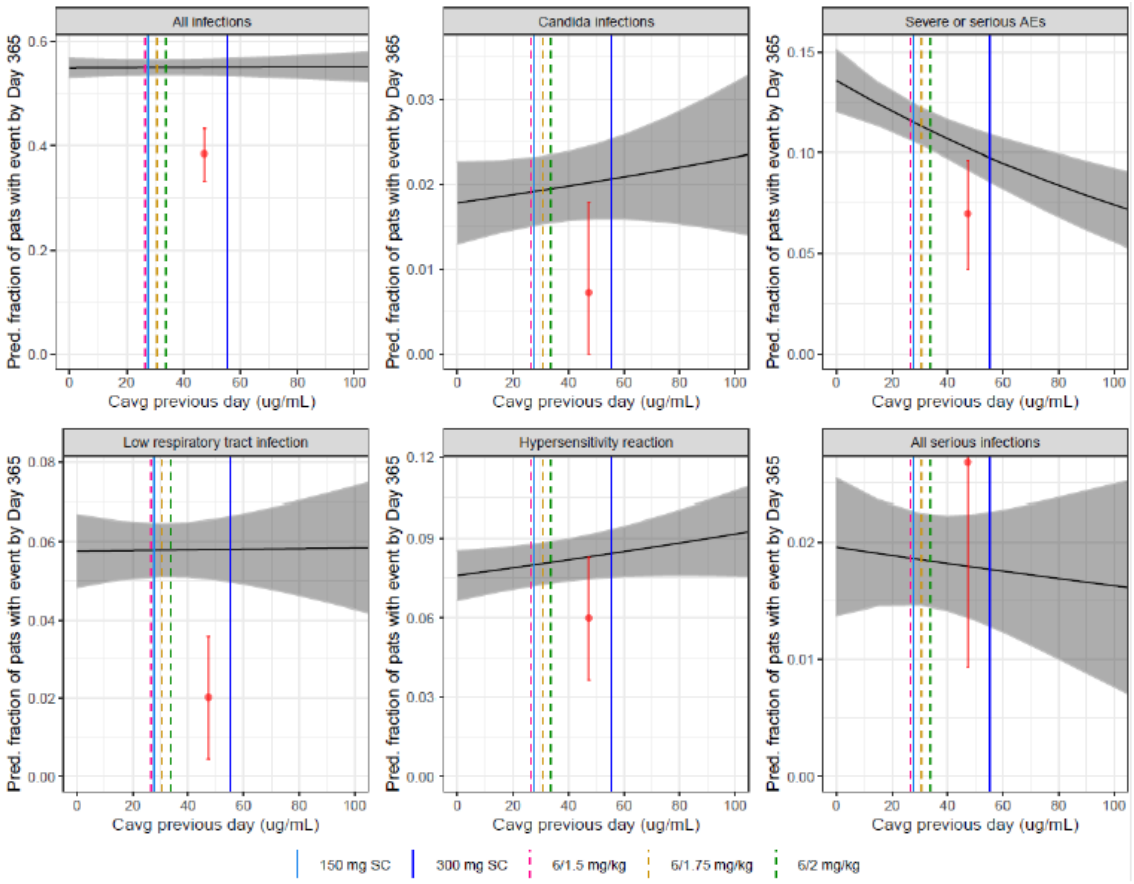
Source: Sponsor's Pharmacometrics Report, Page 106, Figure 5-49.

Figure 42. Estimated E-R relationships between AE and C_{avg} of previous 56 days in model 1.



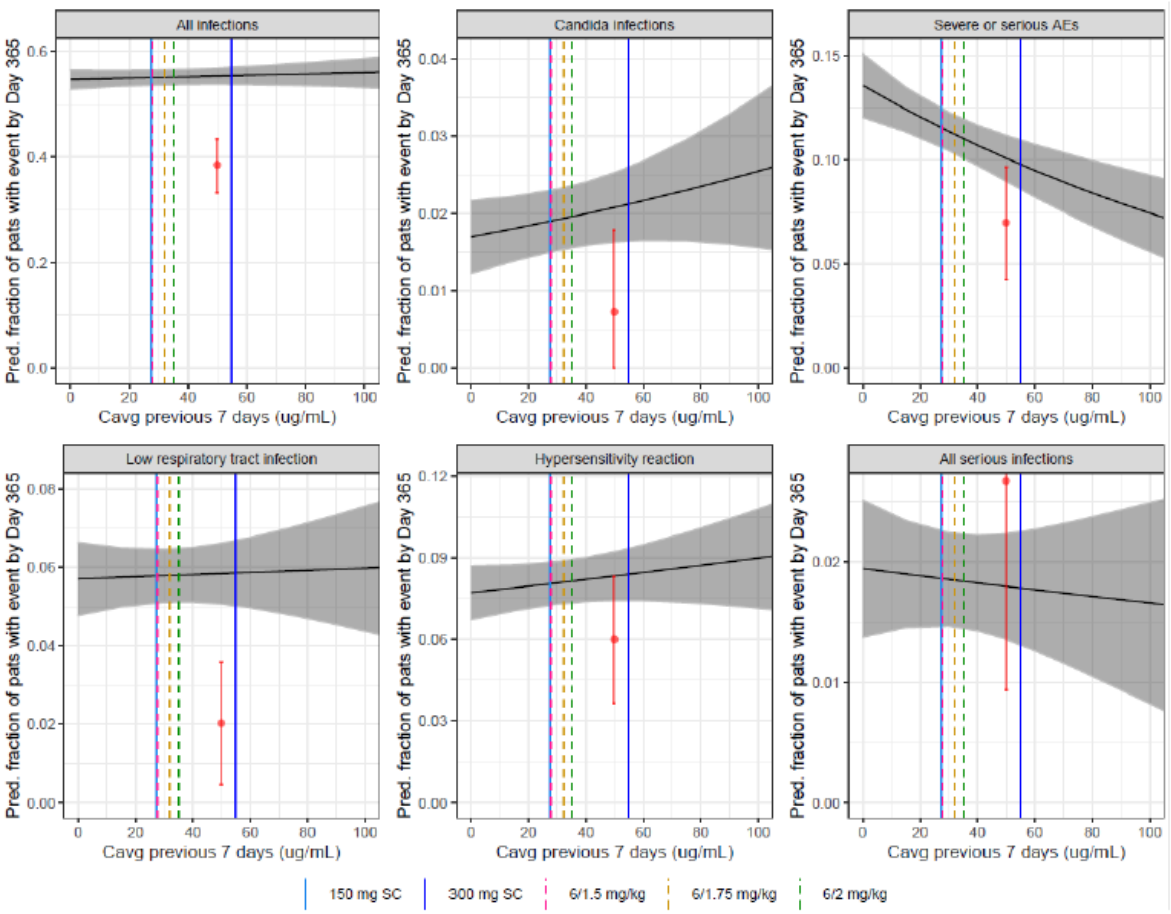
Source: Sponsor's Pharmacometrics Report, Page 107, Figure 5-50.

Figure 43. Estimated E-R relationships between AE and C_{avg} of previous day in model 2.



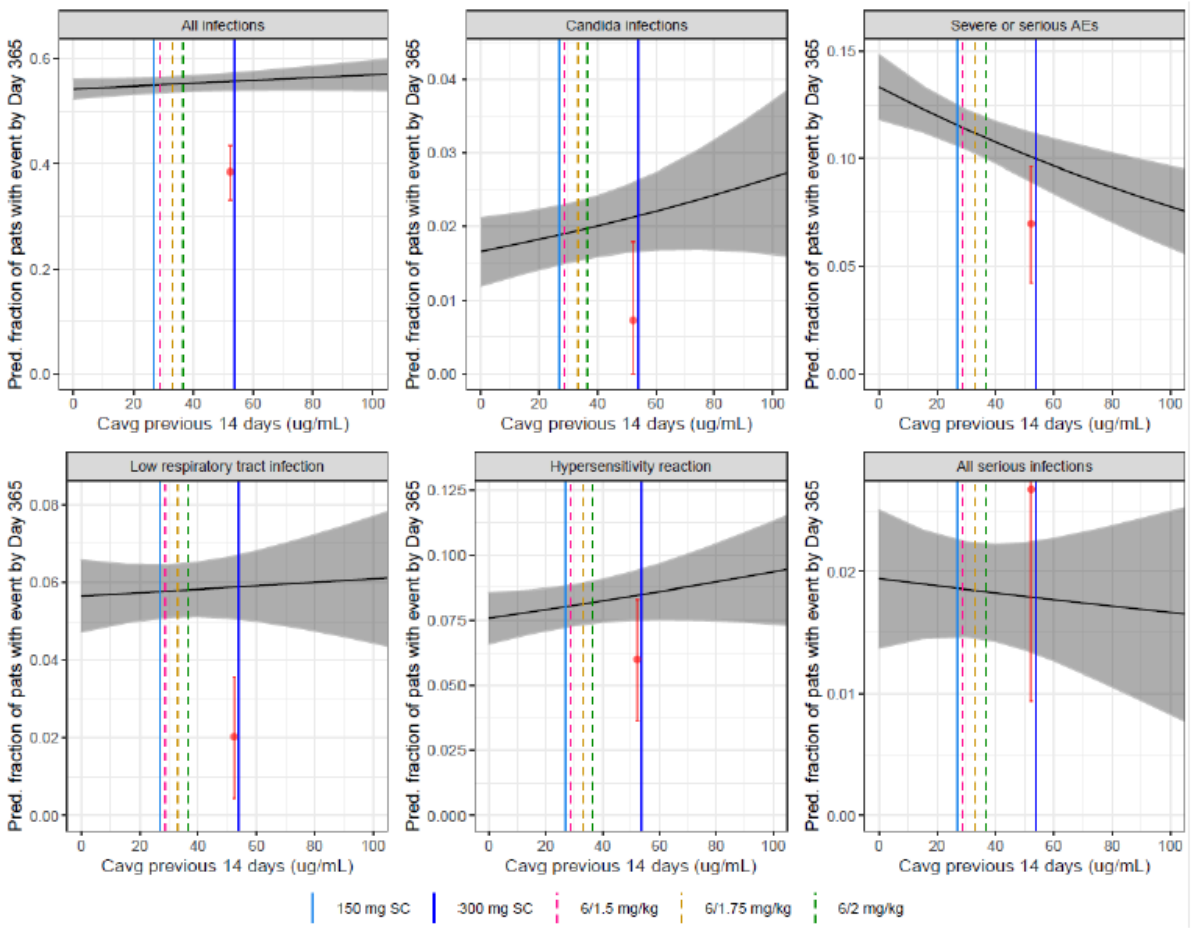
Source: Sponsor's Pharmacometrics Report, Page 108, Figure 5-51.

Figure 44. Estimated E-R relationships between AE and C_{avg} of previous 7 days in model 2



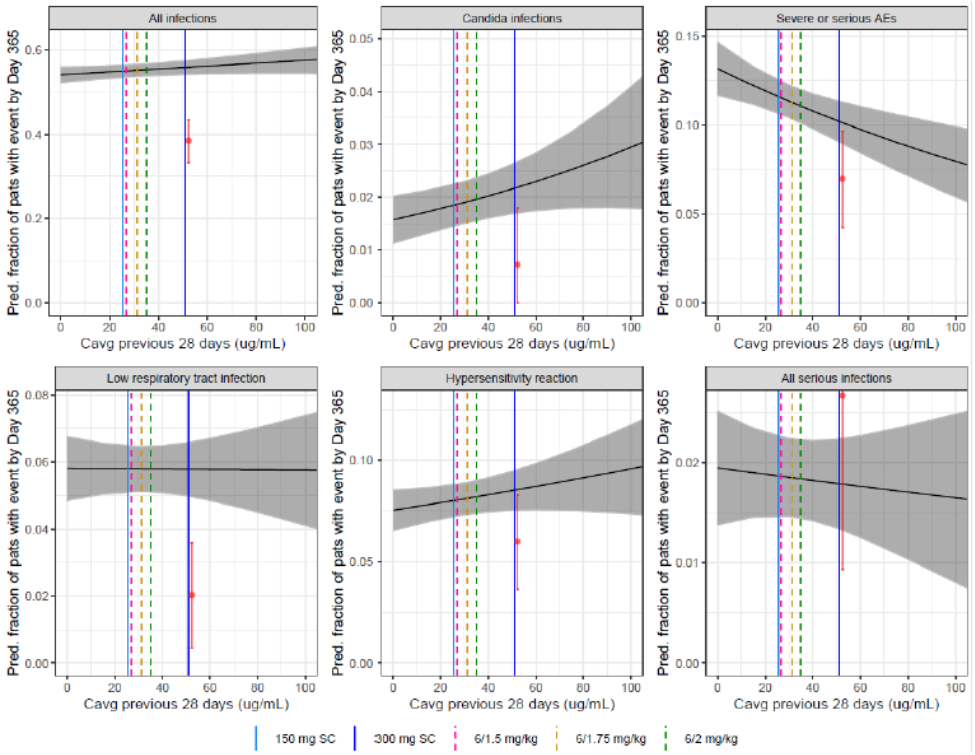
Source: Sponsor's Pharmacometrics Report, Page 109, Figure 5-52.

Figure 45. Estimated E-R relationships between AE and C_{avg} of previous 14 days in model 2.



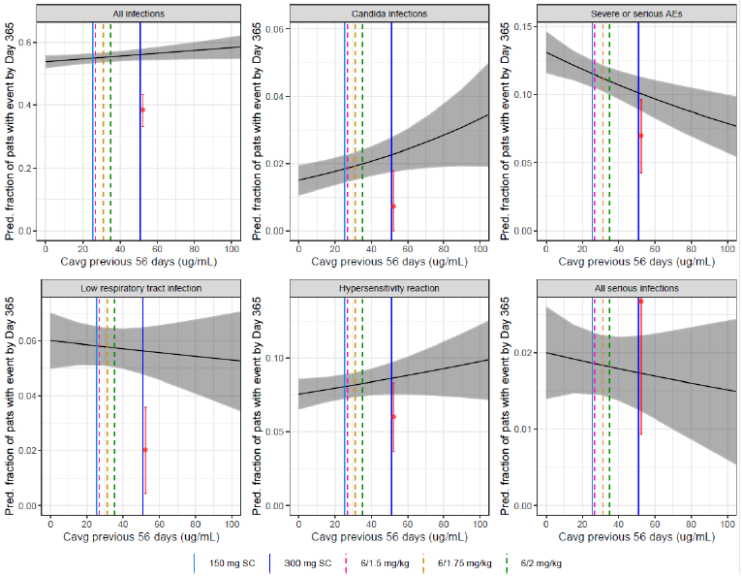
Source: Sponsor's Pharmacometrics Report, Page 110, Figure 5-53.

Figure 46. Estimated E-R relationships between AE and C_{avg} of previous 28 days in model 2.



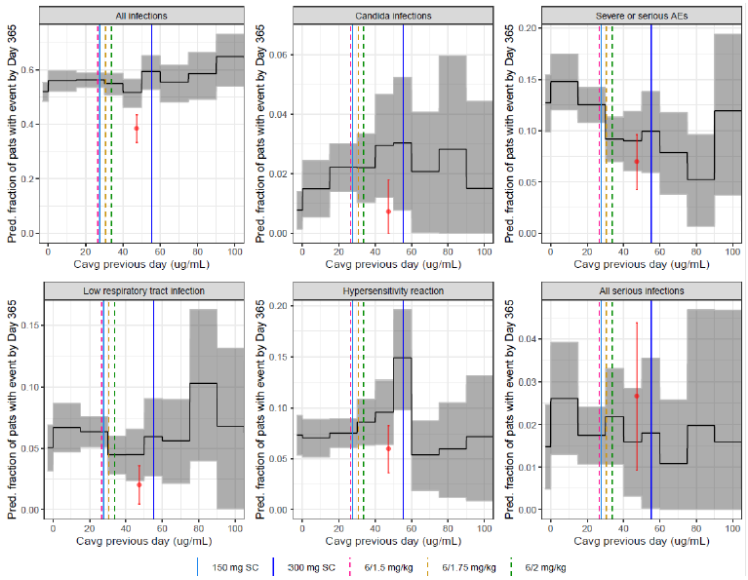
Source: Sponsor's Pharmacometrics Report, Page 111, Figure 5-54.

Figure 47. Estimated E-R relationships between AE and C_{avg} of previous 56 days in model 2.



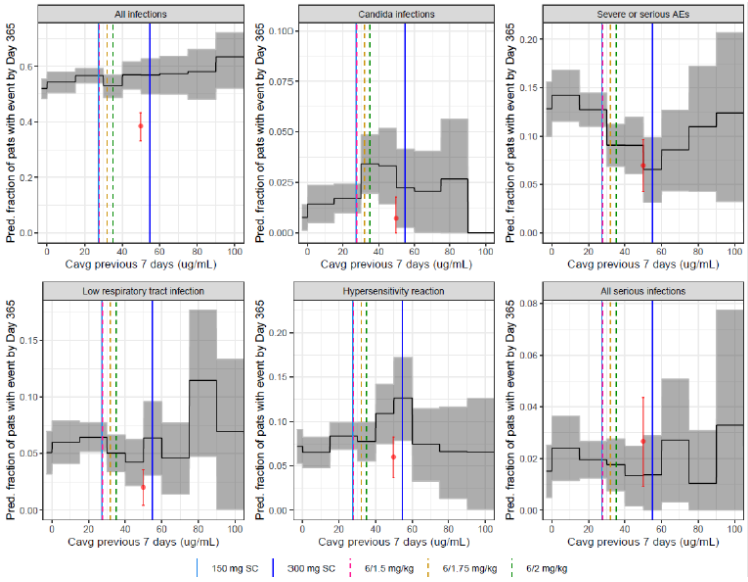
Source: Sponsor's Pharmacometrics Report, Page 112, Figure 5-55.

Figure 48. Estimated E-R relationships between AE and C_{avg} of previous day in model 3.



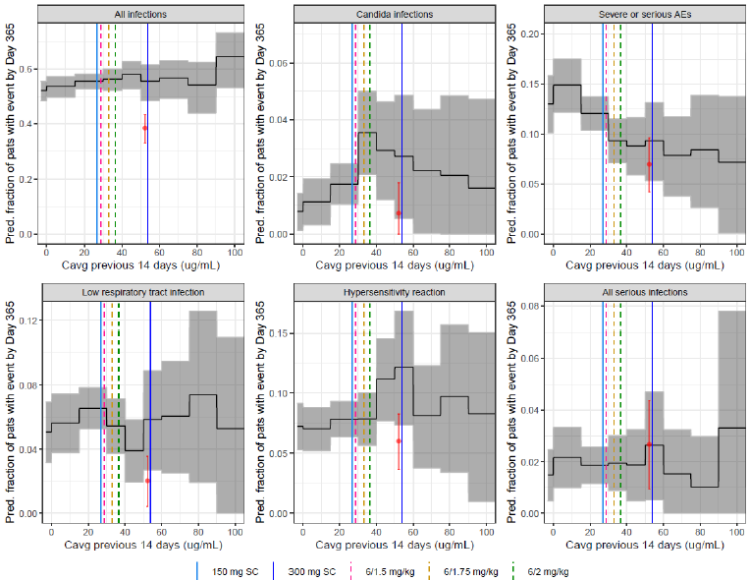
Source: Sponsor's Pharmacometrics Report, Page 113, Figure 5-56.

Figure 49. Estimated E-R relationships between AE and C_{avg} of previous 7 days in model 3



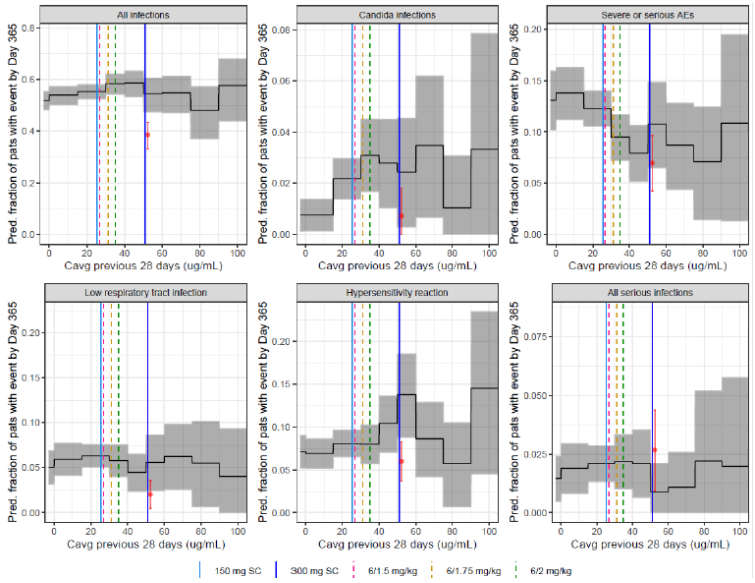
Source: Sponsor's Pharmacometrics Report, Page 114, Figure 5-57.

Figure 50. Estimated E-R relationships between AE and C_{avg} of previous 14 days in model 3.



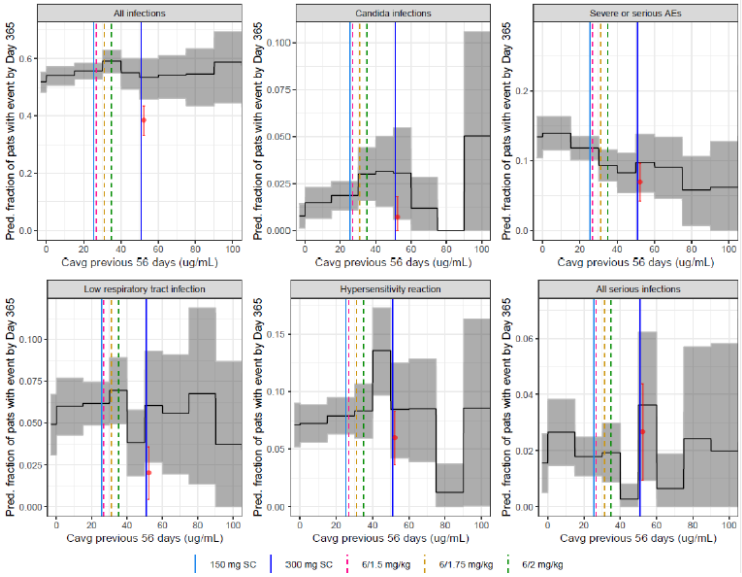
Source: Sponsor's Pharmacometrics Report, Page 115, Figure 5-58.

Figure 51. Estimated E-R relationships between AE and C_{avg} of previous 28 days in model 3.



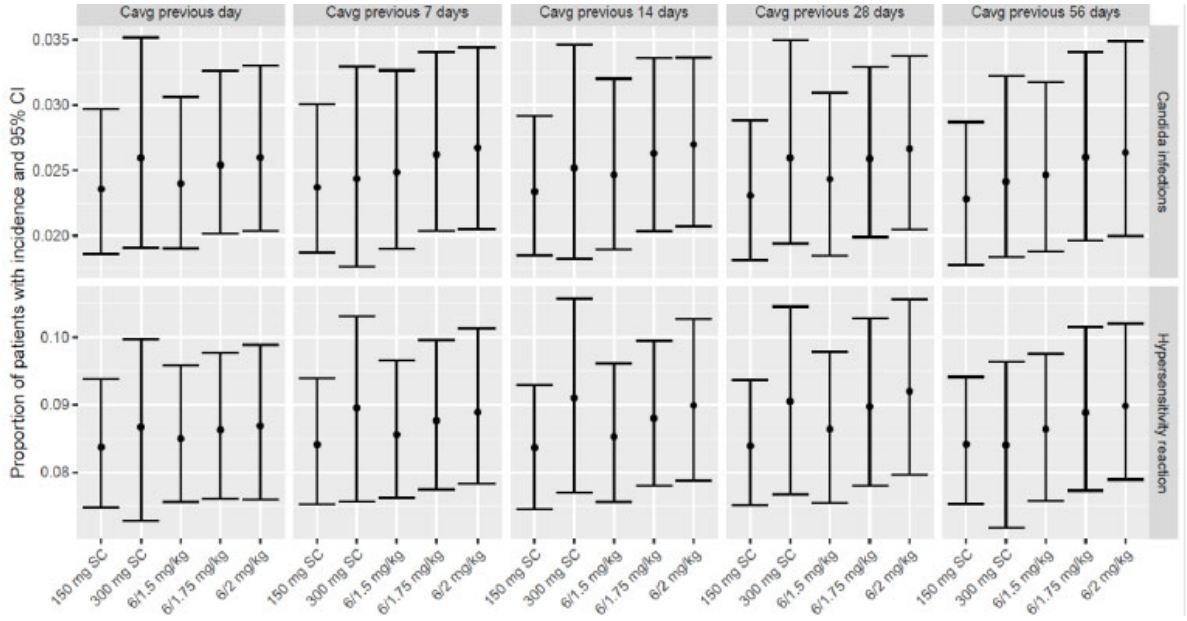
Source: Sponsor's Pharmacometrics Report, Page 116, Figure 5-59.

Figure 52. Estimated E-R relationships between AE and C_{avg} of previous 56 days in model 3.



Source: Sponsor's Pharmacometrics Report, Page 117, Figure 5-60.

Figure 53. Predicted incidence of Candida infections and hypersensitivity reactions at 52 weeks by regimen and exposure metric from model 1.



Source: Sponsor's Pharmacometrics Report, Page 118, Figure 5-61.

The FDA's Assessment:

E-R safety simulation were checked by the reviewer. The predicted incidences of most AEs are similar between the proposed IV regimen and approved SC regimens. Slight increase for Candida infections and hypersensitivity reactions were predicted for IV regimen over 150 mg SC regimen. It was also noticed that the observed AE incidence in secukinumab regimen in studies P12301 and P12302 were generally lower than the prediction. This might be due to the between-study variability, as the placebo incidences were also lower in those studies.

16.4. Additional Clinical Outcome Assessment Analyses

N/A

16.5. Efficacy Results of IV studies P12301 and P12302

16.5.1. Study Design - CAIN457P12301

Trial Design

The primary objective was to demonstrate that the efficacy of secukinumab IV at Week 16 is superior to placebo in subjects with active axspA (AS and nr-axSpA) based on the proportion of subjects achieving an ASAS40 (Assessment of SpondyloArthritis International Society criteria) response.

This multicenter study uses a randomized, double-blind, placebo-controlled, parallel-group design to study the efficacy, safety, and tolerability of treatment with intravenous secukinumab (initial dose of 6 mg/kg followed thereafter with 3 mg/kg administered every four weeks starting at Week 4) in subjects with active axSpA.

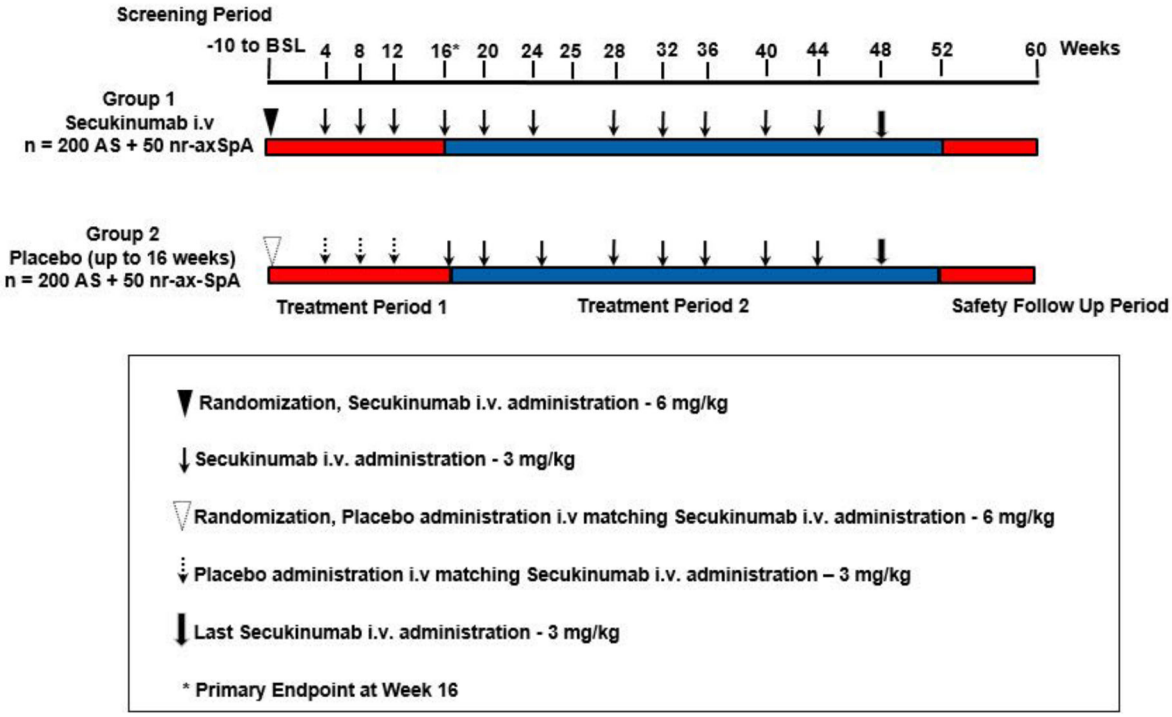
The study population consists of approximately 400 subjects with active AS and approximately 100 subjects with active nr-axSpA, despite current or previous NSAID, conventional DMARD and/or TNF inhibitor therapy, or intolerance to these therapies.

At baseline (BSL), subjects were randomized to one of the following two treatment groups in a 1:1 ratio. Randomization was stratified according to disease condition (i.e., AS or nr-axSpA). The treatment groups were as follows.

- Group 1 (200 AS subjects and 50 nr-axSpA subjects): secukinumab 6 mg/kg IV at BSL, followed by the administration of secukinumab 3 mg/kg IV every four weeks starting at Week 4 through Week 48 (exposure through Week 52).
- Group 2 (200 AS subjects and 50 nr-axSpA subjects): placebo at BSL, Weeks 4, 8, and 12, followed by the administration of secukinumab 3 mg/kg IV at Week 16 and every four weeks through Week 48 (exposure through Week 52).

This study consists of 4 periods for a total study duration of 70 weeks (Figure 54): the screening period (up to 10 weeks), treatment period 1 (total duration of 16 weeks) and treatment period 2 (total duration of 36 weeks) followed by a safety follow up period of 8 weeks after the end of treatment visit (i.e., Week 52). A post treatment follow-up visit (Week 60) is to be done 8 weeks after end of the treatment visit for all subjects (regardless of whether they complete the entire study as planned or discontinue prematurely). The current review is based on the CSR week 16 analyses and includes efficacy data up to Week 16 in treatment period 1. The safety data includes information from all visits up to the data cut-off point of 2/17/2022 (data lock point 4/19/2022), when the last enrolled participant completed the Week 16 visit.

Figure 54 Study Design – Study P12301



Source: Figure 9-1 of the Clinical Study Report CAIN457P12301

The study population consisted of male and female subjects aged at minimum 18 years at time of consent, with active axSpA (AS or nr-axSpA). The diagnosis of axSpA fulfilled the ASAS criteria of inflammatory back pain for at least 6 months and onset before 45 years of age. Subjects with AS fulfilled the Modified New York criteria with prior documented radiological evidence and subjects with nr-axSpA fulfilled ASAS classification criteria for axSpA criteria (sacroiliitis on MRI with ≥1 SpA feature OR HLA-B27 is positive with ≥2 SpA features AND objective signs of inflammation at screening evident by either MRI with SI joint

inflammation AND/OR hsCRP >ULN) and had no definitive radiographic evidence for AS by Modified New York Criteria. Subjects had to have active disease despite current or previous NSAIDs, DMARDs and/or anti-TNF therapy. Concomitant therapy with MTX (≤25 mg/week) or sulfasalazine (≤3 g/day) was acceptable, if dose and route of administration had been stable for at least 4 weeks prior to the randomization visit.

Subjects fulfilling any of the following key criteria were not eligible for inclusion in this study: subjects with total ankylosis of the spine; chest x-ray or MRI with evidence of ongoing infectious or malignant process obtained within 3 months of screening and evaluated by a qualified physician; subjects taking moderate and high potency opioid analgesics (e.g. methadone, hydromorphone, morphine); any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization; active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefits of secukinumab therapy, including inflammatory bowel disease or uveitis.

Study Endpoints

The primary efficacy variable is response to treatment according to the ASAS40 criteria at Week 16:

- The ASAS Response Criteria (ASAS40) response is defined as a ≥ 40% improvement and an ≥2 units on a scale of 10 in at least three of the following 4 domains: back pain, patient global assessment of disease activity, physical function (BASFI) and inflammation (mean score of items 5 and 6 of the BASDAI) without any worsening in the remaining domain.

The secondary efficacy variables include:

- response to treatment at Week 16 according to the ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score – C-reactive protein) major improvement criteria
- change from baseline in BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) at Week 16
- response to treatment at Week 16 according to the ASAS 5/6 criteria
- change from baseline in total BASFI (Bath Ankylosing Spondylitis Functional Index) score at Week 16
- change from baseline in SF-36 PCS (Short Form-36 Physical Component Summary) at Week 16
- change from baseline in ASQoL (Ankylosing Spondylitis Quality of Life) at Week 16
- change from baseline in hsCRP (high sensitivity C-Reactive Protein) at Week 16
- response to treatment at Week 16 according to the ASAS20 criteria
- response to treatment at Week 16 according to the ASDAS-CRP inactive disease criteria
- response to treatment at Week 16 according to the ASAS partial remission

- change from baseline in PSQI (Pittsburgh Sleep Quality Index) at Week 16

Statistical Analysis Plan

The following analysis sets were used in this study:

- Randomized set: The randomized set was defined as all subjects who were randomized.
  - Misrandomized subjects (mis-randomized in IRT) were excluded from the randomized set. Mis-randomized subjects were defined as those subjects who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized subjects were treated as screen failures.
- Full analysis set: The FAS included all subjects from the randomized set to whom study treatment had been assigned. Following the intent-to-treat principle, subjects were evaluated according to the treatment assigned to at randomization.
- Safety set: The safety set included all subjects who took at least one dose of study treatment during the treatment period. Subjects were evaluated according to treatment received.

FAS was used for all efficacy analysis.

The estimand for primary endpoint is defined as follows:

- Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted axSpA population (AS and nr-axSpA)
- Variable: composite of remaining in the study and on randomized treatment through 16 weeks and achieving ASAS40 response at Week 16
- Intercurrent event: the intercurrent events of discontinuing treatment or study are captured through the variable definition and are handled with the composite strategy.
- Population-level summary: difference in proportions of responders between the secukinumab and placebo arms

The statistical hypothesis for ASAS40 being tested was that there is no difference in the proportion of subjects fulfilling the ASAS40 criteria at Week 16 in the secukinumab IV regimen versus placebo regimen. The primary analysis was conducted via logistic regression with treatment and stratification factor (disease condition) as factors and baseline weight as a covariate. Difference in marginal response proportions with p-value and 95% confidence interval (CI) were presented comparing secukinumab IV regimen to placebo.

Missing data and intercurrent events for ASAS40 response for data up to Week 16 were handled as follows:

1. Patients who dropped out of the trial for any reason were considered as non-responders from the time they dropped out through Week 16.
2. Patients who did not have the required data to compute responses at the specific

timepoint were classified as non-responders at the specific timepoint.

The hypothesis testing for the primary endpoint and all secondary endpoints listed in **Study Endpoints** section were included in the prespecified testing hierarchy with control of family-wise type I error rate of 5%.

Protocol Amendments

There were no amendments to the study protocol.

16.5.2. **Study Results - P12301**

Compliance with Good Clinical Practices

The applicant provided a statement this study was conducted in compliance with Good Clinical Practice (GCP).

Financial Disclosure

See section 16.2 Financial Disclosures.

Patient Disposition

In total, 769 subjects were screened in the study. Of these, 527 subjects completed the screening phase and were deemed eligible to participate in the study. The 527 subjects were subsequently randomized at baseline, with 1 subject being mis-randomized, and therefore excluded from the randomization set as per SAP. The remaining 526 subjects were randomized in a 1:1 ratio to receive secukinumab 6 mg/kg-3 mg/kg (n=264) or placebo (n=262) (Table 43). All 526 subjects were included in the full analysis set (FAS).

Table 43 **Subject disposition (Randomized set – Study P12301)**

Disposition/Reason	Secukinumab IV N=264 n (%)	Placebo N=262 n (%)
Completed Treatment	255 (96.6)	253 (96.6)
Discontinued study treatment during treatment period 1	8 (3.0)	8 (3.1)
Primary reason for discontinuing study treatment in P1	5 (1.9)	1 (0.4)
Adverse event	1 (0.4)	1 (0.4)
Lost to follow-up	2 (0.8)	5 (1.9)
Subject decision	0 (0)	1 (0.4)

Progressive disease		
Primary reason for discontinuing from study up to DLP*		
Adverse event	7 (2.7)	6 (2.3)
Lost to follow up	4 (1.5)	2 (0.8)
New therapy for study indication	1 (0.4)	0 (0)
Physician decision	1 (0.4)	0 (0)
Subject decision	9 (3.4)	9 (3.4)
Progressive disease	0 (0)	1 (0.4)

*Data Lock Point (February 17, 2022)
Source: Table 10-1 of the Clinical Study Report CAIN457P12301

The majority of randomized subjects in both the secukinumab 6 mg/kg-3 mg/kg (255/264; 96.6%) and placebo (253/262; 96.6%) groups completed Treatment period 1. The reasons for discontinuing from the study in the treatment period until data lock point (DLP) were similar between the treatment groups. The most frequent reason for discontinuing from the study was subject decision (3.4%, for both secukinumab 6 mg/kg-3 mg/kg and for placebo group), followed by AE (2.7% for secukinumab 6 mg/kg-3 mg/kg vs. 2.3% for placebo group).

Protocol Violations/Deviations

The proportion of subjects with at least one protocol deviation (PD) up to Week 16 was similar in both the secukinumab 6 mg/kg-3 mg/kg and placebo groups (29.5% vs. 34.0%, respectively). The most frequent PD reported overall belonged to “Other” category (22.2%) with 19.7% in the secukinumab 6 mg/kg-3 mg/kg and 24.8% in the placebo group, followed by use of prohibited concomitant medication (7.2%) with no meaningful difference between the treatment groups.

Demographic Characteristics

Subject demographics were comparable between treatment groups and consistent with the intended target population (Table 44). Most of the subjects were male (65.2%), Caucasian (white) (68.3%) of which (83.5%) of subjects self-identified as Not Hispanic or Latino. Overall, the subjects ranged from 18 to 79 years of age with most of them (97.0%) aged <65 years. The overall mean age was 39.5 years, and the mean BMI was 26.9 (kg/m^2). Female subjects counted for 37.5% and 32.1% of the population in the secukinumab 6 mg/kg-3 mg/kg and placebo groups respectively. At baseline, most of the subjects (81.7%) were not smokers.

Table 44 Baseline subject demographics (Randomized set)

Demographic Parameters	**Secukinumab IV** (N= 264)	**Placebo** (N= 262)
Sex, n (%)		
Male	165 (62.5)	178 (67.9)
Female	99 (37.5)	84 (32.1)
Age		
Mean years (SD)	39.8 (12.4)	39.1 (11.7)
Median (years)	38	39
Min, max (years)	18 - 78	18 - 79
Age Group, n (%)		
<65 years	253 (95.8)	257 (98.1)
65 - 74 years	8 (3.0)	4 (1.5)
≥ 75 years	3 (1.1)	1 (0.4)
Race, n (%)		
White	180 (68.2)	179 (68.3)
Black or African American	7 (2.7)	6 (2.3)
Asian	59 (22.4)	47 (17.9)
American Indian or Alaska Native	17 (6.4)	25 (9.5)
Multiple	1 (0.4)	5 (1.9)
Ethnicity, n (%)		
Hispanic or Latino	35 (13.3)	44 (16.8)
Not Hispanic or Latino	225 (85.2)	214 (81.7)
Unknown	4 (1.5)	4 (1.5)
BMI (kg/m^2)		
Mean (SD)	26.8 (5.7)	27.0 (5.9)
Median	26.2	25.8
Min - Max	15.8 – 53.8	15.1 – 57.1
Smokers at baseline, n (%)		
No	222 (84.1)	208 (79.4)
Yes	42 (15.9)	54 (20.6)

Source: Statistical Reviewer and Table 10-4 of Clinical Study Report CAIN457P12301

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

The treatment groups were balanced in terms of baseline disease characteristics (**Table 45**).

Table 45 Baseline disease characteristics (Randomized set – Study P12301)

Characteristic	**Secukinumab IV** (N= 264)	**Placebo** (N= 262)
Time since first diagnosis of axSpA (years)		
Mean (SD)	5.5 (7.7)	4.6 (6.1)
Median	2.7	2.2
Min - Max	0 – 54.4	0 – 36.9
Methotrexate use at randomization, n (%)		
Yes	34 (12.9)	35 (13.4)
No	230 (87.1)	227 (86.6)
Dose of methotrexate at randomization (mg/week)		
mean (SD)	17.1 (6.1)	16.6 (5.5)
median	15	15
Min - Max	5 - 25	5 - 25
Sulfasalazine use at randomization, n (%)		
Yes	54 (20.5)	56 (21.4)
No	210 (79.5)	206 (78.6)
Dose of sulfasalazine at randomization (g/day)		
Mean (SD)	1.7 (0.7)	1.8 (0.7)
Median	2	2
Min -Max	0.2 - 3	1 - 3
Corticosteroid use at randomization, n (%)		
Yes	25 (9.5)	21 (8.0)
No	239 (90.5)	241 (92.0)
Dose of corticosteroid at randomization (mg/day)		
Mean (SD)	5.9 (2.9)	6.2 (2.5)
Median	5	5
Min - Max	1.4 - 10	1.4 - 10
TNF alpha inhibitors history, n (%)		
TNF Naive	233 (88.3)	216 (82.4)
TNF IR	31 (11.7)	46 (17.6)
Disease condition – n(%)		
AS – n(%) TNF Naïve TNF IR	208 (78.8) 181 (87.0) 27 (13.0)	205 (78.2) 167 (81.5) 38 (18.5)
Nr-axSpA – n (%)	56 (21.2)	57 (21.8)

TNF Naïve	52 (92.9)	49 (86.0)
TNF IR	4 (7.1)	8 (14.0)

Source: Statistical Reviewer and Table 10-5 of Clinical Study Report CAIN457P12301

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

According to the CSR, most subjects used at least one concomitant medication up to Week 16 in the safety analysis set in both secukinumab 6 mg/kg-3 mg/kg (94.7%) and placebo groups (98.1%). The most commonly reported concomitant medications were sulfasalazine (secukinumab 6 mg/kg-3 mg/kg 20.5% vs. placebo 21.5%), meloxicam (secukinumab 6 mg/kg-3 mg/kg 16.3% vs. placebo 14.6%), etoricoxib (secukinumab 6 mg/kg-3 mg/kg 15.9% vs. placebo 16.1%) and omeprazole (secukinumab 6 mg/kg-3 mg/kg 14.4% vs. placebo 14.9%). Other commonly reported (≥10% in either group) concomitant medications were colecalciferol (secukinumab 6 mg/kg-3 mg/kg 12.5% vs. placebo 18.4%), celecoxib (secukinumab 6 mg/kg-3 mg/kg 12.9% vs. placebo 14.2%), methotrexate (secukinumab 6 mg/kg-3 mg/kg 12.5% vs. placebo 13.4%) and folic acid (secukinumab 6 mg/kg-3 mg/kg 11.7% vs. placebo 12.3%)

Efficacy Results – Primary Endpoint

As the primary basis for approval of the proposed IV dosing regimen of 6 mg/kg single loading dose, followed by 1.75 mg/kg every four weeks thereafter with a maximum dose of 300 mg IV is the modeled exposure of secukinumab to match the approved subcutaneous (SC) doses of 150 mg and 300 mg with or without loading, the efficacy results of this study, which has dose of secukinumab 6 mg/kg IV at BSL, followed by the administration of a higher dose of secukinumab, 3 mg/kg IV, every four weeks starting at Week 4, will be considered supportive only.

The statistical reviewer verified the applicant's results (Table 46), based on a logistic regression model with treatment and randomization stratum (disease condition: AS or nr-axSpA) as factors and baseline weight as a covariate, that secukinumab 6 mg/kg -3 mg/kg demonstrated superiority over placebo for ASAS40 response using non-responder imputation for those with missing data or who discontinued treatment or study at Week 16 (108/264 [40.9%] vs. 60/262 [22.9%]; $p<0.0001$) with a marginal difference of 17.9 and 95% CI of (10.1, 25.7). A comparison of ASAS40 response rates between the two treatment groups by normal approximation showed similar results (95% CI of the response rate difference of [10.2, 25.8]) and the same conclusion that secukinumab IV group had statistically significantly higher ASAS40 response rate compared with the placebo group.

Table 46 ASAS40 response using non-responder imputation* at Week 16 (FAS)

Treatment	Responder, n (%) 95% CI	Response rate difference compared to Placebo (95% CI) / P-value
Secukinumab IV N=264	108 (40.9) (34.9, 46.8)	17.9 (10.1, 25.7) <0.0001
Placebo N=262	60 (22.9) (17.9, 28.0)	

* There were 12 subjects (3 on secukinumab and 9 on placebo) who were non-responders due to missing data and 14 subjects (8 on secukinumab and 6 on placebo) who were non-responders due to treatment/study discontinuation.
Source: Statistical Reviewer and Table 14.2-1.1 of Clinical Study Report CAIN457P12301

Data Quality and Integrity

Data were submitted by the Applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, program code, and study reports were accessed through EDR \\CDSESUB1\evsprod\BLA761349\0000.

Based on the information provided in this submission, the study appeared to be conducted properly and was consistent with the history of regulatory interactions and protocol.

Efficacy Results – Secondary and other relevant endpoints

Based on the study report, secukinumab 6 mg/kg-3 mg/kg was shown to be superior to placebo at Week 16 for all endpoints in the pre-defined statistical testing hierarchy. The study met all secondary efficacy endpoints listed in the **Study Endpoints** section above.

Dose/Dose Response

The current study did not assess dose and dose response.

Persistence of Effect

The study report noted that Secukinumab IV (6 mg/kg-3 mg/kg) showed a significantly greater ASAS40 response (primary endpoint) compared to placebo at Week 16 with an onset of action as early as Week 4 that was sustained throughout the 16-week period.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Some of the secondary endpoints are COA endpoints, including SF-36 PCS and ASQoL change from baseline at Week 16. The study report also included other patient reported outcomes

results including FACIT-Fatigue, EQ-5D, patient's global assessment of disease activity (VAS), and patient's assessment of back pain intensity (VAS). All these PRO assessments showed numerically better results for secukinumab grup compared to the placebo group.

Additional Analyses Conducted on the Individual Trial

Subgroup analyses, condition sub-population (AS vs. nr-axSpA) and previous anti-TNF use, showed numerically higher efficacy for secukinumab 6 mg/kg-3 mg/kg compared to placebo, across all primary and secondary endpoints. Subgroup analyses for demographics (age, sex, race and region [Europe, US, Asia, South and Central America]) also showed higher ASAS40 response rates for secukinumab IV compared to placebo among all subgroups with sufficient number of patients.

16.5.3. Study Design - CAIN457P12302

Trial Design

This multicenter study uses a randomized, double-blind, placebo-controlled, parallel-group design to study the efficacy, safety, and tolerability of treatment with intravenous secukinumab in patients with active PsA. The study population comprises 381 subjects with active PsA, despite current or previous NSAID, DMARD and/or TNF inhibitor therapy or intolerance to these therapies.

At baseline, subjects were randomized to one of the following two treatment groups in a 1:1 ratio:

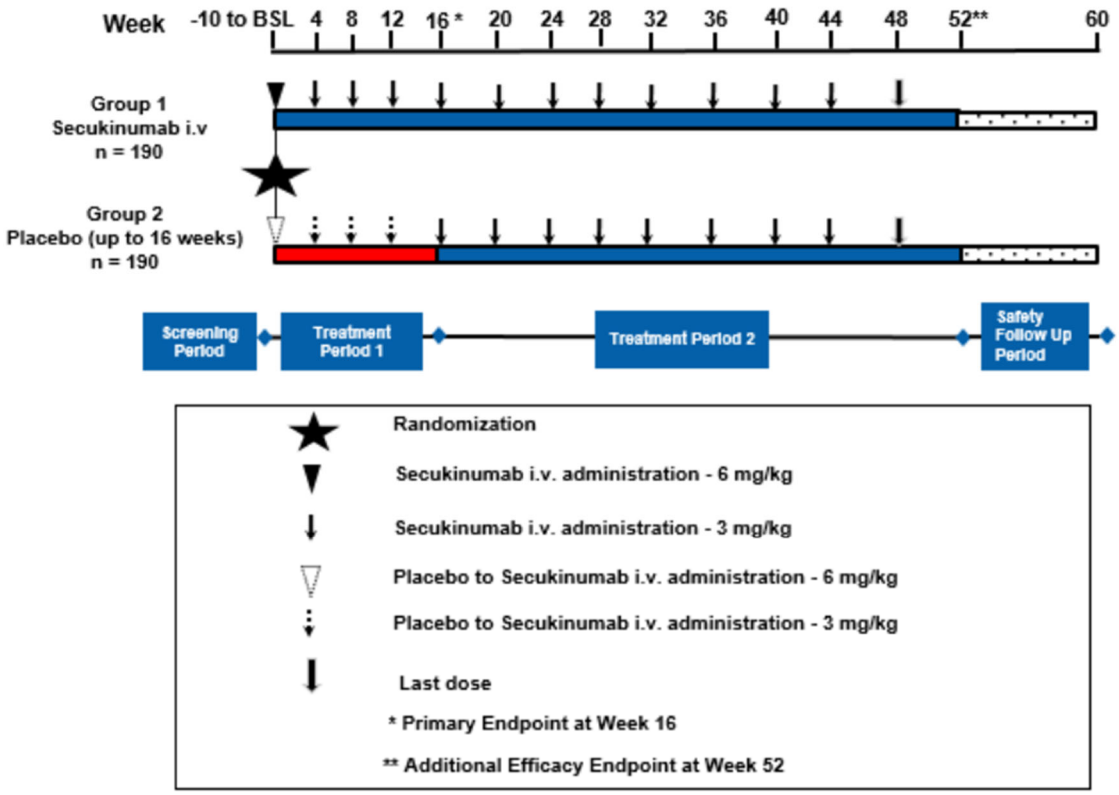
- Group 1: secukinumab 6 mg/kg IV at baseline, followed by the administration of secukinumab 3 mg/kg IV every four weeks starting at Week 4.

- Group 2: placebo at baseline, Weeks 4, 8, and 12, followed by the administration of secukinumab 3 mg/kg IV every four weeks starting at Week 16.

To ensure a balance across both arms, patients previously treated with TNF-inhibitors were stratified at randomization. No more than 25% of previously treated TNF-inhibitor patients were enrolled in the study, with this cutoff applied to each group at randomization (no more than 48 patients per group).

This study consists of 4 periods (**Figure 55**): a screening period (up to 10 weeks), treatment period 1 (total duration of 16 weeks) and treatment period 2 (total duration of 36 weeks) followed by a safety follow up period of 8 weeks after the end of treatment visit (i.e., Week 52). The current review is based on the CSR week 16 analyses and includes efficacy data up to Week 16 in treatment period 1 and safety data up to a cut-off of 7/14/2021 when the last enrolled participant completed the Week 16 visit.

Figure 55 Study Design – Study P12302



Source: Figure 9-1 of Clinical Study Report CAIN457P12302

The study population consisted of male and female subjects aged at minimum 18 years at time of consent, with diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who had at Baseline ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each). Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs. Subjects taking corticosteroids must have been on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should have remained on a stable dose up to Week 16.

The main exclusion criteria include chest X-ray or chest MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician; subjects taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine); ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization; any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization; any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization; subjects who had ever received biologic immunomodulating agents, investigational or approved except for those targeting TNF-alpha.

Study Endpoints

The primary efficacy variable was ACR50 response at Week 16. A subject was defined as an ACR50 responder if, and only if, the following three conditions held:

4. they had a ≥ 50% improvement in the number of tender joints (based on 78 joints)
5. they had a ≥ 50% improvement in the number of swollen joints (based on 76 joints)
6. they had a ≥ 50% improvement in three of the following five domains: Patient's global assessment of disease activity (measured on a VAS scale, 0-100), Physician's global assessment of disease activity (measured on a VAS scale, 0-100), Patient's assessment of PsA pain (measured on a VAS scale, 0-100), Health Assessment Questionnaire – Disability Index (HAQ-DI®) score, Acute phase reactant (hsCRP or ESR)

The secondary efficacy variables include

- ACR20 response at Week 16
- Minimal disease activity (MDA) response at Week 16
- PASI90 response for psoriasis subset at Week 16
- Change from baseline in PASDAS score at Week 16
- Change from baseline in HAQ-DI score at Week 16
- Change from baseline in SF36-PCS at Week 16
- Change from baseline in FACIT-Fatigue score at Week 16
- Change from baseline in mNAPSI for nail subset at Week 16
- Resolution of dactylitis for dactylitis subset at Week 16
- Resolution of enthesitis for enthesitis subset at Week 16

Statistical Analysis Plan

The following analysis sets were used in this trial:

- Randomized set: The randomized set was defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in Interactive Voice Response (IVR) were excluded from the randomized set.
  - Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IVR prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized subjects are treated as screen failures.
- Full analysis set (FAS): The FAS comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects were analyzed according to the treatment assigned to at randomization, but with actual anti-TNF status.
- The safety set included all subjects who took at least one dose of study treatment during the treatment period. Subjects were evaluated according to treatment received.

FAS was used for all efficacy analysis.

The primary estimand is defined as follows:

- Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted psoriatic arthritis population
- Variable: composite of remaining on the study and on randomized treatment through 16 weeks and achieving ACR50 response at 16 weeks
- Intercurrent event: the intercurrent events of discontinuing treatment or study are captured through the variable definition and are handled with the composite strategy.
- Population-level summary: Difference in marginal response proportions for comparison between treatments

The primary endpoint of ACR50 at Week 16 in the FAS will be evaluated using a logistic regression with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate. Difference in marginal response proportions will be computed for comparisons of IV secukinumab vs. placebo regimen utilizing the logistic regression model fitted.

Missing data for ACR50 response were handled as follows:

- Subjects who dropped out of the trial for any reason were considered non-responders from the time they dropped out through Week 16 based on the estimands.
- Subjects who did not have the required data to compute ACR response (i.e. tender and swollen joint counts and at least three of the five ACR core set variables) at the specific time point will be classified as non-responders.

The hypothesis testing for the primary endpoint and all secondary endpoints listed in Study Endpoints section were included in the prespecified testing hierarchy with control of family-wise type I error rate of 5%.

Protocol Amendments

There were no amendments to the study protocol.

16.5.4. Study Results – P12302

Compliance with Good Clinical Practices

The applicant provided a statement this study was conducted in compliance with Good Clinical Practice (GCP).

Financial Disclosure

See section 16.2 Financial Disclosures.

Patient Disposition

In total, 479 subjects were screened in the study. Of these, 382 subjects completed the screening phase and were deemed eligible to participate in the study. While 381 subjects were subsequently randomized at baseline in a 1:1 ratio to receive secukinumab (n=191) or placebo (n=190) (Table 47), the remaining one subject withdrew consent after screening. All 381 subjects were included in the full analysis set (FAS).

The majority of randomized subjects in both the secukinumab (186/191; 97.4%) and placebo (183/190; 96.3%) groups completed Treatment period 1 (until 16 weeks). The remaining 12 subjects discontinued during Treatment period 1. The reasons for discontinuing from the study in the treatment period until data lock point were similar between the treatment groups. The most frequent reason for discontinuing from the study was subject decision (6/191; 3.1% for secukinumab vs. 7/190; 3.7% for placebo).

Table 47 Subject disposition (randomized set Study P12302)

Disposition/Reason	Secukinumab IV N=191 n (%)	Placebo N=190 n (%)
Completed Treatment period 1*	186 (97.4)	183 (96.3)
Discontinued during treatment period 1	5 (2.6)	7 (3.7)
Primary reason for discontinuing study treatment during treatment period 1	1 (0.5)	1 (0.5)
Adverse event	4 (2.1)	5 (2.6)
Subject decision	0 (0)	1 (0.5)
Death		
Primary reason for discontinuing from study (Treatment period (up to data lock point))		
adverse event	2 (1.0)	3 (1.6)
physician decision	4 (2.1)	2 (1.1)
subject decision	6 (3.1)	7 (3.7)
death	0 (0)	1 (0.5)
progressive disease	1 (0.5)	0 (0)

*Up to 16 weeks
Source: Table 10-1 of the Clinical Study Report CAIN457P12302.

Protocol Violations/Deviations

The proportion of subjects with at least 1 protocol deviation was similar in both the secukinumab and placebo groups (38.7% vs. 37.9%, respectively). The most frequent protocol deviation reported overall belonged to “Other” category (27.3%) followed by use of prohibited concomitant medication (9.2%), with no meaningful difference between the treatment groups

Demographic Characteristics

Subject demographics were comparable between treatment groups and consistent with the intended target population as specified in the inclusion criteria. The majority of subjects were female (54.9%) and Caucasian (79.0%) and 59/381 (15.5%) of subjects self-identified as Hispanic or Latino. Overall, the subjects ranged in age from 19 to 81 years old with most of them (87.9%) aged <65 years.

Table 48 Baseline subject demographics (Randomized set – Study P12302)

Demographic Parameters	**Secukinumab IV** (N= 191)	**Placebo** (N= 190)
Sex, n (%)		
Male	87 (45.6)	85 (44.7)
Female	104 (54.5)	105 (55.3)
Age		
Mean years (SD)	47.5 (13.5)	48.1 (13.7)
Median (years)	47	48
Min, max (years)	20 - 81	19 - 76
Age Group, n (%)		
<65 years	170 (89.0)	165 (86.8)
65 - 74 years	17 (8.9)	24 (12.6)
≥ 75 years	4 (2.1)	1 (0.5)
Race, n (%)		
White	148 (77.5)	153 (80.5)
Black or African American	5 (2.6)	1 (0.5)
Asian	25 (13.1)	26 (13.7)
American Indian or Alaska Native	10 (5.2)	9 (4.7)
More than one race	3 (1.6)	1 (0.5)
Ethnicity, n (%)		
Hispanic or Latino	34 (17.8)	25 (13.2)
Not Hispanic or Latino	155 (81.2)	163 (85.8)
Unknown	2 (1.0)	2 (1.1)
BMI (kg/m^2)		
Mean (SD)	29.7 (6.8)	30.0 (7.4)
Median	28.9	28.7
Min - Max	16.1 – 58.3	16.9 – 59.8
Smokers at baseline, n (%)		
No	165 (86.4)	158 (83.2)
Yes	26 (13.6)	32 (16.8)

Source: Statistical Reviewer and Table 10-3 of Clinical Study Report CAIN457P12302

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

The treatment groups were balanced in terms of baseline disease characteristics (Table 49). Most subjects in both secukinumab (86.4%) and placebo (85.3%) groups were naive to anti-TNF PsA therapies. The majority of subjects in both secukinumab (59.2%) and placebo (57.9%) groups reported use of methotrexate or other csDMARD at randomization.

Table 49 Baseline disease characteristics (Randomized Set - Study P12302)

Characteristic	Secukinumab IV (N= 191)	Placebo (N= 190)
TNF alpha History, n (%)		
Naive	165 (86.4)	162 (85.3)
Inadequate responder	26 (13.6)	28 (14.7)
Number of prior anti-TNF PsA therapies, n (%)		
=0	165 (86.4)	162 (85.3)
=1	17 (8.9)	22 (11.6)
≥2	9 (4.7)	6 (3.2)
MTX or other csDMARD use at randomization, n (%)		
Yes	113 (59.2)	110 (57.9)
No	78 (40.8)	80 (42.1)
Dose of MTX at randomization (mg/week)		
mean (SD)	16.7 (6.1)	16.1 (5.6)
median	15	15
Min - Max	2.5 - 40	7.5 - 25
Time since first diagnosis of PsA (years)		
Mean (SD)	6.0 (7.3)	5.8 (7.1)
Median	3.5	3.3
Min -Max	0.07 – 52.4	0.5 – 38.0
Patient's assessment of PsA pain	N = 188	N = 189
Mean (SD)	55.5 (23.6)	57.3 (22.9)
Median	61	61
Min - Max	6 - 100	0 - 100

Source: Statistical Reviewer and Table 10-5 of Clinical Study Report CAIN457P12302

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Most patients reported at least one concomitant medication up to Week 16 in both secukinumab (188/191 (98.4%)) and placebo groups (189/190 (98.5%)). The most commonly reported concomitant medications were folic acid (secukinumab: 112/191; 58.6%; placebo:

112/190; 58.9%) and methotrexate (secukinumab: 97/191; 50.8%; placebo: 104/190; 54.7%). Other commonly reported (≥10% in either group) concomitant medications were omeprazole (secukinumab: 29/191; 15.2%; placebo: 29/190; 15.3%), cholecalciferol (secukinumab: 20/191; 10.5%; placebo: 30/190; 15.8%), etoricoxib (secukinumab: 17/191; 8.9%; placebo: 19/190; 10.0%), meloxicam (secukinumab: 37/191; 19.4%; placebo: 30/190; 15.8%), and paracetamol (secukinumab: 25/191; 13.1%; placebo: 19/190; 10.0%).

Efficacy Results – Primary Endpoint

As mentioned earlier in the review, the primary basis for approval of the proposed IV dosing regimen of 6 mg/kg single loading dose, followed by 1.75 mg/kg every four weeks thereafter with a maximum dose of 300 mg IV is the modeled exposure of SEC to match the approved subcutaneous (SC) doses of 150 mg and 300 mg with or without loading. Hence the efficacy results of this study, which has dose of secukinumab 6 mg/kg IV at baseline, followed by the administration of a higher dose of secukinumab, 3 mg/kg IV, every four weeks starting at Week 4, will be considered supportive only.

The statistical reviewer verified the applicant's results (Table 50), based on a logistic regression model with treatment and randomization stratum (TNFa status: naive or IR) as factors and baseline weight as a covariate, that secukinumab 6 mg/kg -3 mg/kg demonstrated superiority over placebo for ACR50 response using non-responder imputation for patients with missing data or who discontinued treatment or study at Week 16 (60/191 (31.4%) vs. 12/190 (6.3%); p<0.0001) with a marginal difference of 25.0 and 95% CI of (17.6, 32.4). A comparison of ACR50 response rates between the two treatment groups by normal approximation showed similar results (95% CI of the response rate difference of [17.7, 32.5]) and the same conclusion that secukinumab IV group had statistically significantly higher ACR50 response rate compared with the placebo group.

Table 50 ACR50 response using non-responder imputation* at Week 16 (FAS)

Treatment	Responder, n (%) 95% CI	Response rate difference compared to Placebo (95% CI) / P-value
Secukinumab IV N=191	60 (31.4) (24.8, 37.9)	25.0 (17.6, 32.4) <0.0001
Placebo N=190	12 (6.3) (2.9, 9.8)	

* There were 13 subjects (5 on secukinumab and 8 on placebo) who were non-responders due to missing data and 10 subjects (5 on secukinumab and 5 on placebo) who were non-responders due to treatment/study discontinuation.
Source: Statistical Reviewer and Table 14.2-1.1 of Clinical Study Report CAIN457P12302

Data Quality and Integrity

Data were submitted by the Applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, program code, and study reports were accessed through EDR \\CDSESUB1\evsprod\BLA761349\0000.

Based on the information provided in this submission, the study appeared to be conducted properly and was consistent with the history of regulatory interactions and protocol.

Efficacy Results – Secondary and other relevant endpoints

Based on the study report, secukinumab 6 mg/kg-3 mg/kg was shown to be superior to placebo at Week 16 for all endpoints in the pre-defined statistical testing hierarchy. The study met all secondary efficacy endpoints listed in the Study Endpoints section above.

Dose/Dose Response

The current study did not assess dose and dose response.

Persistence of Effect

The study report noted that secukinumab 6 mg/kg-3 mg/kg demonstrated nominal statistical significance over placebo for the primary endpoint (ACR50 response) with an onset of action as early as Week 4 that was sustained at all subsequent visits until and including at Week 16.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Some of the secondary endpoints are COA endpoints, including SF-36 PCS and FACIT-Fatigue change from baseline at Week 16. The study report also included other patient reported outcomes results including EQ-5D, PsAQoL, Percent Impairment while Working due to Health, and Percent Activity Impairment due to Health. All these PRO assessments showed numerically better results for secukinumab group compared to the placebo group.

Additional Analyses Conducted on the Individual Trial

In both TNF-naive and TNF-IR subgroups, secukinumab 6 mg/kg - 3 mg/kg displayed numerically higher ACR50 response rate compared to placebo with an onset of action as early as Week 4. The better response rate was sustained at all subsequent visits until and including Week 16. Subgroup analyses for demographics (age, sex, race and region [Europe, US, Asia, South and Central America, South Africa]) also showed higher ACR50 response rates for secukinumab IV compared to placebo among all subgroups with sufficient number of patients.

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