NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	125504/S-043
Priority or Standard	Standard
Submit Date(s)	July 30, 2020
Received Date(s)	July 30, 2020
PDUFA Goal Date	May 30, 2021
Division/Office	Dermatology and Dentistry/Office of Drug Evaluation II
Review Completion Date	
Established/Proper Name	secukinumab
(Proposed) Trade Name	Cosentyx
Pharmacologic Class	Fully human monoclonal Interleukin-17A antibody
Code name	
Applicant	Novartis Pharamceuticals
Dosage form	0.75mg/0.5 mL
Applicant proposed Dosing Regimen	Recommended dosage is based on body weight and administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks: Body Weight at Time of Dosing | Recommended Dose (b) (4) ≥ 50 kg | 150 mg (b) (4) (b) (4)
Applicant Proposed Indication(s)/Population(s)	For the treatment of moderate to severe plaque psoriasis in patients 6 years and older who are candidates for systemic therapy or phototherapy (referred to as pediatric plaque psoriasis or pediatric psoriasis in this submission)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	N/A
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of moderate to severe plaque psoriasis in patients 6 years and older who are candidates for systemic therapy or phototherapy (referred to as pediatric plaque psoriasis or pediatric psoriasis in this submission)

<table>
<tr><td>Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)</td><td>N/A</td></tr>
<tr><td>Recommended Dosing Regimen</td><td>The recommended dose for pediatric patients 6 years of age and older is based on body weight and administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks.
<table>
<tr><th>Body Weight at Time of Dosing</th><th>Recommended Dose</th></tr>
<tr><td>Less than 50 kg</td><td>75 mg</td></tr>
<tr><td>Greater than or equal to 50 kg</td><td>150 mg</td></tr>
</table></td></tr>
</table>

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Kimberle Searcy
Nonclinical Reviewer	N/A
Nonclinical Team Leader	N/A
Office of Clinical Pharmacology Reviewer(s)	Yunzhao Ren
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla, Jiang Liu (Pharmacometrics)
Clinical Reviewer	Maryjoy Mejia
Clinical Team Leader	Amy Woitach
Statistical Reviewer	Hyoyoung Choo-Wosoba and Matthew Guerra
Statistical Team Leader	Mohamed Alosh
Cross-Disciplinary Team Leader	Amy Woitach
Division Director (OHOP) DDD	Tatiana Oussova
Office Director (or designated signatory authority)	

Additional Reviewers of Application

OPMA	Qiong Fu A. Shukla (Application Team Lead)
Microbiology	Smith/Palmer/Gomez-Broughton
OPDP	Buonaccorsi
OSI	
OSE/DEPI	Little, Chan, Weintraub
OSE/DMEPA	Whaley (Human Factors)
OSE/DRISK	
Other	Pt. Labeling R. Mayrosh

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Microbiology Team Lead	Candace Gomez-Broughton, Ph.D.	OPQ/OPMA/DBM	Sections:4.2	Select one: ___ Authored _X_ Approved
	Signature: {See appended electronic signature page}			
Nonclinical Reviewer	N/A		Sections:	Select one: ___ Authored ___ Approved
	Signature:			
Nonclinical Supervisor	N/A		Sections:	Select one: ___ Authored ___ Approved
	Signature:			
Clinical Pharmacology and Pharmacometrics Reviewer	Yunzhao Ren, M.D., Ph.D.		Section: 6	Select one: _X__ Authored ___ Approved
	Signature: {See appended electronic signature page}			
Clinical Pharmacology Team Leader	Chinmay Shukla, Ph.D.		Section: 6	Select one: ___ Authored _X_ Approved
	Signature: {See appended electronic signature page}			
Pharmacometrics Team Leader	Jiang Liu, Ph.D.		Section: 6	Select one: _x__ Authored _X__ Approved
	Signature: {See appended electronic signature page}			

Clinical Reviewer	Maryjoy Mejia, MD	OII/DDD	Sections: 1, 2, 3, 4.1, 4.4, 7, 8, 9, 10, 11, 12, 13, 19.2	Select one: _X__ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Amy Woitach, D.O., M.S.	OII/DDD	Sections: 1, 2, 3, 4.1, 4.4, 7, 8, 9, 10, 11, 12, 13, 19.2	Select one: ___ Authored __X_ Approved
	Signature: {See appended electronic signature page}			
Division Director (Clinical)			Sections:	Select one: ___ Authored ___ Approved
Deputy Division Director for Safety (Clinical)	Tatiana Oussova, M.D., M.P.H.		Sections:	Select one: ___ Authored _X__ Approved
	Signature: {See appended electronic signature page}			
Statistical Reviewer	Hyoyoung Choo-Wosoba, Ph.D.	OTS/OB/DBIII	Sections: 8.1, 8.3	Select one: _X_ Authored ___ Approved
	Signature: {See appended electronic signature page}			
Statistical Reviewer	Matthew Guerra, Ph.D.	OTS/OB/DBIII	Sections: 8.1, 8.3	Select one: ___ Authored _X _ Approved
	Signature: {See appended electronic signature page}			
Statistical Team Leader	Mohamed Alosh, Ph.D.	OTS/OB/DBIII	Sections: 8.1, 8.3	Select one: ___ Authored _X_ Approved

	Signature: {See appended electronic signature page}

Glossary

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

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Secukinumab is a human monoclonal IgG1κ antibody that selectively binds to the pro-inflammatory cytokine interleukin-17A (IL-17A) and blocks its interaction with the IL-17 receptor. Secukinumab is considered to inhibit the release of proinflammatory cytokines, chemokines, and mediators of tissue damage resulting from IL-17A mediated autoimmune and inflammatory diseases. It is marketed under the trade name COSENTYX and received initial approval for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy on January 21, 2015. The approval letter included a post-marketing requirement for pediatric study in patients ages 6 to less than 18 years:

> 2848-1 Conduct a study to evaluate the safety and efficacy of secukinumab in pediatric subjects ≥ 6 years of age with plaque psoriasis.

The pediatric study requirement for ages 0 to less than 6 years was waived because necessary studies are impossible or highly impracticable; the number of pediatric patients under the age of 6 years with psoriasis is so small.

In the efficacy supplement that is the subject of this review (sBLA-043), the Applicant proposes extension of the patient population for the psoriasis indication to include treatment of children down to 6 years of age using a weight-based dosing approach, relying on data from two phase 3 studies (CAIN457A2310 and CAIN457A2311) for the approval of S-043. Specifically, the Applicant is proposing the following:

> "COSENTYX is indicated for the treatment of moderate to severe plaque psoriasis in patients 6 years and older who are candidates for systemic therapy or phototherapy".

Secukinumab is currently also indicated for the treatment of adults with

- moderate to severe plaque psoriasis,
- active ankylosing spondylitis,
- active psoriatic arthritis, and
- active non-radiographic axial spondyloarthritis with objective signs of inflammation.

Approval of S-043 would represent the first pediatric indication for secukinumab in the United States.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The submitted evidence has met the evidentiary standard for providing substantial evidence of effectiveness. The Applicant has established that secukinumab is effective for treatment of pediatric plaque psoriasis.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Secukinumab is a human monoclonal IgG1κ antibody that selectively binds to the pro-inflammatory cytokine interleukin-17A (IL-17A) and blocks its interaction with the IL-17 receptor. Current indications include the treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, active ankylosing spondylitis, active psoriatic arthritis, and active non-radiographic axial spondyloarthritis with objective signs of inflammation. In the efficacy supplement that is the subject of this review, the Applicant proposes to extend the psoriasis indication to include treatment of children down to 6 years of age using a weight-based dosing approach. Approval of this supplement would represent the first pediatric indication for secukinumab in the United States.

Plaque psoriasis is a common, chronic, immune-mediated, inflammatory skin disease that is typically characterized by symmetrically distributed, erythematous, scaly plaques with sharply-defined margins. The overall U.S. prevalence of plaque psoriasis is approximately 2 percent, and prevalence in childhood and adolescence is reported to be between 0.3 percent and 2 percent.

To establish the effectiveness of secukinumab in the treatment of plaque psoriasis in pediatric patients from 6 to less than 18 years of age, the Applicant submitted results from a randomized, double-blind, multicenter, placebo- and active-controlled, Phase 3 study evaluating 2 doses of secukinumab per weight strata in 162 subjects with severe chronic plaque psoriasis. The protocol-specified co-primary efficacy endpoints were the proportion of subjects who achieve PASI 75 response at Week 12 and the proportion of subjects who achieve IGA response at Week 12. Both low and high doses of secukinumab were statistically superior to the placebo for both co-primary efficacy endpoints (p-values less than 0.0001). Furthermore, comparison of secukinumab Ctrough values between children and adults with plaque psoriasis indicated that most of Ctrough values obtained from the majority of pooled pediatric dosing groups [75 mg for body weight (BW) <25 kg; 75 mg BW ≥25 kg and <50 kg; 150 mg for BW ≥25 kg and <50 kg; and 150 mg for BW ≥50 kg] were within the adult reference range. Secukinumab Ctrough values in pediatric subjects ≥50 kg on 300 mg were considerably higher than Ctrough values in adults on 300 mg dose. At certain time points, the median/mean secukinumab Ctrough values in this pediatric dosing group were about 2-fold as high as those of adults following 300 mg dose. With regards to assessment of benefit for 300 mg, subgroup analyses of pediatric subjects who weighed ≥50 kg with severe disease at baseline showed that PASI response rate/improvement from baseline at Week 12 was numerically similar between the 150 mg and 300 mg treatment groups. Additional exploratory analyses beyond the primary time point (i.e., Week 12) show that the 300 mg does not offer meaningful benefits over the 150 mg dose for the ≥ 50kg weight group. It should be noted that the number of subjects in each comparison is relatively small to make a meaningful conclusion.

It was noted that for 3 pediatric subjects with very high weight (>85kg) on the 300 mg dose, the Ctrough values at any time point were within the adult Ctrough range. These adolescent subjects, whose body weight was consistent with the median body weight of adult plaque psoriasis subjects, did demonstrate efficacy with 2 of the 3 subjects achieving success on the co-primary endpoints. No subjects >85 kg were treated with 150 mg of secukinumab for comparison. Regarding risk assessment, there were too few >85 kg pediatric subjects to determine whether pediatric safety correlates with exposure as was seen in analyses of adverse events in adult subjects. Due to this limited sample size and uncertainties surrounding the safety profile of secukinumab due to its immunosuppressive pharmacodynamic effects, the risk in the pediatric population whose immune and hematopoietic systems are immature, is not fully apparent.
Given the scant number of U.S. children who weigh >85 kg as demonstrated by the National Center for Health Statistics Weight-for-age charts, which showed the 95th percentile weight in older adolescents (e.g., 16 to 17 years) is approximately 84kg, the number of patients that would potentially benefit from a higher dose of 300 mg would be extremely small. (b) (4)

The Applicant provided substantial evidence of effectiveness in the treatment of plaque psoriasis for doses 75 mg in pediatric patients weighing <50 kg and 150 mg in pediatric patients weighing ≥50 kg.

The Applicant conducted a comprehensive assessment of the safety of secukinumab in the target population. The size of the safety database and the safety evaluations were adequate to identify treatment emergent adverse reactions. The safety profile in the pediatric population appears to be comparable to the characterized safety in the adult population. The Applicant provided adequate evidence of safety of secukinumab in children 6 years of age and older, and no safety signals that would preclude an approval were identified.

An approval for BLA 125504/Supplement 43 is recomended. The addition of secukinumab to the armamentarium of limited treatments for moderate-to-severe pediatric plaque psoriasis provides for an important systemic product in this population. The labeling will be updated to describe COSENTYX treatment for patients 6 years and older with moderate-to-severe plaque psoriasis who are candidates for systemic or phototherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Plaque psoriasis is a common, chronic, immune-mediated, inflammatory skin disease that is typically characterized by symmetrically distributed, erythematous, scaly plaques with sharply-defined margins. The overall U.S. prevalence of plaque psoriasis is approximately 2 percent, and prevalence in childhood and adolescence is reported to be between 0.3 percent and 2 percent. • Chronic plaque psoriasis is the most common clinical form of psoriasis in children. • An estimated 20 percent of patients have moderate to severe disease, affecting at least 3 percent body surface area (BSA) or involving body areas such as the hands, feet, face, and genitalia. • Comorbidities include obesity, diabetes, dyslipidemia, hypertension, depression, anxiety, and psoriatic arthritis.	The face, scalp, and other exposed skin areas are particularly common distributions of psoriasis in children and may negatively impact their feelings of self-worth. Childhood onset of psoriasis correlates with impaired social development, social withdrawal, sleep problems and substance abuse. Safe and effective treatment has the potential to greatly improve the quality of life for a patient with moderate to severe psoriasis.
Current Treatment Options	• Currently approved drugs for the treatment of moderate to severe psoriasis in children include the antimetabolite methotrexate (MTX); tumor necrosis factor inhibitors such as etanercept (approved for children down to 4 years of age); anti-interleukin (IL) agents like ustekinumab (an IL-12/IL-23 antagonist) and ixekizumab (an anti-IL-17A agent); T-cell inhibitor cyclosporine (CSA); and off-label use of the retinoid Soriatane (acitretin). Phototherapy, either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy (narrow or broadband) is also a standard of care treatment for moderate to severe psoriasis in children. • Significant safety concerns for the moderately and highly efficacious approved products include immunosuppression with the associated risk for serious and in some cases opportunistic or unusual infections, cytopenias, hepatotoxicity and hypersensitivity events.	There remains an unmet medical need for safe and effective treatment of moderate to severe plaque psoriasis in pediatric patients. Approval of this supplement would add to the limited armamentarium of approved systemic treatments for this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Study CAIN457A2310 (A2310) showed statistically significant and clinically meaningful improvements in efficacy observed for the COSENTYX treatment groups compared to placebo across the co-primary endpoints.	The evidence submitted by the Applicant supports approval of labeling to include the treatment of moderate-to-severe plaque psoriasis down to 6 years of age.
Risk and Risk Management	• The data from pediatric subjects 6 years of age and older provided in this supplement revealed a safety profile generally similar to that seen in the adult psoriasis population. • The risk of COSENTYX is consistent with the known safety profiles for other systemic agents used for the treatment of psoriasis. This includes risks of immunosuppression with serious and in some cases opportunistic or unusual infections, reactivation of latent tuberculosis, cytopenias, inflammatory bowel disease, and hypersensitivity events.	The Applicant has adequately demonstrated that secukinumab is safe and effective for treatment of moderate to severe plaque psoriasis in children 6 years of age and older.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
X	**The patient experience data that were submitted as part of the application include:**			
	X	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	6.1, 6.3, 6.5, 7, 8
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Plaque psoriasis is a common, chronic, immune-mediated, inflammatory skin disease that is typically characterized by symmetrically distributed, erythematous, scaly plaques with sharply-defined margins. The overall U.S. prevalence of plaque psoriasis is approximately 2 percent, and prevalence in childhood and adolescence is reported to be between 0.3 percent and 2 percent. Chronic plaque psoriasis is the most common clinical form of psoriasis in children.
An estimated 20 percent of patients have moderate to severe disease[1], affecting 3 percent or more body surface area (BSA) or involving body areas such as the hands, feet, face, and genitalia.[2]
Comorbidities include obesity, diabetes, dyslipidemia, hypertension, depression, anxiety, and psoriatic arthritis. The negative impact of psoriasis on quality of life has been found to be comparable or in excess of that with cancer, arthritis, hypertension, heart disease, and diabetes. Childhood onset of psoriasis correlates with impaired social development, social withdrawal, sleep problems and substance abuse.

2.2. Analysis of Current Treatment Options

Definitive guidelines regarding the management of moderate to severe plaque psoriasis in children is lacking. A recommendation for systemic therapy or phototherapy is based on clinical judgment, considering disease severity, comorbid conditions, risk tolerance, and prior failed therapy. Such considerations are especially important in treatment decisions for moderate to severe psoriasis in pediatric patients, since the majority of treatments would be used off-label.

Etanercept is licensed for treatment of psoriasis in patients ages 4 to 17 years who are candidates for systemic or phototherapy. Ixekizumab is licensed for treatment of psoriasis in patients ages 6 to 17 years who are candidates for systemic or phototherapy. Therapies presented in the following table are otherwise only approved for use in adults, but may be used off-label in children.

[1] Menter A, Korman NJ, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011;65(1):137-174.
[2] Armstrong AW, Siegel MP, Bagel J, et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. J Am Acad Dermatol. 2017;76(2):290-298.

Table 1. Approved Systemic Therapies for Psoriasis

Small Molecules		
Product	Class	Warnings/Precautions
Acitretin	Retinoid	teratogen; hepatotoxicity; hyperostosis; lipid effects
Methotrexate	folate antagonist	teratogen; liver fibrosis/cirrhosis; hematologic toxicity; interstitial pneumonitis; opportunistic infections
Cyclosporine	inhibits IL-2	hypertension; nephrotoxicity; serious infections; malignancy
Apremilast	phosphodiesterase 4 inhibitor	depression; weight decrease; drug-drug interactions
Biologics		
Etanercept	TNFα-blocker	serious infections (including TB); malignancy; central nervous system demyelinating disorders; hematologic events (pancytopenia); reactivation of hepatitis B; autoimmunity
Adalimumab	TNFα-blocker	serious infections (including TB); malignancy; reactivation of hepatitis B; demyelinating disease; hematologic reactions (pancytopenia); autoimmunity
Infliximab	TNFα-blocker	serious infections (including TB); malignancy; demyelinating disease; hepatotoxicity
Ustekinumab	interleukin-12 and - 23 antagonist	serious infections; malignancy; reversible posterior leukoencephalopathy syndrome
Secukinumab	interleukin-17A antagonist	serious infections; TB, exacerbation of Crohn's disease; hypersensitivity
Ixekizumab	interleukin-17A antagonist	infections; hypersensitivity; inflammatory bowel disease
Guselkumab	interleukin-23 blocker	Infections; TB

Phototherapy

This therapy involves exposures to UVB (including narrowband) or to UVA in combination with the photosensitizer, psoralen, a photochemotherapy regimen that goes by the acronym "PUVA." Long-term phototherapy carries risks of photoaging and skin cancer.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The requirements needed to address Pediatric Research Equity Act (PREA) were initially discussed with the Applicant at a guidance meeting on March 2, 2011. Because the development plan for secukinumab predated the requirements under the Food and Drug Administration Safety and Innovation Act (FDASIA), the Applicant was not required to submit an initial Pediatric Study Plan (iPSP) within 60 days of an EOP2 meeting. However, Novartis submitted an iPSP for secukinumab on February 11, 2013 requesting a partial waiver in pediatric psoriasis patients who are less than 6 years of age and a deferral in patients 6-17 years of age. This plan was reviewed and discussed with the Pediatric Review Committee (PeRC) on February 27, 2013. PeRC and DDD determined that it was premature to agree with the proposed deferred studies as outlined at the time and the plan should be replaced with a broader plan which would address the informational needs for safety and efficacy in pediatric patients. Written comments regarding the iPSP were sent to the Applicant on April 5, 2013. The Applicant decided not to follow the process for pediatric plans under FDASIA and submit a plan to address PREA with the BLA submission.

The approval letter dated January 21, 2015 communicated deferral of the required pediatric studies as below:

> We are deferring submission of your pediatric study for ages 6 to 17 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected. Serious safety signals have been observed in clinical trials for biologic agents in adult patients with arthritis, inflammatory bowel disease and psoriasis, and the Agency has determined that pediatric studies should be deferred until after adult studies have been completed and additional safety data are collected and reviewed for adult psoriasis patients. The original timelines were as follows:
>
> Final Protocol Submission: 01/2022
> Study Completion: 12/2025
> Final Report Submission: 02/2026

These timelines were based on the prior experience with other biologics to allow additional safety (and efficacy) data in adults to be collected and reviewed prior to initiating pediatric studies.

On August 09, 2017 during a teleconference between Novartis and FDA, it was agreed that Novartis could initiate pediatric trials for plaque psoriasis in the U.S. immediately. The protocol for Study CAIN457A2310 (A2310) was submitted to IND 100418 on September 15, 2017 and to BLA 125504 on October 20, 2017.

The global recruitment of study A2310 began in September 2015 but U.S. enrollment started only in July 2018 and the last patient in the study was recruited in August 2018.

The protocol for Study CAIN457A2311 (A2311) was submitted to IND 100418 on March 15, 2018. The Agency communicated that the protocol was appropriate to meet PMR 2848-1 on June 29, 2018.

A pre-sBLA teleconference was held on September 4, 2019 with final minutes conveyed to the Applicant on September 9, 2019 highlighting the importance of including safety data from Study A2311 to inform the risk/benefit determination for the pediatric population. The Agency advised that 52 week safety data from Study A2310 in combination with 24-week data from the open-label A2311 study should be submitted in an efficacy supplement. The Applicant adhered to this recommendation and submitted 52 week efficacy and safety data for all pediatric subjects in Study A2310 as well as long-term safety data of varying duration (up to about 3 years) collected up to the cut-off date of September 18, 2019. Study A2311 recruited subjects over nine months. Analysis of data was performed after all subjects completed their Week 24 visit. The Applicant submitted safety data collected until the last visit of each patient prior and up to the cut-off date of November 14, 2019.

3.2. Summary of Presubmission/Submission Regulatory Activity

Refer to Section 3.1.

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

4.1. Office of Scientific Investigations (OSI)

No site inspections were requested for Study CAIN457A2310 or Study CAIN457A2311. The Division determined that the yield from inspection would be limited and unlikely impact decision making on this non-NME supplement due to the small number of subjects who were spread across multiple study centers. Randomized controlled Study 2310 was conducted outside of the U.S. and at the time of review there were also logistical challenges for international inspection due to COVID-19 travel restrictions. Study 2311 was conducted in the U.S. and was an open-labelled trial.

4.2. Product Quality

Product Quality Microbiology Assessment: Drug Product
SUMMARY

Formulation and pharmaceutical forms

The drug product is currently supplied as follows

- 150 mg powder for solution for injection
- 150 mg/mL solution for injection in a prefilled syringe
- 150 mg/mL solution for injection in a prefilled pen.

The proposed new strength is 75 mg/0.5 mL solution for injection in prefilled syringe, as an aqueous solution for subcutaneous administration.

The applicant stated that this 75 mg/0.5 mL solution for injection in a prefilled syringe is made of the same bulk drug product solution formulation as the marketed 150 mg/mL solution for injection in prefilled syringe, filled with half the amount, in the same container closure system and assembled with the same devices (same rug substance and excipients leading to same bulk drug product solution, same syringe half-filled, same stoppers, same plunger rod and same needle safety device).

Container closure system

The container closure system for the proposed new indication of the drug product remains unchanged from previously approved.

Configuration	Component	Description	Manufacturer

75 mg/0.5 mL	Syringe barrel	(b) (4) 1 mL (b) (4) glass syringe barrel with staked needle	(b) (4)
	Plunger stopper	(b) (4)	
	Rigid needle shield (RNS)	(b) (4) plastic shell	(b) (4)
		Grey rubber needle shield, (b) (4)	(b) (4)

Manufacturers

Manufacturer/Site	FEI	Responsibilities
Novartis Pharma Stein AG2 Schaffhauserstrasse 4332 Stein Switzerland	3002653483	Drug Product Manufacture, All Quality Control Testing and Secondary Packaging

Reviewer's note: The facility used for manufacturing and testing of the proposed new indication of the drug product has not changed from the approved BLA.

Description and composition of the drug product

The description and composition of the proposed new indication of the drug product remain unchanged from previously approved.

(b) (4)

Description of the Manufacturing Process and Process Controls

The manufacturing process for the proposed new indication of the drug product remains unchanged from previously approved.

The manufacturing process for AIN457 75 mg/0.5 mL solution for injection in pre-filled syringes is a (b) (4)

The applicant states that there are (b) (4) defined for AIN457 75 mg/0.5 mL solution for injection in pre-filled syringes.

Control of Critical Steps and Intermediates

The control of critical steps and intermediates for the manufacturing of the proposed new indication of the drug product remain unchanged from previously approved.

The microbiological approved in-process controls are as follows:

(b) (4)

Process Validation and/or Evaluation

Process Validation Lots

The applicant states that only one batch record of AIN457 75 mg/0.5 mL solution for injection in a pre-filled syringe is provided in the supplement submission, and that all batch records will be available at the site of manufacture during the pre-approval inspections or may be requested for review prior to that time, if necessary.

Table 2-1 Batch information for AIN457 75 mg/0.5 mL solution for injection in a pre-filled syringe

Batch #	SPP32	SPP32P
Strength	75 mg/0.5 mL	75 mg/0.5 mL
Date of manufacture	Jul-2019	Jul-2019
Date of assembly	-	Nov-2019
Place of manufacture	Novartis Pharma Stein AG, Schaffhauserstrasse, 4332 Stein, Switzerland	Novartis Pharma Stein AG, Schaffhauserstrasse, 4332 Stein, Switzerland
Batch size (theoretical)	(b) (4) units	(b) (4) units
Type of batch	(b) (4) validation	(b) (4) validation
Use of batch	Process validation bulk PFS	Process validation assemble and packaged finished product and registration stability

(b) (4)

Control of Drug Product

The microbiological specifications for the proposed new indication of the drug product remain unchanged from previously approved.

Test	Test Method	Specification
Bacterial Endotoxins	USP <85>	(b) (4) EU/mg
Sterility	USP <71>	No growth

Summarized information is provided in the supplement submission for bacterial endotoxins and sterility testing; however, since there were no further changes to the (b) (4) of the proposed new indication of the drug product, the referenced summarized information was not reviewed.

The applicant provides the batch analysis for batch numbers SPP30, SPP31. SPP32, and SRC48 in support of the proposed new indication of the drug product. The bacterial endotoxins and sterility specifications were met.

Stability

No changes are proposed for the new indication of the drug product. The applicant indicates that the stability studies for the proposed AIN457 75 mg/0.5 mL solution for injection in a prefilled syringe assembled in a needle safety device are ongoing. The microbiological stability

data (bacterial endotoxins and sterility) for batch SPP32 at T=0 met the corresponding specification.

Conclusion

1. This efficacy supplement was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval.
2. Product quality aspects other than microbiology should be reviewed by OBP and/or CDRH.
3. No inspectional follow-up items were identified. Refer to Panorama for the compliance status of the facilities.

4.3. Clinical Microbiology

Refer to Section 4.2.

4.4. Devices and Companion Diagnostic Issues

The review by Center for Devices and Radiological Health (CDRH) identified deficiencies in the Applicant's analyses of the device constituent parts of the combination product. According to the CDRH review, the provided literature studies did not validate the device specifications for activation of the Needle Safety Device (NSD) or for removal of the Rigid Needle Shield (RNS) for pediatric use. Failure to activate needle safety and properly remove the needle cap leads to incomplete injections and needle sticks, especially in a vulnerable population (i.e., pediatric patients).

Based on these listed device deficiencies, an adult caregiver will need to administer COSENTYX pre-filled syringe in pediatric patients.

The reader is referred to the CDRH review by Dunya Karimi and Rumi Young, for detailed analyses of the validation of specifications and essential performance requirements control strategy determining that the device constituent parts of the combination product are Approvable ONLY for adult/caregiver delivery.

The Applicant previously submitted Human Factors (HF) study results to support use of the 150 mg/mL Sensoready Pen in pediatric patients age 12 -17 years old . The Division of Medication Error Prevention and Analysis (DMEPA) reviewed this data as part of the initial BLA review and concluded that the Applicant has provided HF data to support use of the 75 mg/0.5 mL PFS and 150 mg/mL Sensoready Pen in pediatric patients.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical data was sumitted for this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Novartis submitted pediatric supplement (supplement 043, SDN 3240) of BLA 125504 on July 30, 2020 under Supplemental Document Number 3240 seeking the marketing approval of secukinumab (AIN457), a human IgG1 monoclonal anti-17A antibody, for treating plaque psoriasis in children (6 to <18 years of age). The proposed subcutaneous dose is based on body weight:

(b) (4)

- ≥ 50 kg: 150 mg (b) (4)

(b) (4)

The submission of this pediatric supplement is to fulfill the pediatric Post-marketing Requirement issued in the approval letter for plaque psoriasis on January 21, 2015:

2848-1 Conduct a study to evaluate the safety and efficacy of secukinumab in pediatric subjects ≥ 6 years of age with plaque psoriasis.

Final Protocol Submission: 01/2022
Study Completion: 12/2025
Final Report Submission: 02/2026

Two pediatric studies (A2310 and A2311) and two pharmacometrics reports were submitted in this pediatric supplement.

Recommendation: The Office of Clinical Pharmacology Division of Immune and inflammation Pharmacology and Division of Pharmacometrics have reviewed the information submitted under sBLA 125504/S-043. This pediatric supplement is approvable from a Clinical Pharmacology perspective. Most proposed pediatric doses are acceptable. (b) (4)

The clinical pharmacology review will focus on following items:

1. The acceptability of the validated bioanalytical assay for measuring secukinumab serum concentration from pediatric studies CAIN457A2310 (A2310) and CAIN457A2311 (A2311).
2. The comparison of secukinumab Ctrough values between children and adults with plaque psoriasis.
3. The adequacy of the population PK (popPK) model in describing secukinumab PK in children with plaque psoriasis.
4. The evaluation of dose-response relationship in children on secukinumab treatment.

5. The immunogenicity results from the two pediatric studies.
6. The acceptability of proposed dose in children with plaque psoriasis.

Summary of key review items: The evaluation of key review items with specific recommendations/comments are summarized below:

Review Items	Recommendations and Comments
Bioanalytical assay for measuring secukinumab plasma concentration	Some minor changes were introduced after the validated bioanalytical assay submitted during the original BLA 125504 review cycle was transfer from (b) (4) in 2019. The cross-validation report and the validated bioanalytical assay report of the new Method (b) (4) for measuring secukinumab serum concentration obtained from pediatric studies A2310 and A2311 are acceptable. The pediatric secukinumab trough concentrations can be used for comparison to that of adults directly.
Comparison of secukinumab pediatric Ctrough values to those from adults with plaque psoriasis.	Most of Ctrough values obtained from most of pediatric dosing groups (< 25 kg on 75 mg, 25 - < 50 kg on 75 mg, 25 - < 50 kg on 150 mg, and >50 kg on 150 mg) in Studies A2310 and A 2311 were within the adult reference range following 150 mg and/or 300 mg dose by the same Q1W × 5 + Q4W regimen. Pediatric Ctrough values obtained from dosing group >50 kg on 300 mg were noticeably higher than Ctrough values from adult on 300 mg dose. At certain time points, the median/mean secukinumab Ctough values in this pediatric dosing group were about 2-fold as high as those of adults following 300 mg dose. In addition, at certain time points, about half of secukinumab Ctrough values in this pediatric dosing group were greater than 95th percentile of adult value following 300 mg dose. However, the exposure of secukinumab decreases significantly in both pediatrics and adults as body weight increases. The median body weight in the pediatric dosing group > 50 kg on 300 mg is ~63 kg which is significantly lower than the median body weight of 84 kg in adult trials. For adolescents whose body weight is higher than the median body of adults, their Ctrough values at any time points are within the adult Ctrough range on 300 mg dose and also comparable to the exposure observed in pediatrics < 25 kg on 75 mg of secukinumab.
Evaluation of popPK model	Sponsor's pediatric-adult pooled popPK model reasonably describes the observed secukinumab concentrations in adults and children, though the median cocentrations at Week 4 and Week 12 in the high dose regimen (< 25 kg on 75 mg, 25 - < 50 kg on 150 mg, and ≥ 50 kg on 300 mg) was slightly under-predicted and the 95th percentile of the

	low dose regimen (< 25 kg on 75 mg, 25 - < 50 kg on 75 mg, and ≥ 50 kg on 150 mg) and the 5th percentile of the high dose regimen at later time points were slightly over-predicted by the model. To account for slightly higher concentrations in pediatric patients observed in Studies A2310 and A2311, the pooled popPK model was modified to include separate estimates of bioavailability for pediatric and adult patients. This resulted in a (relative) 25% higher bioavailability in pediatric patients (73% for the adult population vs. 91% for the pediatric population). However, the underneath cause for this "higher bioavailability" in children is unclear. By considering that 1) The mean body weight in pediatric studies and adult studies is 54.5 and 87.0, respectively. 2) Model estimated allometric exponent of body weight effect on secukinumab clearance is 0.90. 3) Model estimated that pediatric bioavailability is about 25% higher than that of adults. The observed pediatric mean Ctrough values at certain time points in children weighing ≥ 50 kg was about 2-fold as high as in adults following 300 mg dose can be partly explained by popPK model.
Evaluation of dose-response relationship in children with plaque psoriasis	The primary endpoint (PASI 75 response rate) and one of the secondary endpoints (%PASI improvement from baseline) at Week 12 were assessed by pooling two pediatric studies A2310 and A2311. The results demonstrate that PASI response rate/improvement from baseline in all these groups were better than placebo group. In addition, exploratory analysis showed that in children weighing 25 to <50 kg with severe disease at baseline, the response to secukinumab treatment at Week 12 was numerically better on 150 mg dose than 75 mg secukinumab treatment. The response in children weighing ≥50 kg with severe disease at baseline at week 12 was numerically similar between 150 mg and 300 mg treatment groups, however the number is relatively small.
Immunogenicity Results from pediatric studies A2310 and A2311	Only two samples were anti-drug antibody (ADA) positive with low titiers: 1) One patient in the etanercept group from Study A2310 was ADA-positive (titer 1:1) at baseline. 2) One patient in 300 mg treatment group was ADA-positive (titer of 1: 7.98) at baseline.
Overall clinical pharmacology conclusion of secukinumab dosing in	By considering that 1) Secukinumab Ctrough values in following dosing groups pooled from studies A2310 and A2311

pediatric patients with plaque psoriasis	a) < 25 kg on 75 mg b) 25 - < 50 kg on 75 mg c) 25 - < 50 kg on 150 mg d) >50 kg on 150 mg were mostly within the adults reference range following 150 mg and/or 300 mg dose. 2) Subgroup exploratory analysis showing that PASI response rate/improvement from baseline in all these groups were better than placebo group. And PASI response rate/improvement from baseline at Week 12 was numerically better in 150 mg group than 75 mg group in children weighing 25 - < 50 kg. The following proposed doses are reasonable from clinical pharmacology perspective: (b) (4) • ≥ 50 kg: 150 mg By considering that: 1) Although secukinumab Ctrough values in children >50 kg on 300 mg were noticeably higher than Ctrough values from adult on 300 mg dose, this could be primarily explained by the body weight difference in this pediatric dosing group compared to that in the adult trials. The median body weight in this dosing group in the pediatric trials is ~63 kg which is significantly lower than the median body weight of 84 kg in adult trials. For adolescents whose body weight is higher than the median body of adults, their Ctrough values at any time points are within the adult Ctrough range on 300 mg dose and also comparable to the exposure observed in pediatrics < 25 kg on 75 mg of secukinumab. 2) Subgroup exploratory analysis showing that PASI response rate/improvement from baseline at Week 12 in children weighing ≥50 kg with severe disease at baseline was numerically similar between 150 mg and 300 mg treatment groups. However, the number of subjects is relatively small for a reliable dose-response comparison across the entire body weight range. Strong positive exposure-response relationship was observed in previous adult trials. • the proposed alternative dose of 300 mg for some patients ≥ 50 kg: We consider that 300 mg might be reasonable for some adolescents with high body weight (e.g., >85 Kg, the median body weight of subjects in adult plaque psoriasis trials) from the clinical pharmacology perspective. The acception of the proposed alternative dose of 300

	mg in some patients ≥ 50 kg will depend on clinical's evaluation.

6.2. Assessment of Bioanalytical Assay

Conclusion: the validated bioanalytical assay used to determine secukinumab serum concentration from PK samples obtained from pediatric Studies A2310 and A2311 is acceptable.

Methods and cross-validations
During the review of original submission of BLA 125504 in 2014, the validated bioanalytical report RS686053 [developed by Novartis and conducted by (b) (4) for measuring secukinumab serum concentration was deemed acceptable. However, due to the challenges of clinical sample import and export in and out (b) (4) the same competitive ELISA method (by principle) was transferred from (b) (4) in 2019. Two minor changes were introduced in the transition:

1. Biotinylated secukinumab (the compatiter) concentration changed to 1:10000 in assay buffer (Table 6.2.2). It is unclear if it is the different batches of the biotinylated secukinumab, or different methods for manufacturing biotinylated secukinumab that causes this change.

2. During sample preparation, after application of population specific pre-dilution and assay minimal required dilution (MRD), samples were incubated in (b) (4) tubes for 1 hour at room temperature without shaking.

Two new bioanalytical reports CP175487 (for Study A2310) and CP185021 (for Study A2311) and a cross-validation report (R1701288) were submitted in this supplement. The comparison of competitive ELISA methods described from four different bioanalytical reports is summarized in Table 6.2.1.

Table 6.2.1: Comparison of Four Bioanalytical Reports

Report	RS686053	R1701288/CP175374	CP175487	CP185021
Release year	2011	2020	2019	2020
CRO	(b) (4)			
Bioanalytical method	Competitive ELISA			
Clinical Studies	Healthy subjects, adult plaque psoriasis studies	Cross validation	Pediatric plaque psoriasis study A2310	Pediatric plaque psoriasis study A2311
LLOQ (ng/mL)	80	500	1000[1]	1000[1]
ULOQ (mg/mL)	2500	2500	5000[1]	5000[1]

Sample volume (µL)	50	100	unclear	unclear
Minimum required dilution (MRD)	1:3 with biontinylated secukinumab	1:2 in HSerPool piror to 1:8 MRD		
Secukinumab standard	Y1050509[2] 150 mg/mL	S0024[2] 150 mg/mL	S0024[2] and S2002[2] 150 mg/mL	S2002[2] 150 mg/mL
Coating antibody	Norvatis 02/290605[2]	Norvatis PR120515I[2] 0.86 mg/mL		
Biotinylated secukinumab	[redacted] (b) (4) AIN181110YNL[2] 1.95 mg/mL	Bio_AIN457_20171124_AH[2] Bio_AIN457_20180810_JB[2] ~ 2500 µg/mL	BIO_AIN457_20180810_JB[2] BIO_AIN457_20181116_JB[2] ~ 2500 µg/mL	BIO_AIN457_20181116_JB[2] 2360 µg/mL
HRP-streptavidin	[redacted] (b) (4)			

[1] in human serum
[2] Batch/lot #
[3] Catlogue#
Source: reviewer's summary

In the cross-validation report R1701288 (both int1 and int2), 30 samples previously analyzed at Norvatis by Method RS686053 were reanalyzed at [redacted] (b) (4). However, the lowest concentration of these 30 samples was 3390 ng/mL as measured by Method RS686053 (BLQ by [redacted] (b) (4)). Norvatis consider the cross-validation is valid as the results showed that at least 2/3 of QC samples retain the bias and %CV within 20% and the normalized difference of results between [redacted] (b) (4) and Novartis was within ±30% (pre-defined) for 26 out of 30 (87%) cross-validation samples.

Cross-validation was further performed using 50 study samples from A2310 showing normalized differences within ±30% for 42 out of 50 (84%) cross-validated samples. Selectivity was assessed using 15 study samples from A2310 at 500 ng/mL and at 1000 ng/mL [using 1:2 dilution in an adult human serum pool prior to MRD (1:8)]. The results from selectivity at 1000 ng/mL showed 93% of secukinumab spiked samples within a bias of ±25% (pre-defined). Therefore, 1:2 pre-dilution in adult human serum pool was implemented for A2310 and A2311 study sample analysis. However, selectivity at 500 ng/mL did not meet the acceptance criteria. Therefore, 1000 ng/mL was accepted as the LLOQ. Parallelism and ISR assay were successfully performed using A2310 study samples (DMPK RCAIN457A2310-pk-int and DMPK RCAIN457A2310-pk-int2).

Based on the materials that Norvatis has submitted, this reviewer considers the cross-validation report R1701288 is acceptable. The cross-validation report is summarized in Table 6.2.3.

Table 6.2.2: Summary of Method Modifications and Cross-Validation Results

Bioanalytical method validation report name	dmpk-r1701288-pk-int--pre-clinical-study-report.pdf dmpk-r1701288-pk-int2--pre-clinical-study-report.pdf

Changes in method	No major changes to assay platform and detection system were implemented. Minor adjustments at (b) (4) were: 1. Biotinylated AIN457 concentration changed to 1:10000 in assay buffer 2. During sample preparation, after application of population specific pre-dilution and assay MRD, samples were incubated in (b) (4) tubes for 1 hour at room temperature without shaking		
Newly valideated assay range	500-2500 ng/mL		
Validation parameters	Cross-validation performance		Source location[1]
Standard calibration curve performance during accuracy and precision runs	Cumulative accuracy (% bias) in standard calibrators from LLOQ to ULOQ (from all accepted validation runs)	-1 to 2% (Runs 1-32) -1 to 2% (Runs 33- 94)	Table 7-6 and Table 7-7
	Cumulative precision (% CV) from LLOQ to ULOQ (from all accepted validation runs)	≤ 6%	
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 5 QCs (from all accepted validation runs)	-2% to 2%	Table 7-10
	Inter-batch % CV (from all accepted validation runs)	≤ 11%	Table 7-10
	Percent TE	≤ 12%	Table 7-10
Cross-validation using adult PK samples	30 samples for cross-validation of the method between (b) (4) and (b) (4) labs were measured. Results showed 26 out of 30 (87%) cross-validation samples were within normalized difference of ±30%		Table 7-18
Cross-validation using pediatric PK samples	50 incurred samples for A2310 study were measured in cross-validation. Results showed 42 out of 50 (84%) of incurred study samples were within the normalized differences of ±30%.		Table 7-32

[1] Source: since most of dmpk-r1701288-pk-int tables were recapitulated in dmpk-r1701288-pk-int2, dmpk-r1701288-pk-int2 was used as source.

Although the cross-validation report R1701288 is acceptable, due to different LLOQ values established by two methods, the reviewer explored the popPK dataset submitted in this supplement and found that among near 30,000 adult concentrations, about 3.2% (946/29956) concentrations were less than 1000 ng/mL. Therefore, adopting different LLOQ values is unlikely to affect the distribution of 5th percentile value in adult studies.

Key performance

The key performance of validated bionalyatical assay that was used for measuring secukinumab serum concentrations from two pediatric studies (A2310 and A2311) is summarized in Table 6.2.3. The validated bioanalytical method is acceptable.

Table 6.2.3: Key Performance of Method (b) (4) from Reports CP 175487 and CP185021

Review Issues	Recommendations and Comments
Bioanalytical method validation report name and amendments	dmpk-ain457a2310-pk--compliance-and-drug-concentration-data.pdf dmpk-ain457a2311-pki--compliance-and-drug-concentration-data.pdf
Method description	Competitive ELISA • A purified polyclonal anti-idiotypic antibody against secukinumab was coated on the microtiterplate. • Serum samples (calibration, Quality Control or unknown samples) and biotin-labelled secukinumab were mixed and added to the plate to compete for binding on the coating antibody. • Non-bound material was removed by washing. Bound biotinylated-secukinumab was detected by incubating horseradishperoxidase-conjugated to streptavidin with O-phenylenediamine dihydrochloride (OPD) as enzyme substrate.
Key Materials used for standard calibration curve and concentration	• Coating antibody: 0.86 mg/mL provided by (b) (4) with batch number PR120515I • Bionylated secukinumab: Batch numbers 135331 and 136861 at 1 mg, product number (b) (4) purchased from (b) (4)
Validated assay range	1000 to 5000 ng/mL in human serum
Material used for quality controls (QCs) and concentration	150 mg/mL secukinumab reference standard obtained from Novartis Pharma AG with batch number of S0024 and S2002. Sera used to prepare HSerPool (batch numbers BRH1429072, BRH1429073, BRH1429074, BRH1429085, BRH1429086 and BRH1429087) were provided by (b) (4) Concentrations of caliberation standard are 300, 400, 500, 750, 1000, 1250, 1500, 2000, 2500, and 10000 ng/mL. Concentrations of QCs are 800, 1400, and 2000 ng/mL.

Minimum required dilutions (MRDs)	Study samples must be diluted at least at 1:2 in human serum pool (HSerPool) prior to the 1:8 MRD	
Regression model and weighting	4-Parameter Logistic (logistic autoestimate) Fit y=((A-D)/(1+(x/C)^B))+D	
Standard calibration curve performance during accuracy and precision runs	CP 175487	CP185021
	Accuracy (% bias): -1% to 2% Precision (% CV): 1% to 5%	Accuracy (% bias): 0% to 22% (excluding 300 and 400 ng/mL) Precision (% CV): 1% to 5%
Performance of QCs during accuracy and precision runs	Accuracy (% bias): 6% to 10% Precision (% CV): 7% to 9%	Accuracy (% bias): 2% to 6% Precision (% CV): 9% to 12%
Selectivity & matrix effect	Refer to study report of CP175374, no matrix effect was observed starting 500 ng/mL (81% of secukinumab spiked samples with bias within ±25%).	
Dilution linearity & hook effect	The maximum validated dilution factor is 1:2000	
Long-term storage stability	Stability of sacukinumab in human serum at -75°C±10°C was demonstrated for up to 39 months (1184 days) under Novartis Study Reference No. 0450380. This stability period covers the maximum length of time from specimen collection (first sample collected on 29-Jun-2016) to analysis (last sample analyzed on 17-Apr-2019) i.e., 1022 days.	
Room temperature stability	As demonstrated under Novartis bioanalytical report RS686053, secukinumab is stable in huma serum at room temperature for at least 24 hours.	

Source: reviewer's summary from dmpk-ain457a2310-pk--compliance-and-drug-concentration-data.pdf and dmpk-ain457a2311-pki--compliance-and-drug-concentration-data.pdf.

6.3. Comparison of systemic exposure of secukinumab between children and adults with plaque psoriasis

Conclusion: When secukinumab pediatric Ctrough concentrations were compared to that of adults following either approved SC 150 mg or 300 mg following Q1W × 5 + Q4W regimen, most of Ctrough values obtained from most of pediatric dosing groups (< 25 kg on 75 mg, 25 - < 50 kg on 75 mg, 25 - < 50 kg on 150 mg, and >50 kg on 150 mg) were within the adults reference range following 300 mg dose. In addition, most secukinumab Ctrough values in children 25 - < 50 kg following 75 mg dose were also within the adult reference range following 150 mg dose.

However, pediatric Ctrough values obtained from dosing group >50 kg on 300 mg were noticeably higher than Ctrough values from adult on 300 mg dose. At certain time points, the median/mean secukinumab Ctough values in this pediatric dosing group were about 2-fold as high as those of adults following 300 mg dose. In addition, at certain points, about half of

secukinumab Ctrough values in this pediatric dosing group were greater than 95th percentile of adult value following 300 mg dose at Week 4 and Week 52.

Summary of studies
In order to compare the systemic exposure of secukinumab between children and adults with plaque psoriasis, the sponsor collected PK results from two pediatric studies (A2310 and A2311) and 10 adult studies. These 12 studies are summarized in Table 6.3.1.

Table 6.3.1: Summary of Sixteen Studies

Study #	Studied Design	Study Population	PK Population	Dosing Regimen of Secukinumab	Drug Product
A2102	Phase 2a POC	PsA adults	18	SD IV 3 mg/kg	Lyophilized powder
A2103	Phase 1 BA, CO	PsA adults	14	SD IV 3 mg/kg SC 150 mg	Lyophilized powder
A2211	Phase 2 DR	PsA adults	401	SC 150 mg X1 150 mg Q4W X3 150 mg at W 1, 2, 3, 5	Lyophilized powder
A2212	Phase 2 PG, efficacy/safety	PsA adults	118	IV 3 mg/kg X1 10 mg/kg X1 30 mg/kg Q2W X3	Lyophilized powder
A2220	Phase 2 DR	PsA adults	103	SC Q4W 25 mg 75 mg 150 mg	Lyophilized powder
A2302	Phase 3 efficacy/safety	PsA adults	632	SC W0, 1, 2, 3, 4 followed by Q4W 150 mg 300 mg	Lyophilized powder
A2303	Phase 3 efficacy/safety	PsA adults	935	SC W0, 1, 2, 3, 4 followed by Q4W 150 mg 300 mg	Lyophilized powder
A2304	Phase 3 efficacy/safety	PsA adults	966	SC W0, 1, 2, 3, 4 followed by Q4W 150 mg 300 mg	Lyophilized powder
A2308	Phase 3 efficacy/safety	PsA adults	174	SC W0, 1, 2, 3, 4 followed by Q4W 150 mg 300 mg	150 mg/1 mL PFS

A2309	Phase 3 efficacy/safety	PsA adults	177	SC W0, 1, 2, 3, 4 followed by Q4W 150 mg 300 mg	150 mg/1 mL autoinjector
A2310	Phase 3 efficacy/safety	PsA children 6 to <18 yo	120	SC W0, 1, 2, 3, 4 followed by Q4W 75 mg 150 mg 300 mg	75 mg/0.5 mL 150 mg/1 mL PFS
A2311	Phase 3 efficacy/safety	PsA children 6 to <18 yo	84	SC W0, 1, 2, 3, 4 followed by Q4W 75 mg 150 mg 300 mg	75 mg/0.5 mL 150 mg/1 mL PFS

PsA = plaque psoriasis; POC = proof of concept; BA = bioavailability; CO=cross-over, DR = dose-ranging, PG = parallel group; PFS = pre-filled syringe
Source: adapted from aint457a-modeling-report.pdf, opage 14-15, Table 4-2.

- Relavant adult studies and ranges of trough concentrations

In total three drug presentations [lyophilized powder (LYO), pre-filled-syringe (PFS), and autoinjector (AI)] were used in adult plaque psoriasis clinical program and the results were submitted during the original review cycle. The relative bioavailability comparison of these three drug presentations in adults with plaque psoriasis was assessed by Dr. Jie Wang in Clinical Pharmacology Review dated September 5, 2014:

- *The LYO and the PFS have been shown to have comparable PK in a dedicated PK comparability study (CAIN457A2106). Results in the PK comparability study CAIN457A2106) with the LYO and the PFS presentations showed that the 90% confidence intervals for geometric mean ratio (PFS-to-LYO ratio) of AUCinf, AUClast, and Cmax were [0.92, 1.08], [0.93, 1.08], and [0.96, 1.12], respectively, all within the [0.8,1.25] no effect boundaries.*

- *The AI was shown to achieve higher exposures than the PFS and the LYO based on the comparisons of secukinumab trough concentrations across multiple Phase 3 trials (CAIN457A2302 with the LYO, CAIN457A2303 with the LYO, CAIN457A2308 with the PFS, and CAIN457A2309 with the AI). The results showed that compared to the LYO, the concentrations resulting from the AI were approximately 10%-30% higher across the two doses and two time-points. Similarly, the cross-study comparison also showed that compared to the PFS, the concentrations resulting from the AI were approximately 16%-26% higher.*

According to the approved BLA 125504 COSENTYX® label, *"At the 300 mg dose at Week 4 and Week 12, the mean trough concentrations resulted from the Sensoready pen (i.e. AI)*

were 23% to 30% higher than those from the lyophilized powder and 23% to 26% higher than those from the prefilled syringe based on cross-study comparisons".

Based on the aforementioned information, the median, 5th, and 95th percentile values of adult trough concentrations at Week 4, 12, 24, and 52 following subcutaneous administration of either 150 mg or 300 mg with the same dosing regimen that adopted in pediatric studies A2310 and A2311 (i.e., Studies A2302, A2303, A2304, A2308, and A2309, N=2328) were summarized in Table 6.3.2. In addition, the values of according trough concentrations from Study A2308 (N=174) were summarized separately due to the same presentation (PFS) used in pediatric studies.

Table 6.3.2: Summary of Secukinumab Trough Serum Concentrations by Time in Adult Studies

Study/Dose		Time	Minimum (µg/mL)	5th percentile (µg/mL)	Median (µg/mL)	95th percentile (µg/mL)	Maximum (µg/mL)
A2308	150 mg (N=59)	Week 4	12.8	20.85	41.80	68.50	80.1
		Week 12	4.84	10.89	23.80	40.25	43.3
		Week 16	3.95	8.15	19.35	36.58	40.8
		Week 24	2.38	4.72	17.15	30.73	36.5
		Week 52	1.94	5.31	14.40	24.60	27.6
	300mg (N=59)	Week 4	34.8	40.68	81.90	127.25	156
		Week 12	9.6	17.3	46.7	84.7	87.1
		Week 16	11	14.80	36.30	76.20	88.4
		Week 24	9.98	11.27	32.55	59.90	65.9
		Week 52	7.93	9.98	27.95	50.15	60.8
A2302 A2303 A2304 A2308 A2309	150 mg (N=1174)	Week 4	0	22.13	43.6	72.25	103
		Week 12	0	8.53	22.40	40.39	82.3
		Week 16	3.95	7.26	20.7	38.04	102
		Week 24	0	3.04	15.5	32.89	110
		Week 52	0	2.09	14.40	32.03	94.9
	300mg (N=1173)	Week 4	16.3	40.72	84.10	146.80	226
		Week 12	0	14.88	43.20	85.05	120
		Week 16	11	16.95	39.50	85.46	111
		Week 24	0.13	5.72	28.20	64.50	109
		Week 52	0	1.27	26.90	60.04	105

Source: reviewer's analysis based on MT79933.xpt.

It appears that the distribution of adult trough concentrations following PFS presentation (Study A2308) is similar to that following all three presentations. Excluding the timepoint of Week 52, the median values and 95th percentile values between two algorithms were generally comparable (difference < 14%). The difference of 5th percentile values between two algorithms were less than 50%. The LLOQ value of 1 µg/mL (1000 ng/mL) is located about 1.17th percentile of all 8950 trough concentrations summarized in Tabale 6.3.2.

- Pediatric studies

  - Clinical Study CAIN457A2310 (A2310)

Study A2310 was a global, 52-week, randomized, double-blind, placebo- and active (etanercept)-controlled efficacy safety study in children (6 to <18 years of age) with severe chronic plaque psoriasis. Approximately 160 patients were planned to be enrolled and 162 were randomized (secukinumab low dose: 40, secukinumab high dose: 40, placebo: 41 and etanercept: 41). Doses are specified in Figure 6.3.1. Of the total 156 patients who completed Induction period, 151 entered in to the Maintenance period.

The primary objective was to demonstrate the superiority of secukinumab (low and high dose) in pediatric patients with severe chronic plaque psoriasis with respect to both Psoriasis Area and Severity Index (PASI 75) and Investigator's Global Assessment modified 2011 (IGA mod 2011) 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo.

The study consists of 5 periods: Screening (up to 4 weeks), Induction (of 12 weeks), Maintenance (of 40 weeks), Extension treatment period (of 184 weeks) and Post-treatment follow-up period (of 16 weeks) (Figure 6.3.1).

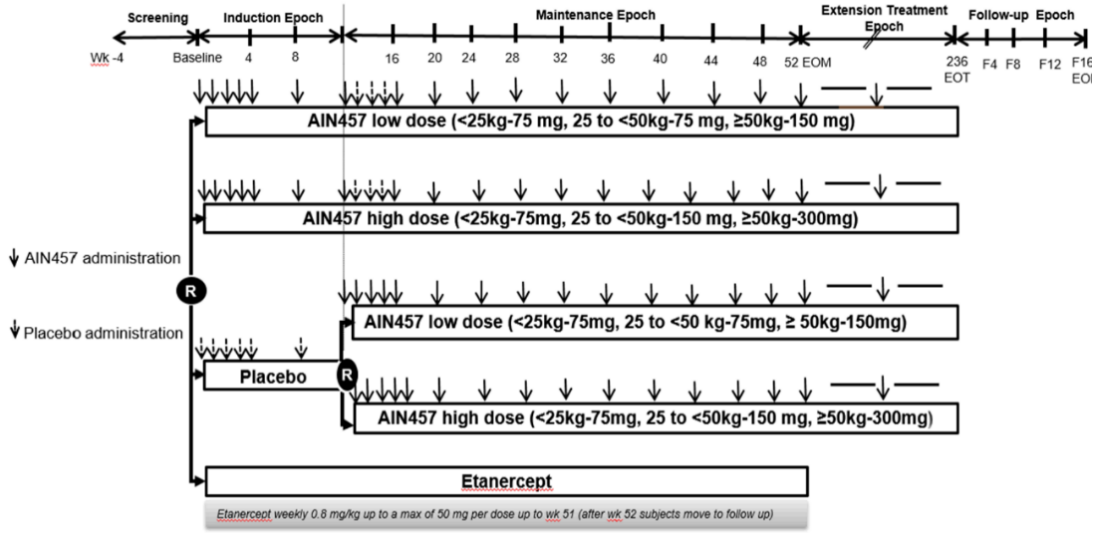


Figure 6.3.1 Study design and treatment scheme of pediatric trial A2310 (source: CSR AINT457A2310 page 46, Figure 9-1)

Randomization was stratified by age and body weight collected at Randomization Visit. Patients were randomized using a 1:1:1:1 ratio into one of the subcutaneous treatment arms (Figure 6.3.1):

- secukinumab low dose (N=40): <25 kg (75 mg); 25 to <50 kg (75 mg); ≥ 50 kg (150 mg);
- secukinumab high dose (N=40): <25 kg (75 mg); 25 to <50 kg (150 mg); ≥ 50 kg (300 mg);
- placebo (N=41)
- etanercept (N=41): open label with 0.8 mg/kg (up to 50 mg) once weekly

Of note, children <25 kg received the same 75 mg dose and are randomized into both low dose group and high dose group by the randomization scheme. Technically, there was no high and low dose in this body weight group.

The dosing regimen of secukinumab and placebo treatment groups was Weeks 0, 1, 2, 3, and 4 followed by every 4 weeks. Because the injection volume could be different between different dosing levels of secukinumab, to maintain the treatment blind, all patients in secukinumab or placebo arms received 2 subcutaneous injections at each dose, except for patients <25 kg.

Placebo PASI 75 non-responders at Week 12 were switched to either secukinumab low dose or secukinumab high dose treatment group in the Maintenance period according to the pre-assignment at their baseline randomization visit (loading dose was administered on Weeks 12, 13, 14, 15, and 16). Placebo patients who were PASI 75-responders at Week 12 had to terminate the study.

Pre-dose blood samples for measuring serum concentration of secukinumab were collected at Weeks 0, 4, 12, 24, 52/end of maintenance, 104, 156, 208, 236/end of extension treatment, and 252/end of follow-up.

Immunogenicity blood samples were collected at Weeks 0, 12, 24, 52/end of maintenance, 104, 156, 208, 236/end of extension treatment, and 252/end of follow-up.

Of the total 156 patients who completed the Induction period, 151 (~97%) entered the Maintenance period and 5 patients in the placebo group who were PASI 75 responders at Week 12 did not proceed into the Maintenance period as expected per protocol. One placebo patient (A2310-1281-006) who was a PASI 75 responder completed the Induction period and continued into the Maintenance period, as the site erroneously entered PASI non-responder in the IRT system; the patient was allowed to proceed in Maintenance and was treated actively until and including Week 16.

Eleven patients (7.1%) did not complete the Maintenance period. One patient each in the secukinumab low dose and secukinumab high dose groups discontinued the Maintenance period due to adverse event and lack of efficacy, respectively. Among

the patients originally randomized to placebo who completed the Induction period and were PASI 75 non-responders at Week 12, 16 patients were assigned to secukinumab low dose and 18 patients were assigned to secukinumab high dose starting at Week 12.

In this study, an Interactive Response Technology (IRT, a randomization and treatment assignment tool) error led to additional dosing of patients. The dosing errors happened after the primary endpoint (Week 12) assessment. Specifically, 36 patients who were assigned to the low dose (16 patients) and high dose (20 patients) secukinumab groups were dispensed active medication at Weeks 13, 14, 15 visits. At these visits, the patients who were randomized to active treatment groups were expected to receive placebo medication as to maintain the blind. Five patients in the secukinumab high dose group (25 to <50 kg/150 mg dose) were dispensed in error secukinumab 150 mg at these visits; 16 patients in the secukinumab low dose group (≥50 kg/150 mg dose) were dispensed in error secukinumab 300 mg at these visits; and 15 patients in the secukinumab high dose group (≥50 kg/300 mg dose) were dispensed in error secukinumab 300 mg at these visits. The incident was communicated to Investigators and Health Authorities, was presented to internal Novartis boards and a corrective action plan was put in place by the IRT vendor. The dosing error is taken into account in additional efficacy, safety and PK reports and its impact on the results is assessed and documented.

The baseline demographic information is summarized in Table 6.3.3.

Table 6.3.3: Baseline Demographic Characteristics in Study A2310

	<25 kg 75 mg	25 - <50 kg 75 mg	25 - <50 kg 150 mg	≥ 50 kg 150 mg	≥ 50 kg 300 mg	Placebo	Etanercept
Patient N	5	17	15	22	21	41	41
Age (year)*	7.8 ± 1.5	12.2 ± 2.5	11.7 ± 3.2	15.5 ± 1.5	15.1 ± 1.6	13.7 ± 3.2	13.5 ± 3.4
Body weight (Kg)*	22.4 ± 1.7	42.4 ± 6.6	40.8 ± 7.5	63.2 ± 10.3	67.3 ± 17.0	55.6 ± 22.3	52.0 ± 19.4
Male (%)	2 (40%)	4 (24%)	4 (27%)	10 (45%)	10 (48%)	19 (46%)	16 (39%)

* mean ± SD
Source: reviewer's analysis based on pc.xpt and adbs.xpt.

The statistical summary of pre-dose serum concentrations of secukinumab by body weight and dose in secukinumab treatment groups (at randomization) up to Week 52 is listed in Table 6.3.4. The mean trough concentrations of secukinumab were higher in the high dose group. The steady-state of secukinumab was reached approximately at Week 12-24 for certain treatment groups.

Table 6.3.4: Arithmatic Mean (%CV) Secukinumab Pre-Dose Serum Concentrations (µg/mL) in Secukinumab Treatment Groups (at Randomization) in Study A2310[1]

Visit	<25 kg 75 mg	25 - <50 kg 75 mg	25 - <50 kg 150 mg	≥ 50 kg 150 mg	≥ 50 kg 300 mg
Baseline	0 (N=4)	0 (N=17)	0 (N=15)	0 (N=20)	0 (N=21)
Week 4	105 ± 17 (N=4)	52 ± 11 (N=14)	124 ± 42 (N=12)	74 ± 23 (N=19)	151 ± 32 (N=19)
Week 12	32 ± 11 (N=5)	27 ± 10 (N=13)	58 ± 28 (N=11)	36 ± 18 (N=20)	84 ± 28 (N=21)
Week 24	31 ± 9 (N=5)	21 ± 7 (N=16)	29 ± 19 (N=7)	27 ± 8 (N=5)	72 ± 25 (N=6)
Week 52	27 ± 7 (N=4)	20 ± 9 (N=16)	40 ± 15 (N=6)	30 ± 11 (N=5)	54 ± 20 (N=6)

[1] Patients who were affected by IRT dosing error at Week 13 or Week 14 or Week 15 are excluded at Week 24 and week 52 timepoint. PK samples affected by recent dosing errors, without time label, or not on scheduled visit are also excluded.
Source: reviewer's analysis based on pc.xpt.

The statistical summary of pre-dose serum concentrations of secukinumab by body weight and dose in placebo treatment groups (at randomization) after Week 12 is listed in Table 6.3.5. Similarly, the mean trough concentrations of secukinumab were higher in the high dose group.

Table 6.3.5: Arithmatic Mean (%CV) Secukinumab Pre-Dose Serum Concentrations (µg/mL) in Placebo Groups (After Week 12) in Study A2310[1]

Visit	<25 kg 75 mg	25 - <50 kg 75 mg	25 - <50 kg 150 mg	≥ 50 kg 150 mg	≥ 50 kg 300 mg
Week 24	46 ± 20 (N=3)	21 ± 9 (N=5)	49 ± 12 (N=6)	45 ± 7 (N=6)	55 ± 24 (N=9)
Week 52	28 ± 12 (N=3)	16 ± 6 (N=6)	28 ± 10 (N=6)	30 ± 7 (N=6)	37 ± 16 (N=8)

[1] two placebo patients ((b) (6)) who switched to secukinumab treatment at Week 12, had measurable pre-dose concentration of 10.1 µg/mL and 41.7 µg/mL, respectively
Source: reviewer's analysis based on pc.xpt.

No anti-drug antibodies (ADA) were detected in any sample of patients of the secukinumab treatment group. One patient in the etanercept group ((b) (6) was ADA-positive with low titier (1:1) at baseline.

o Clinical Study CAIN457A2311 (A2311)

Study A2311 was a multi-center, randomized, open-label, study to assess the efficacy of secukinumab following 12-week treatment and long-term safety/tolerability in children (6 to <18 years of age) with moderate to severe chronic plaque psoriasis. The study is currently ongoing.

The primary objective was to evaluate the efficacy of secukinumab in pediatric subjects aged 6 years to less than 18 years old with moderate to severe chronic plaque psoriasis with respect to PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to historical control.

The study consists of 3 periods: screening (up to 4 weeks), treatment (of 208 weeks) and post-treatmentfollow-up (of 16 weeks).

Approximately 80 patients were planned to be enrolled. In total 84 subjects completed the screening phase and were randomized to secukinumab low dose and high dose groups in a 1:1 ratio (Figure 6.3.2):

- secukinumab low dose (N=40): <25 kg (75 mg); 25 to <50 kg (75 mg); ≥ 50 kg (150 mg);
- secukinumab high dose (N=40): <25 kg (75 mg); 25 to <50 kg (150 mg); ≥ 50 kg (300 mg);

Of note, children <25 kg receiving 75 mg dose are randomized into both low dose group and high dose group by randomization scheme. .

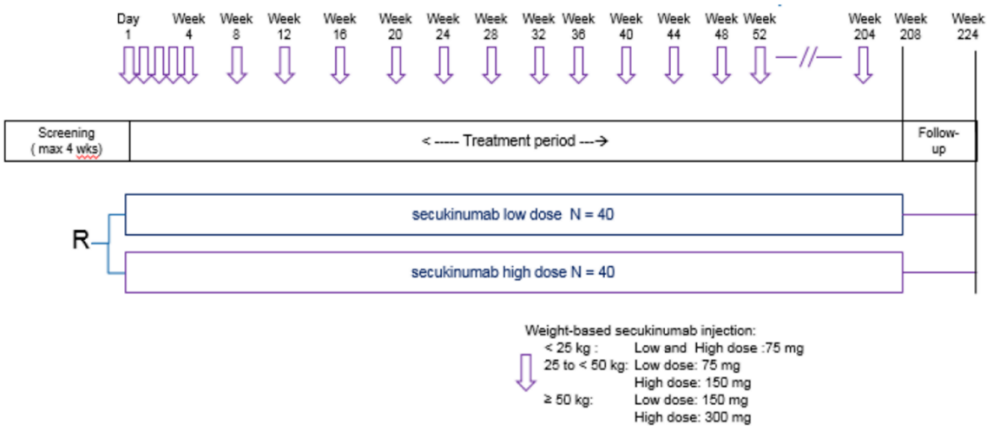


Figure 6.3.2 Study design and treatment scheme of pediatric trial A2311 (source: CSR AINT457A2311 page 40, Figure 9-1)

The dosing regimen of secukinumab and placebo treatment groups is Weeks 0, 1, 2, 3, and 4 followed by every 4 weeks.

Pre-dose blood samples for measuring serum concentration of secukinumab were collected at Weeks 0, 4, 12, 13, 14, 15, 16, 24, 52, 104, 156, 208, and 224.

Immunogenicity blood samples were collected at Weeks 0, 16, 24, 52/end of maintenance, 104, 156, 208, and 224.

81 our of 84 patients completed Week 24 visit. Two subjects discontinued treatment due to AEs (elevation of liver enzymes and hemorrhagic diarrhea). One subject discontinued due to lack of aefficacy. In total, 12 subjects missed at least one dose or changed the dose prior to Week 24 visit.

The baseline demographic information is summarized in Table 6.3.6.

Table 6.3.6: Baseline Demographic Characteristics in Study A2311

	<25 kg 75 mg	25 - <50 kg 75 mg	25 - <50 kg 150 mg	≥ 50 kg 150 mg	≥ 50 kg 300 mg
Patient N	8	13	12	25	26
Age (year)*	6.6 ± 0.7	10.5 ± 1.9	10.3 ± 2.0	14.4 ± 2.4	14.8 ± 2.0
Body weight (Kg)*	21.4 ± 2.2	38.6 ± 8.7	43.0 ± 5.7	67.7 ± 11.5	67.0 ± 13.6
Male (%)	3 (37.5%)	8 (62%)	6 (50%)	13 (52%)	9 (35%)

* mean ± SD
Source: reviewer's analysis based on pc.xpt, dm.xpt, ex.xpt, and vs.xpt.

The secukinumab serum concentration time profiles by body weight group and dose are summarized in Figure 6.3.3. At randomization, none of the subjects had quantifiable concentrations. The trougn concentrations roughly increase dose-proportionally within the same body weight group. The mean trough concentrations at Week 16 in different groups were about 14 to 28% higher than those of Week 24. The results indicate that the steady state of secukinumab was not reached by Week 16.

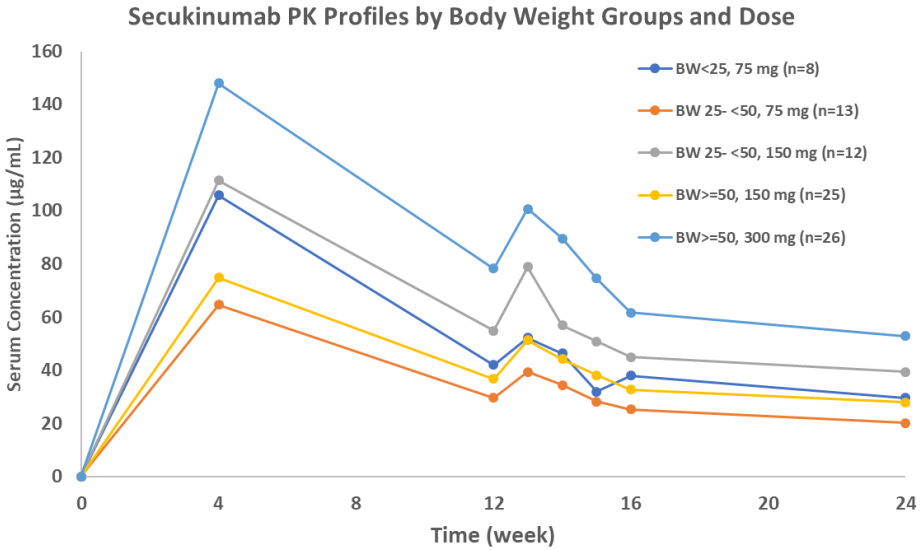


Figure 6.3.3 Secukinumab arithmetic mean concentration time profiles by body weight group and dose assigned at randomization in Study A2311. Subjects with missing dose or dose changes during the study were excluded from subsequent timepoints (N=12 prior to Week 24) (source: Reviewer's analysis)

None of the patients in the study developed treatment emergent ADA until Week 24 cut-off date. Only one patient (# (b) (6)) with severe psoriasis in 300 mg treatment group was positive for ADA at randomiazation with titer of 1: 7.98. The ADA results for the same patient were negative at Week 16 and Week 24.

o Comparison of pediatric and adult trough concentrations

The distribution of secukinumab pediatric Ctrough values at different time points by using adult as reference range (5th to 95th percentile) from pooled five studies (Table 6.3.2) is listed in Table 6.3.7.

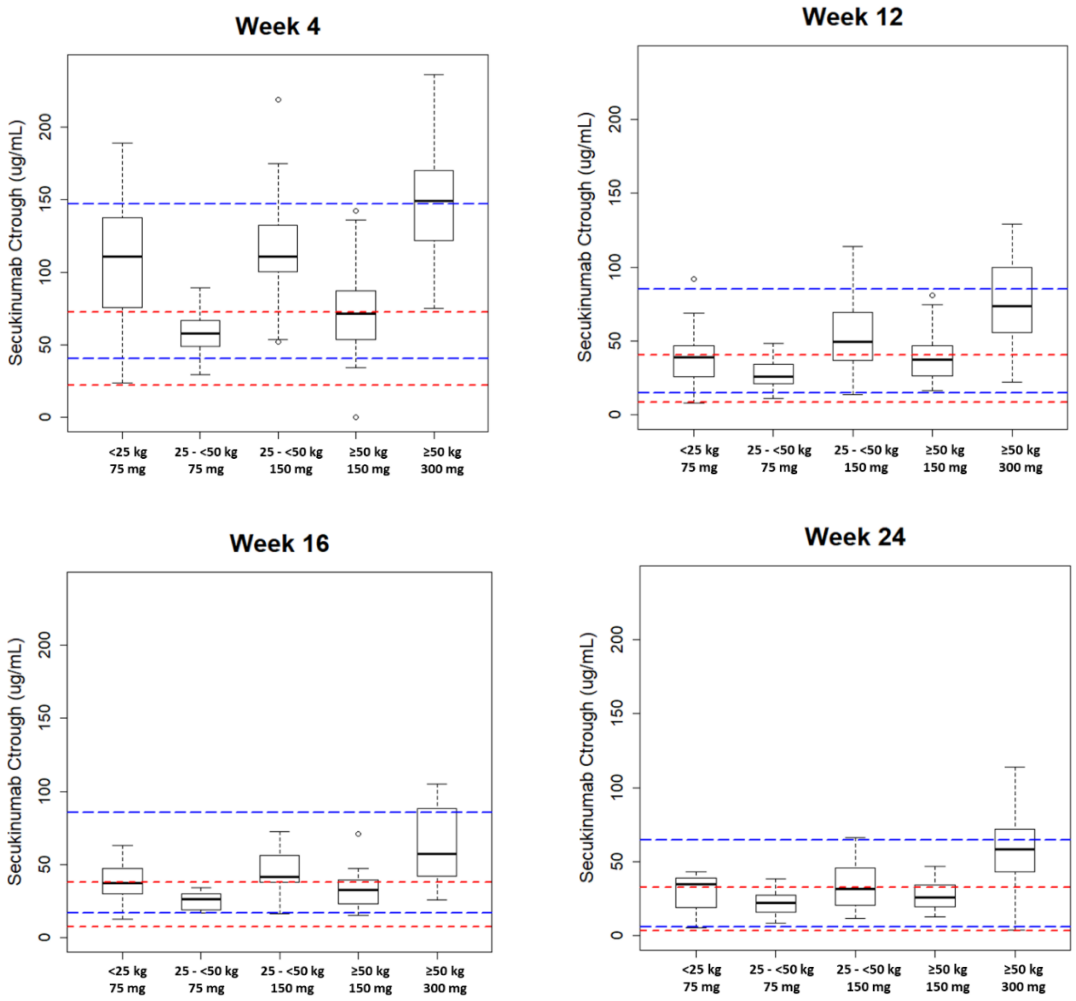
Table 6.3.7: Distribution of Secukinumab Pediatri Ctrough Values* Relative to AdultsReference Range at Different time Points [N(%)]

Dosing Group	Visit	Reference: 5th to 95th range of adult 150 mg			Reference: 5th to 95th range of adult 300 mg		
		Lower	Within	Higher	Lower	Within	Higher
<25 kg, 75 mg	Week 4	0 (0%)	3 (25%)	9 (75%)	2 (17%)	8 (67%)	2 (17%)
	Week 12	1 (6%)	8 (50%)	7 (44%)	2 (13%)	13 (81%)	1 (6%)
	Week 16	0 (0%)	4 (50%)	4 (50%)	1 (13%)	7 (88%)	0 (0%)
	Week 24	0 (0%)	6 (46%)	7 (54%)	1 (7%)	12 (92%)	0 (0%)
	Week 52	0 (0%)	4 (80%)	1 (20%)	0 (0%)	5 (100%)	0 (0%)
	Within Range	25 – 80%			67 – 100%		
25 - <50 kg, 75 mg	Week 4	0 (0%)	24 (89%)	3 (11%)	2 (7%)	25 (93%)	0 (0%)
	Week 12		30 (97%)	1 (3%)	2 (6%)	29 (94%)	
	Week 16		13 (100%)	0 (0%)	0 (0%)	13 (100%)	
	Week 24		27 (93%)	2 (7%)	0 (0%)	29 (100%)	
	Week 52		16 (89%)	2 (11%)	0 (0%)	18 (100%)	
	Within Range	89 – 100%			93 – 100%		
25 - <50 kg, 150 mg	Week 4	0 (0%)	3 (13%)	20 (87%)	0 (0%)	18 (78%)	5 (22%)
	Week 12		10 (36%)	18 (64%)	1 (4%)	22 (79%)	5 (18%)
	Week 16		3 (33%)	6 (67%)	1 (11%)	8 (89%)	0 (0%)
	Week 24		8 (50%)	8 (50%)	0 (0%)	15 (94%)	1 (6%)
	Week 52		3 (43%)	4 (57%)	0 (0%)	7 (100%)	0 (0%)
	Within Range	13 – 50%			78 – 100%		
≥50 kg, 150 mg	Week 4	1 (2%)	25 (57%)	18 (41%)	4 (9%)	40 (91%)	0 (0%)
	Week 12	0 (0%)	30 (59%)	21 (41%)	0 (0%)	51 (100%)	
	Week 16	0 (0%)	18 (72%)	7 (28%)	3 (12%)	22 (88%)	
	Week 24	0 (0%)	21 (70%)	9 (30%)	0 (0%)	30 (100%)	
	Week 52	0 (0%)	6 (67%)	3 (33%)	0 (0%)	9 (100%)	
	Within	57 – 72%			88 – 100%		

	Range						
≥50 kg, 300 mg	Week 4	0 (0%)	0 (0%)	45 (100%)	0 (0%)	21 (47%)	24 (53%)
	Week 12		7 (13%)	48 (87%)	0 (0%)	34 (62%)	21 (38%)
	Week 16		6 (24%)	19 (76%)	0 (0%)	18 (72%)	7 (28%)
	Week 24		4 (13%)	27 (87%)	1 (3%)	19 (61%)	11 (35%)
	Week 52		1 (13%)	7 (88%)	0 (0%)	4 (50%)	4 (50%)
	Within Range	0 – 24%			47 – 72%		

*Inclusion/exclusion criteria refer to Tables 6.3.4 and 6.3.5, and Figure 6.3.3.
Source: reviewer's analysis.

Similarly, the boxplots depicting the pediatric secukinumab Ctrough values at different timepoints are displayed in Figure 6.3.4.



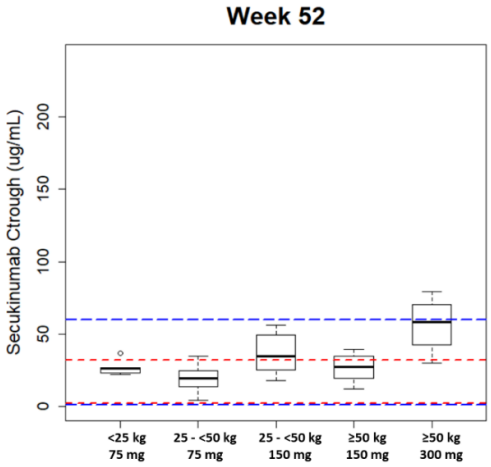


Figure 6.3.4 Boxplots of distribution of secukinumab pediatric Ctrough values relative to adult reference range (red dashed line: adults Ctrough following 150 mg dose; blue dashed line: adults Ctrough following 300 mg dose). (Source: reviewer's analysis)

In general, most secukinumab Ctrough values (81-100%) in children < 25 kg following 75 mg dose were within the adult range following 300 mg dose after Week 12. Most secukinumab Ctrough values (89-100%) in children 25 - < 50 kg following 75 mg dose were within the adult range following either 150 or 300 mg dose. Most secukinumab Ctrough values (78-100%) in children 25 - < 50 kg following 150 mg dose were within the adult range following 300 mg dose. Most secukinumab Ctrough values (88-100%) in children ≥ 50 kg following 150 mg dose were within the adult range following 300 mg dose.

Pediatric Ctrough values obtained from dosing group >50 kg on 300 mg were noticeably higher than Ctrough values from adult on 300 mg dose at certain time points. The median/mean secukinumab Ctough values in this pediatric dosing group were about 2-fold as high as those of adults following 300 mg dose at Week 24 and 52. In addition, about half of secukinumab Ctrough values in this pediatric dosing group were greater than 95th percentile of adult value following 300 mg dose at Week 4 and Week 52. However, this could be primarily explained by the body weight difference in this pediatric dosing group compared to that in the adult trials. The median body weight in this dosing group in the pediatric trials is ~63 kg which is significantly lower than the median body weight of 84 kg in adult trials. The exposure of secukinumab decreases significantly in both pediatrics and adults as body weight increases. For adolescents whose body weight is higher than the median body of adults, their Ctrough values at any time points are within the adult Ctrough range on 300 mg dose and also comparable to the exposure observed in pediatrics < 25 kg on 75 mg of secukinumab (see the figure below).

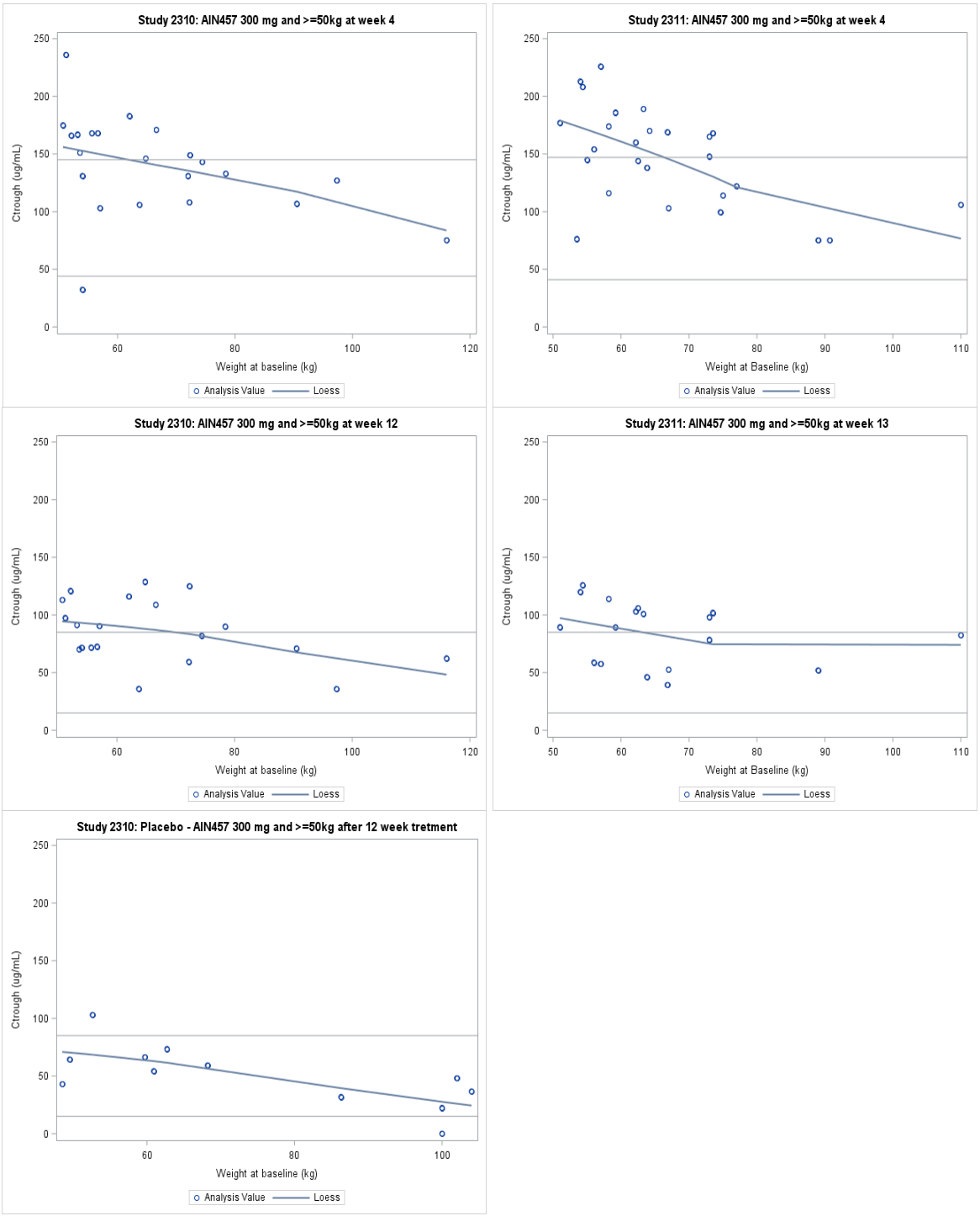


Figure 6.3.5 Secukinumab pediatric Ctrough values vs. body weight relative to adult Ctrough reference range following 300 mg dose (grey reference line). (Source: reviewer's analysis)

Similar results and the same conclusions were obtained when reference adult range was set from Study A2308 (PFS was used).

The reviewer's results were generally in agreement with sponsor's results (Table 6.3.8). Some slight differences were due to the inclusion/exclusion criteria of the concentrations (due to dosing errors) and definition of "high dose" and "low dose" between two pediatric studies.

Table 6.3.7: Distribution of Secukinumab Pediatri Ctrough Values Relative to Adults Reference Range at Different Time Points (Sponsor's Summary)

Visit	AIN dose	Weight Category	Number of Observation	Percentage of pediatric data within 90% range of adult data
WEEK 4	*AIN high dose*	*<25 kg*	*6*	*66.7*
WEEK 4	*AIN high dose*	*25 to 50kg*	*23*	*78.3*
WEEK 4	*AIN high dose*	*>=50 kg*	*47*	*46.8*
WEEK 4	AIN low dose	<25 kg	6	33.3
WEEK 4	AIN low dose	25 to 50kg	30	86.7
WEEK 4	AIN low dose	>=50 kg	44	56.8
WEEK 12	*AIN high dose*	*<25 kg*	*7*	*71.4*
WEEK 12	*AIN high dose*	*25 to 50kg*	*22*	*72.7*
WEEK 12	*AIN high dose*	*>=50 kg*	*46*	*56.5*
WEEK 12	AIN low dose	<25 kg	6	33.3
WEEK 12	AIN low dose	25 to 50kg	29	96.6
WEEK 12	AIN low dose	>=50 kg	45	71.1
WEEK 24	*AIN high dose*	*<25 kg*	*7*	*100*
WEEK 24	*AIN high dose*	*25 to 50kg*	*15*	*100*
WEEK 24	*AIN high dose*	*>=50 kg*	*31*	*61.3*
WEEK 24	AIN low dose	<25 kg	6	33.3
WEEK 24	AIN low dose	25 to 50kg	30	90
WEEK 24	AIN low dose	>=50 kg	29	72.4
WEEK 52	*AIN high dose*	*<25 kg*	*3*	*100*
WEEK 52	*AIN high dose*	*25 to 50kg*	*7*	*100*
WEEK 52	*AIN high dose*	*>=50 kg*	*9*	*66.7*
WEEK 52	AIN low dose	<25 kg	3	100
WEEK 52	AIN low dose	*25 to 50kg*	18	88.9
WEEK 52	AIN low dose	*>=50 kg*	8	75

Source: fda-response-clinical-20201002.pdf, page 16, Table 2-1.

6.4. Evaluation of pediatric-adult pooled popPK model

Conclusion
Sponsor's pediatric-adult pooled popPK model reasonably describes the observed secukinumab concentrations in adults and children, though the median pediatric cocentrations at Week 4 and Week 12 in the high dose regimen was slightly under-predicted and the 95th percentile of the low dose regimen and the 5th percentile of the high dose regimen at later time points were slightly over-predicted by the model.

To account for slightly higher concentrations in pediatric patients observed in Studies A2310 and A2311, the pooled popPK model was modified to include separate estimates of bioavailability for pediatric and adult patients. This resulted in a (relative) 26% higher bioavailability in pediatric patients (73% for the adult population vs. 91% for the pediatric

population). Whereas this approach is quite common in the popPK practice, the reason for the observed higher bioavailability in children compared to adults is unclear.

Model estimated allometric exponent of body weight effect on secukinumab clearance is 0.90.

Data set
A secukinumab popPK model was developed by Novartis by pooling 10 adult studies and 2 pediatric studies in patients with plaque psoriasis (Table 6.3.1) which include both intravaneous and subcutaneous administration routes. The dataset includes 5734 adults and 205 children. The dataset contains 31313 non-baseline secukinumab concentrations. In adults non-zero concentrations, about 2.6% (714/27418) of them were less than 1000 ng/mL (LLOQ of pediatric bioanalytica assay). Therefore, it is unlikely the different LLOQs between adults and children cross-validated bioanalytical assays will have a big impact of the popPK model.

Model construction
The popPK model of adult psoriasis submitted in the original review cycle was borrowed as a reference to build the pediatric-adult pooled model submitted in this supplement. The original adult model is a linear two-compartmental distribution model with first-order absorption for subcutaneous administration and first-order elimination. The development of the pooled model is summarized in Table 6.4.1. Model 3 is the final model.

Table 6.4.1: Pediatric-Adult Pooled Model Development

Data set	Model	Description
Original PK data pool updated with pediatric studies A2310 and A2311	Model 0 = Original Population PK model in adults	Post-hoc Estimation (MAXEVAL=0)
	Model 1	Fit using same structural model as Model 0
	Model 2	Fit using same structural model as Model 0 + fixed standard allometric exponent*
	Model 3	Fit using same structural model as Model 0 + population-specific BAV

BAV: bioavailability
*Standard allometric exponent values: 0.75 for CL and Q, and 1 for V2 and V3.
Source: ain457a-modeling-report.pdf, page 19, Table 5-1.

The model-estimated PK parameters are summarized in Table 6.4.2. The comparison of different models is summarized below:

- Model 1: the allometric coefficient estimates for CL (clearance) and V2 (central volume of distribution) in Model 1 did not meaningfully differ from those of Model 0, whereas more pronounced numerical changes were seen with the allometric coefficient estimates for Q (inter-compartmental clearance) and V3 (peripheral volume of distribution), which must be interpreted cautiously given the lower precision of their estimates in the two models. Other estimated parameters were very similar in the two models.

- Model 2 has a much larger OFV (objective function value) than Model 1 , suggesting that the use of theoretical allometric scaling exponents for all pediatric and adult patients is not adequate.
- Model 3 improved the objective function by 72 units over Model 1. The estimated bioavauilability was 73% for the adult population and 91% for the pediatric population. Compared to Model 1, the distributions of individual CL and V2 tended to be similar in the pediatric and adult studies with Model.

Table 6.4.2: Smmary of PK Parameters Estimated by Different Models

		Model 0: Original Model (fixed adult parameters)		Model 1 (= Model 0 with re-estimated parameters)		Model 2 (= Model 0 with allometric coefficients fixed to standard values)		Model 3 (Model 0 + pediatric effect on BAV),	
Name	**Parameter**	**Value**	**RSE (%)**	**Value**	**RSE (%)**	**Value**	**RSE (%)**	**Value**	**RSE (%)**
Objective Function Value	OFV	194380*	-	194241	-	194402	-	194169	-
CL [L/d]	TH1	0.19	2	0.19	2	0.19	2	0.19	2
V2 [L]	TH2	3.61	3	3.56	3	3.57	3	3.60	3
Q [L/d]	TH3	0.39	5	0.39	5	0.37	4	0.38	5
V3 [L]	TH4	2.87	2	2.84	2	2.87	2	2.86	2
KA [1/d]	TH7	0.18	4	0.18	4	0.18	3	0.18	4
TVF1** ***	TH8	0.99	6	0.99	6	1.00	6	A: 0.98 P Diff: 1.394	A: 6 P: 26
WT on CL	TH10	1.00	3	1.04	2	0.75 FIX	-	0.90	3
WT on V2	TH11	0.81	9	0.93	7	1.00 FIX	-	0.80	8
WT on Q	TH12	0.68	25	1.23	14	0.75 FIX	-	1.01	17
WT on V3	TH13	0.56	10	0.88	7	1.00 FIX	-	0.75	9
IIV CL	OM1:1	0.32	2	0.32	2	0.33	2	0.32	2
IIV V2	OM2:2	0.30	5	0.32	4	0.32	4	0.30	5
IIV CL-V2	OM2:1	0.70	4	0.69	4	0.66	4	0.68	4
IIV V3	OM3:3	0.18	9	0.20	8	0.22	7	0.20	9
IIV CL-V3	OM3:1	0.14	34	0.13	36	0.03	119	0.08	60
IIV V2-V3	OM3:2	0.72	7	0.75	6	0.73	6	0.71	7
IIV KA	OM7:7	0.35	7	0.35	6	0.33	6	0.34	7
Proportional error	SI1:1	0.17	0.4	0.18	0.4	0.18	0.4	0.18	0.4
Additive Error (ng/ml)	SI2:2	371	0.2	368	0.2	370	0.2	369	0.2

TVF1: bioavailability IIV: inter-individual variability

** The BAV estimate is obtained by anti-logit transformation of TVF1, and is equal to 73% (Models 0, 1, and 2) and to 73% (adult) and 91% (pediatric) for Model 3. The pediatric population difference effect on TVF1 is equal to +1.394 (RSE%=26) for Model 3 on the logit scale.

Source: ain457a-modeling-report.pdf, page 28, Table 6-2.

The results of PK parameters of the final model (Model 3) were confirmed by the reviewer.

Model evaluation

The visual prediction checks (VPCs) of Model 3 for adults and children was presented in Figure 6.4.1.

A

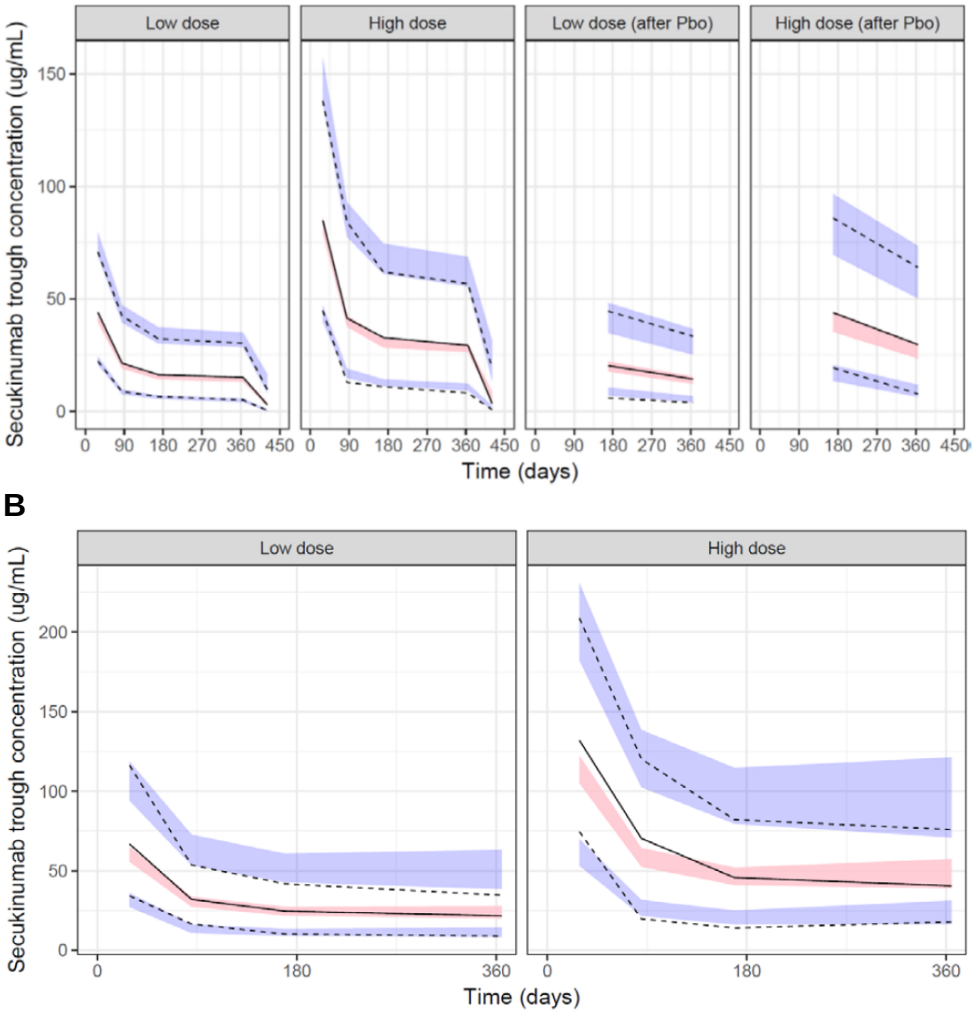


Figure 6.4.1 Visual prediction checks of Model 3 for adults (A, from Study A2302) and children (B, from Studies A2310 and A2311). The solid line represents the median of the observed concentration data. The dashed lines represent the corresponding 5th and 95th percentiles. The colored areas represent the 90% CI for the 5th, 50th, and 95th percentiles of the model predicted concentrations. (Source: response-fda-clinical-20200826.pdf, page 4, Figure 2-1 and 2-2)

Overall, Model 3 can reproduce the concentration data from the adult study as indicated by the observed percentiles generally lying within their predictive intervals derived from the model. Model 3 can reasonably reproduce the pediatric concentration data although it slightly under-predicts the median at Week 4 and Week 12 in the high dose regimen, and overpredicts the 95th percentile of the low dose regimen and 5th percentile of the high dose regimen for certain time points across two pediatric studies.

6.5. Evaluation of dose-response relationship between children and adults

Conclusion
The reviewer assessed the primary endpoint (PASI 75 response rate) and the key secondary endpoints (%PASI improvement from baseline and PASI90) at Week 12 by pooling two pediatric studies A2310 and A2311. The results demonstrate that in children in body weight group 25 to <50 kg with baseline severe disease, the respond to secukinumab treatment was numerically better on 150 mg dose than 75 mg dose. However, the response of children in body weight group ≥50 kg with baseline severe disease was nearly the same between 150 mg dose and 300 mg dose treatment groups.

Sponsor's analysis
Sponsor pooled observed PASI results from pediatric studies A2310 and A2311 and plotted descriptive pediatric exposure-response curves against observed secukinumab Ctrough values. The pediatric exposure-response relationship was further compared to that of adults in sponsor's analysis.

The median % PASI improvement from baseline are displayed by week, patient population, disease severity and pediatric/adult secukinumab concentration quartile bin at week 12.

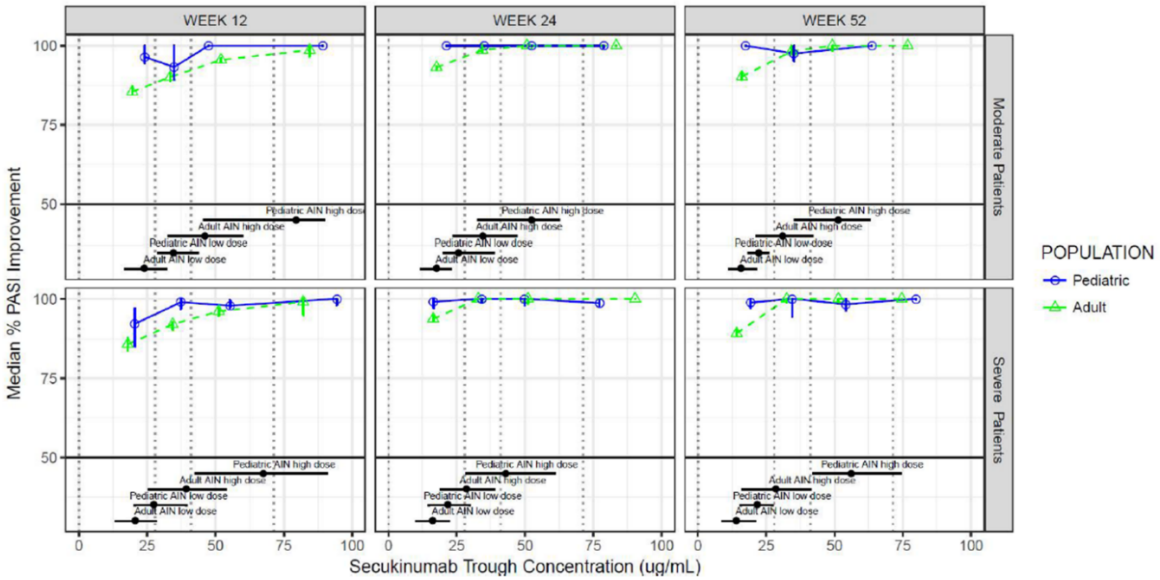


Figure 6.5.1 Median % PASI improvement from baseline at Weeks 12, 24 and 52 versus binned trough secukinumab concentration, by population and severity. Points and vertical bars represent the median %PASI improvement from baseline and the associated 66% confidence interval by secukinumab concentration bin; those points are plotted versus the median concentration in the bin. The vertical dashed lines represent the pediatric quartile bins cut points at week 12. The horizontal bars at the bottom of the plot represents the secukinumab concentration interquartile range (i.e. 50% of the data) by population and dose level; the dots represent the corresponding medians. The Week 24 panel do not include the patients in A2310

who received erroneously additional doses at Weeks 13, 14 and 15. (Source: ain457a-modeling-report.pdf, page 37, Figure 6-13)

Similarly, the PASI response rate pooled from two pediatric studies A2310 and A2311 are plotted against secukinumab concentration quartile bin at different time points and disease severity in Figure 6.5.2. The pediatric trend was compared to adult trend in the same figure.

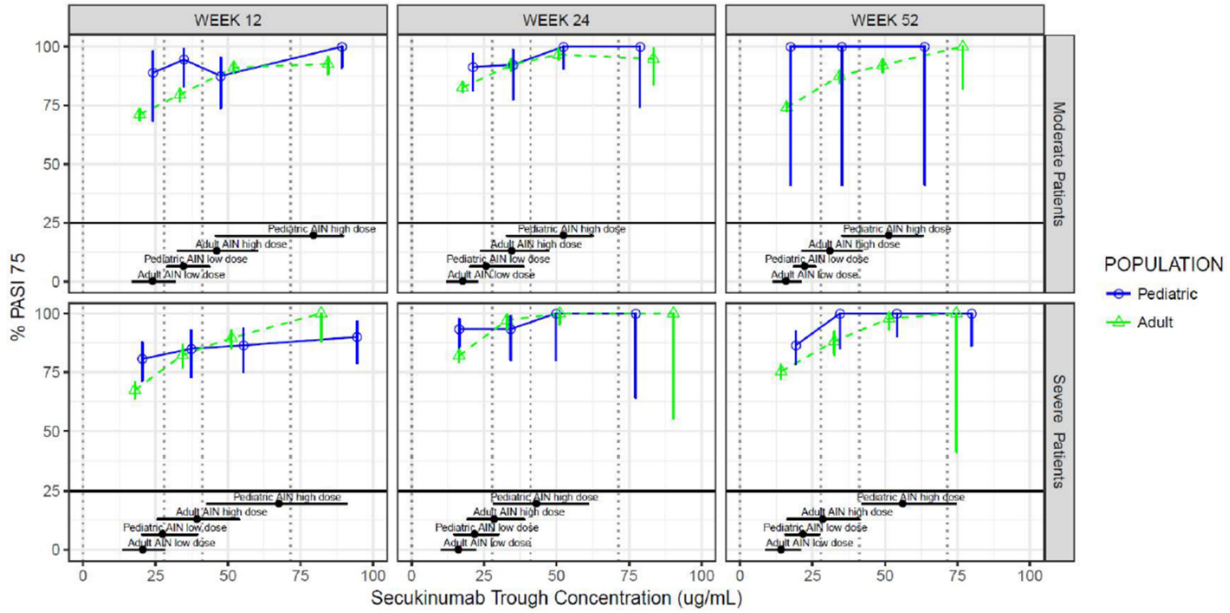


Figure 6.5.2 PASI 75 response rates at Weeks 12, 24 and 52 versus binned trough secukinumab concentration, by population, and severity. Points and vertical bars represent the percentage of PASI 75 responders and the associated 66% confidence interval, obtained by exact method, by secukinumab concentration bin; they are plotted versus the median concentration in the bin. Note that some confidence intervals are large due to limited data. The vertical dashed lines represent the pediatric quartile bins cut points at week 12. The horizontal bars at the bottom of the plot represents the secukinumab concentration interquartile range (i.e. 50% of the data) by population and dose level; the points represent the corresponding medians. The Week 24 panel do not include the patients in A2310 who received erroneously additional doses at Weeks 13, 14 and 15. (Source: ain457a-modeling-report.pdf, page 38, Figure 6-14)

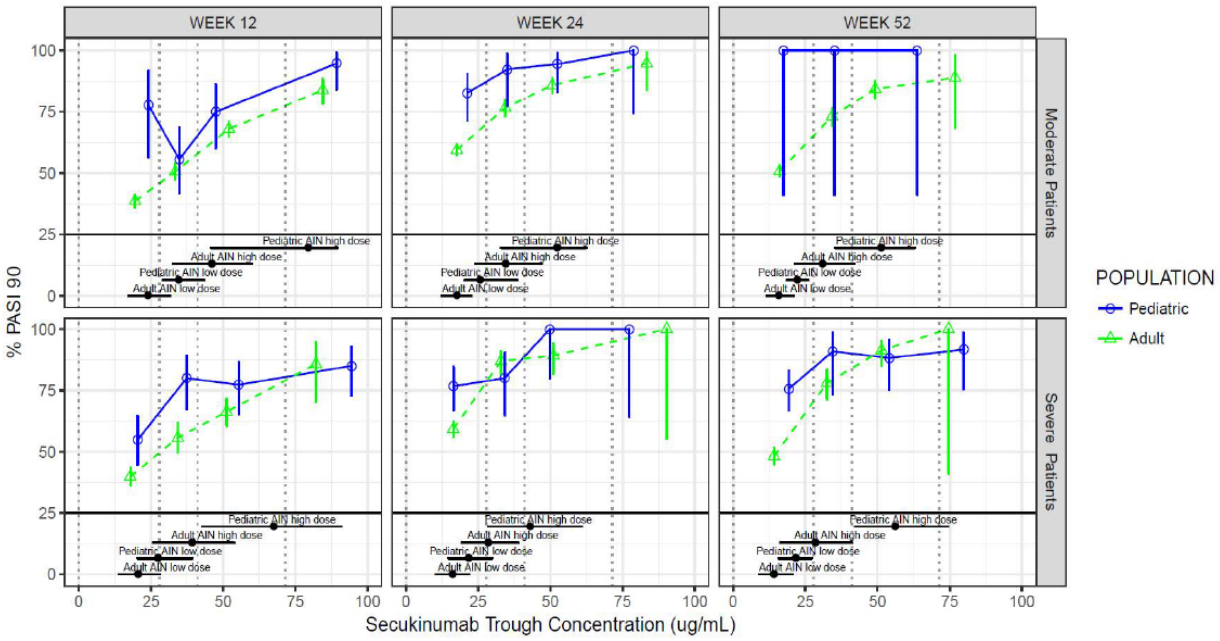


Figure 6.5.3 PASI 90 response rates at Weeks 12, 24 and 52 versus binned trough secukinumab concentration, by population, and severity. Points and vertical bars represent the percentage of PASI 90 responders and the associated 66% confidence interval, obtained by exact method, by secukinumab concentration bin; they are plotted versus the median concentration in the bin. Note that some confidence intervals are large due to limited data. The vertical dashed lines represent the pediatric quartile bins cut points at week 12. The horizontal bars at the bottom of the plot represents the secukinumab concentration interquartile range (i.e. 50% of the data) by population and dose level; the points represent the corresponding medians. The Week 24 panel do not include the patients in A2310 who received erroneously additional doses at Weeks 13, 14 and 15. (Source: ain457a-modeling-report.pdf, page 39, Figure 6-15)

By visual check, the adult exposure-response relationship is generally slightly steeper than that in children, especially at lower concentrations and and/or at later time point. In children, the %PASI improvement from baseline exposure-response curve is flatter than the PASI 75 and PASI 90 exposure-response curves, especially at later time points and in severe patients. Higher exposure appears associated with better PASI 90 response in both pediatrics and adults.

Reviewer's analysis
The reviewer did a similar exploratory analysis by pooling two pediatric studies A2310 and A2311 with the primary endpoint (PASI75 response rate) at Week 12 by pediatric body weight, dosing group, and baseline severity (Table 6.5.1). A similar analysis was conducted based on PASI 90 response rate at Week 12 (Table 6.5.2). The reviewer did not explore any later time points due to the major dosing errors in 36 subjects in Study A2310 starting Week 13.

Table 6.5.1: PASI75 Response Rate (%) at Week 12 by Body Weight-Dose Group and Baseline Disease Severity from Pooled Data of Studies A2310 and A2311

Disease Severity	<25 kg 75 mg	25 - <50 kg 75 mg	25 - <50 kg 150 mg	≥ 50 kg 150 mg	≥ 50 kg 300 mg	Placebo
Moderate	100% (4/4)	100% (8/8)	83.3% (5/6)	88.2% (15/17)	93.8% (15/16)	-
Severe	77.8% (7/9)	77.3% (17/22)	84.2% (16/19)	93.1% (27/29)	93.5% (29/31)	15.0% (6/40)
Total	84.6% (11/13)	83.3% (25/30)	84.0% (21/25)	91.3% (42/46)	93.6% (44/47)	15.0% (6/40)

Moderate disease is defined by baseline PASI score from 12 to 20 (inclusive).
Severe disease is defined by baseline PASI score greater than 20
Source: reviewer's analysis

Table 6.5.2: PASI90 Response Rate (%) at Week 12 by Body Weight-Dose Group and Baseline Disease Severity from Pooled Data of Studies A2310 and A2311

Disease Severity	<25 kg 75 mg	25 - <50 kg 75 mg	25 - <50 kg 150 mg	≥ 50 kg 150 mg	≥ 50 kg 300 mg	Placebo
Moderate	75% (3/4)	88% (7/8)	67% (4/6)	59% (10/17)	81% (13/16)	-
Severe	33% (3/9)	59% (13/22)	68% (13/19)	86% (25/29)	87% (27/31)	2.5% (1/40)
Total	46% (6/13)	67% (20/30)	68% (17/25)	76% (35/46)	85% (40/47)	2.5% (1/40)

Moderate disease is defined by baseline PASI score from 12 to 20 (inclusive).
Severe disease is defined by baseline PASI score greater than 20
Source: reviewer's analysis

Similarily, the exploratory analysis of median Week 12 %PASI improvement from baseline from two pediatric studies A2310 and A2311 is summarized in Table 6.5.3.

Table 6.5.3: Median %PASI Improvement from Baseline at Week 12 by Body Weight-Dose Group and Baseline Disease Severity from Pooled Data of Studies A2310 and A2311

Disease Severity	<25 kg 75 mg	25 - <50 kg 75 mg	25 - <50 kg 150 mg	≥ 50 kg 150 mg	≥ 50 kg 300 mg	Placebo
Moderate	97.7%	100%	96.9%	100%	100%	-
Severe	76.7%	92.2%	98.2%	99.6%	98.5%	26.5%
Total	84.9%	94.9%	98.2%	99.8%	99.2%	26.5%

Moderate disease is defined by baseline PASI score from 12 to 20 (inclusive).
Severe disease is defined by baseline PASI score greater than 20
Source: reviewer's analysis

For both endpoints at Week 12, children in body weight group 25 to <50 kg with baseline severe disease responded numerically better on 150 mg dose than 75 mg dose. The response of children in body weight group ≥50 kg with baseline severe disease was nearly the same between 150 mg dose and 300 mg dose. PASI 90 response for children in body weight group ≥50 kg with baseline moderate disease was observed better for 300 mg dose. However, the number of subjects is relatively small for a reliable dose-response comparison across the entire body weight range. Strong positive exposure-response relationship for efficacy was observed in previous adult trials (especially for more stringent efficacy endpoints such as PASI 90).

6.6. Population PK analysis of secukinumab in Asian patients with plaque psoriasis

A population PK report evaluating the secukinumab PK and exposure-PASI resonse analysis in Asian patients with plaque psoriasis was included in this pediatric supplement. For record purpose, the results are summarized in this section.

Conclusion
In total PK and PASI results from 12 clinical studies in patients with moderate to severe plaque psoriasis including a Chinese Study A2318 were pooled in this popPK analysis. Drug product of either lyophilized powder or PFS was used in these studies (PFS was used in Study A2318). The popPK model estimates that the allometric coefficient on clearance (i.e., effect of body weight on secukinumab clearance) is 0.99, which is similar to the value estimated from the pediatric popPK model (0.90, Table 6.4.2). The model estimated ethnicity coefficient on clearance [i.e., the effect of Asian (including Chinese) on secukinumab clearance] in addition to body weight effect is 1.17 (90% CI : 1.15 to 1.19). The clinical meaning of this small effect is unclear. Study A2318 demonstrated higher PASI 75/90 response rates than other studies.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

In support of their NDA, the Applicant submitted the following two studies:

- AIN457A2310: A Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled (etanercept) study in pediatric subjects aged 6 years to less than 18 years with severe chronic plaque psoriasis. 162 subjects were randomized using a 1:1:1:1 ratio into one of four treatment arms: secukinumab Low dose (40), secukinumab High dose (40), non-US licensed etanercept (41) or placebo (41).

- AIN457A2311: A Phase 3, multicenter, randomized, open-label study in subjects aged 6 years to less than 18 years with moderate to severe chronic plaque psoriasis. 84 subjects were randomized using a 1:1 ratio into secukinumab Low dose (42) or secukinumab High dose (42) arms.

The table below provides a summary of the aforementioned studies submitted for secukinumab to treat moderate to severe plaque psoriasis in pediatric subjects 6 years and older, as well as four studies in adult subjects with moderate to severe psoriasis.

Table 2. Listing of Clinical Trials Relevant to this BLA 125504 S-043

Study Identity NCT no.	Study Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
AIN457A2310 NCT02471144	Phase 3, randomized, double-blind (DB), placebo- and active-controlled multi-centered (MC) study	• low dose subcutaneous (SC) secukinumab (75 mg for body weight (BW) <50 kg or 150 mg for ≥50 kg) at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks (Q4W), • high dose SC secukinumab (75 mg for BW <25 kg, 150 mg for BW ≥25 kg and <50 kg, or 300 mg for BW ≥50 kg) at Weeks 0, 1, 2, 3, and 4 followed by the same dose Q4W, • placebo at Weeks 0, 1, 2, 3, and 4 followed by the same dose Q4W, • etanercept (ETA) (0.8 mg/kg) weekly (up to a maximum of 50 mg).	Co-primary: PASI 75 response and IGA mod 2011 0 or 1 response at Week 12 Key secondary: PASI 90 response at Week 12	236 weeks • induction 0-12 w • maintenance 12-52 w • extension 52-236 w • follow-up 236-252 w	162 1:1:1:1 4 group randomi-zation Low dose: 40 High dose: 40 Placebo: 41 ETA: 41	Patients 6-17 years of age with severe chronic plaque psoriasis	Belgium (3) Colombia (2) Egypt (2) Estonia (1) France (3) Germany (7) Guatemala (3) Hungary (3) Israel (3) Italy (2) Japan (1) Latvia (2) Poland (3) Romania (1) Russia (5) Spain (3) Switzerland (1) United Kingdom (1) United states (1)
Studies to Support Safety							
AIN457A2311 NCT03668613	Phase 3, randomized, open-label, parallel group, two-	• low dose SC secukinumab (75 mg for BW <50 kg or 150 mg for BW ≥50 kg), high dose secukinumab (75	Co-primary: PASI 75 response and IGA mod 2011 0 or 1 response	208 weeks • treatment 0-208 w • follow-up	84 1:1 Low dose: 42	Patients 6-17 years of age with severe chronic	Belgium (2) Czech Republic (2) Estonia (1) Germany (2) Peru (1)

	arm, MC study	mg for BW <25 kg, 150 mg for BW ≥25 kg and <50 kg, or 300 mg for body weight ≥50 kg).	at Week 12 Key secondary: PASI 90 response at Week 12	208-224 w	High dose: 42	plaque psoriasis	Poland (3) Russia (4) Spain (4) United states (4)
Other studies pertinent to the review of efficacy or safety							

AIN457A2302 NCT01365455	Phase 3, DB, placebo-controlled (PC), MC study	Doses of lyophilizate in vial: • secukinumab 150 mg • secukinumab 300 mg • Placebo Regimen: 2 SC injections at Weeks 0, 1, 2, 3, then Q4W until week 48. At week 12, placebo re-randomized based on PASI75 to 150 mg or 300 mg, injections at Weeks 12, 13, 14, 15, then q4W to Week 48 to maintain the blind	Co-primary: PASI 75 response and IGA mod 2011 0 or 1 response at Week 12 Key secondary: PASI 90 response at Week 12	Duration: 52-weeks with 8 week follow-up period	738 1:1:1 150 mg dose: 245 300 mg dose: 245 Placebo: 248	Patients 19-83 years of age with moderate to severe chronic plaque psoriasis	Argentina, Canada, Colombia, Estonia, Iceland, Israel, Japan, Latvia, Lithuania, Mexico, Taiwan, United States
AIN457A2303 NCT01358578	Phase 3, randomized, DB, double-dummy, placebo- and active-controlled, MC study	Doses of lyophilizate in vial: • secukinumab 150 mg • secukinumab 300 mg • Placebo etanercept (ETA) 50 mg/mL solution in a single-use PFS Regimen: secukinumab SC at Weeks 0, 1, 2, 3, then Q4W until week 48. Placebo-etanercept twice weekly from Weeks 0 to 12, then Q4W from Week 16 through Week 51 Placebo-secukinumab	PASI 75 at Week 12	Duration: 52-weeks with 8 week follow-up period	929 1:1:1:1 150 mg dose: 327 300 mg Placebo: 326 ETA: 326	Patients 18-82 years of age with mod- to-sev chronic plaque psoriasis	Argentina, Australia, Belgium, Brazil, Canada, Colombia, Egypt, Finland, France, Germany, Guatemala, Hungary, Iceland, India, Italy, Philippines, Poland, Republic of Korea, Romania, Russian Federation, Singapore, Spain, Sweden, Turkey, United Kingdom,

		administered at Weeks 0, 1, 2, 3, 4, 8, 12, 13, 14, 15, 16 then Q4W to week 48. etanercept twice weekly from Weeks 0 to 12, then once a week from Week 12 through Week 51					United States
AIN457A2308 NCT01555125	Phase 3, DB, PC, MC study	Doses of solution in PFS: • secukinumab 150 mg • secukinumab 300 mg • Placebo	Co-primary: PASI 75 response and IGA mod 2011 0 or 1 response at Week 12	208 weeks	177 1:1:1 59 in each arm	Patients 18-77 years of age with mod- to-sev chronic plaque Ps	Canada, Estonia, France, Germany, United States
AIN457A2309 NCT01636687	Phase 3, DB, PC, MC study	Doses of solution in Autoinjector/Pen: • secukinumab 150 mg • secukinumab 300 mg • Placebo	Co-primary: PASI 75 response and IGA mod 2011 0 or 1 response at Week 12	208 weeks	182 1:1:1 150 mg: 61 300 mg: 60 Placebo: 61	Patients 18-83 years of age with moderate to severe chronic plaque Ps	Canada, Estonia, France, Germany, United States

7.2. Review Strategy

The Applicant conducted two clinical studies, AIN457A2310 (A2310) and AIN457A2311 (A2311) in subjects ages 6 to less than 18 years with moderate to severe chronic plaque psoriasis to assess the safety, tolerability, and long-term efficacy up to one year.

Study A2310 is a Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled (non-US licensed etanercept) study in 162 pediatric patients ages 6 years to less than 18 years with severe chronic plaque psoriasis who were randomized in a 1:1:1:1 ratio into one of four treatment arms: secukinumab Low dose, secukinumab High dose, etanercept, or placebo.

Study A2311 is a Phase 3, multicenter, randomized, open-label study in 84 patients aged 6 years to less than 18 years with moderate to severe chronic plaque psoriasis who were randomized using a 1:1 ratio into secukinumab Low dose or secukinumab High dose arms. Historical placebo data from adult studies were used as the control for primary and key secondary endpoint analyses.

The Applicant submitted supportive pharmacokinetic (PK) and immunogenicity data from studies AIN457A2302, AIN457A2303, AIN457A2308 and AIN457A2309 (A2302, A2303, A2308, and A2309) from the psoriasis development program in adults.

This review will focus on studies A2310 and A2311 given that the drug product, dose, and frequency were the same for pediatric subjects. These studies serve as the primary source of efficacy and safety data to support the proposed labeling change. There will be limited discussion of studies that have been previously reviewed, such as studies from the psoriasis development program in adults.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Design and Endpoints

Study CAIN457A2310 was a randomized, double-blind, placebo and active controlled multicenter trial to demonstrate efficacy of subcutaneous secukinumab compared to placebo and etanercept after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in subjects from 6 to less than 18 years of age with severe chronic plaque psoriasis. As the study was not designed for formal comparisons between secukinumab and etanercept, this review will not discuss the results for etanercept (as noted at the pre-sBLA meeting on September 04, 2019).

For enrollment, the protocol specified the following key inclusion criteria:

- Male and female subjects 6 to less than 18 years of age at the start of study enrollment
- Diagnosis of severe plaque psoriasis, defined as a PASI score ≥ 20, and IGA mod 2011 score of 4, and BSA involvement of ≥10%, at randomization
- Candidate for systemic treatment (i.e., inadequate control of symptoms with topical treatment, or failure to respond to or tolerate previous systemic treatment and/or UV therapy)

The study consisted of the following five periods:

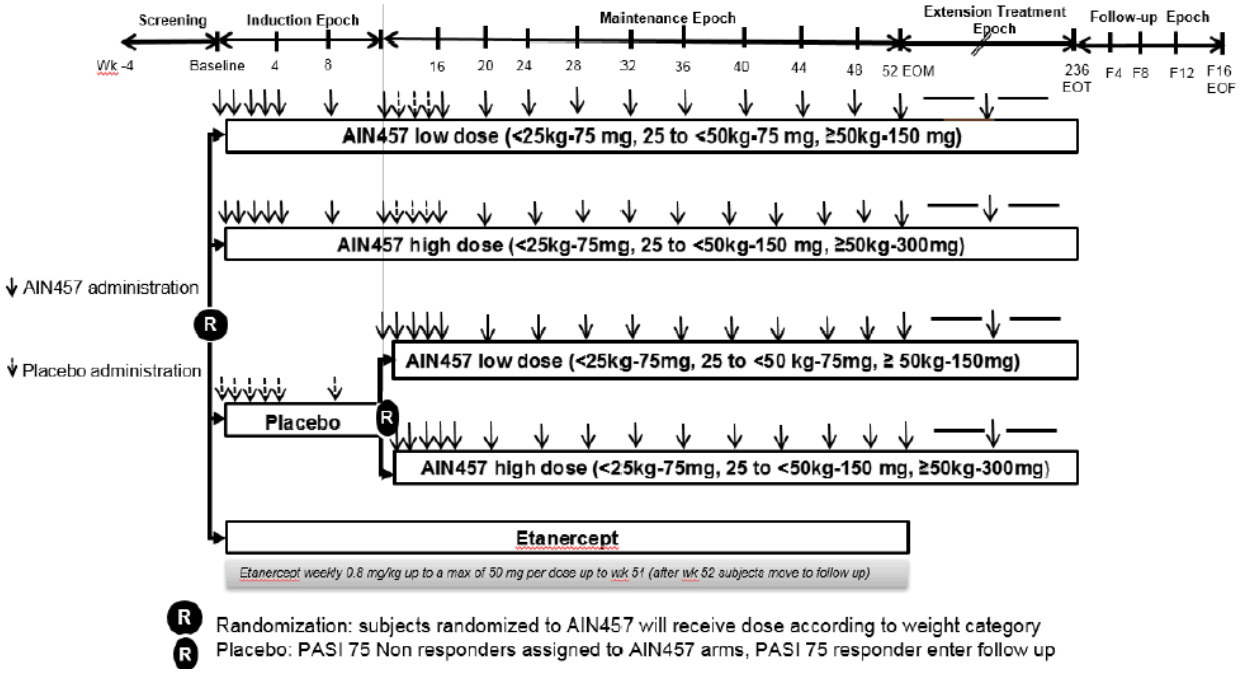
- Period 1: Screening period up to 4 weeks
- Period 2: Induction period of 12 weeks
- Period 3: Maintenance period of 40 weeks
- Period 4: Extension treatment period of 184 weeks
- Period 5: Post-treatment follow-up period of16 weeks.

At the start of the induction period (period 2), eligible subjects would be randomized in a 1:1:1:1 ratio into one of four treatment groups (etanercept, secukinumab low dose group, secukinumab high dose group, or placebo group). According to the study design, the randomization would be stratified by age (<12 years or ≥12 years) and weight (<25 kg, 25-<50 kg, ≥50 kg). Subjects randomized to secukinumab treatment arms (low dose and high dose) would receive a dose based on the weight category as follows: (i) subjects weighing <25 kg receive 75 mg for both dose groups, (ii) subjects weighing 25 to <50 kg receive 75 mg (low dose group) and 150 mg (high dose group), and (iii) subjects weighing ≥50 kg receive 150 mg (low dose group) and 300 mg (high dose group). In order to maintain the treatment blind, all subjects in secukinumab or placebo arms will receive 2 s.c. injections at each dose, except for subjects <25 kg weight category who will receive only 1 injection of either 75 mg secukinumab or matching placebo.

The study was designed to enroll approximately 160 subjects. A total of 187 subjects were screened and 162 were randomized (secukinumab low dose: 40, secukinumab high dose: 40, placebo: 41 and etanercept: 41).

Error! Reference source not found.Figure 1 presents the study design for Study CAIN457A2310. During the double-blind treatment period (period 2), subjects had study visits at baseline and Weeks 1, 2, 3, 4, 8, and 12. At the beginning of the maintenance period (Period 3), the placebo PASI 75 non-responders at Week 12 were switched to either secukinumab low dose or secukinumab high dose treatment group according to the pre-assignment dose at their baseline randomization visit. Placebo subjects who were PASI 75 responders at Week 12 had to terminate the study. At the end of the maintenance period, all subjects on secukinumab entered the extension treatment period (period 4) and continued to receive the same dose of secukinumab. Subjects receiving etanercept were not eligible to enter the extension treatment period (period 4). The post-treatment follow-up period (period 5) is the treatment-free follow-up period.

Figure 1. Design for Study CAIN457A2310



The protocol-specified co-primary efficacy endpoints were proportion of subjects who achieve PASI 75 response at Week 12 and the proportion of subjects who achieve IGA response at Week 12. Response for PASI 75 is defined as a minimum reduction of 75% of PASI total score at baseline and response for the IGA is defined as achieving a score of 0 (clear) or 1 (almost clear) and improvement by at least 2 points on the IGA mod 2011 scale compared to baseline. Table 3. Investigator Global Assessment (IGA mod 2011) ScaleTable 3 shows the description of the IGA mod 2011 scale.

The protocol listed PASI 90 response at Week 12 as a key secondary endpoint. The protocol listed the following secondary efficacy endpoints: PASI 50/100 response at Week 12, PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time, time to PASI 75/90 response (up to Week 12), and PASI score and IGA mod 2011 score over time. In addition, the Patient Reported Outcomes (PRO) included Children's Dermatology Life Quality Index (CDLQI) and Childhood Health Assessment Questionnaire (CHAQ) assessments in subjects with history of psoriatic arthritis. However, such endpoints were not included in the multiplicity testing strategy. Therefore, the results of these endpoints are considered exploratory and are not included in this review.

Table 3. Investigator Global Assessment (IGA mod 2011) Scale

0	Clear, no signs of psoriasis, post-inflammatory hyperpigmentation may be present
1	Almost clear- normal to pink coloration of lesions; no thickening; no to minimal focal scaling
2	Mild- pink to light red coloration; just detectable to mild thickening; predominantly fine scaling
3	Moderate- dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling
4	Severe- bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions

Source: the amended protocol v03 (final version submitted on April 16, 2018)

8.1.2. Statistical Methodologies

The protocol specified conducting analyses using the following populations:

- Randomized set: defined as all subjects who were randomized
- Full analysis set (FAS): comprised of all subjects from the randomized set to whom study treatment has been assigned
- Safety set: includes all subjects who took at least one dose of study treatment during the treatment epoch

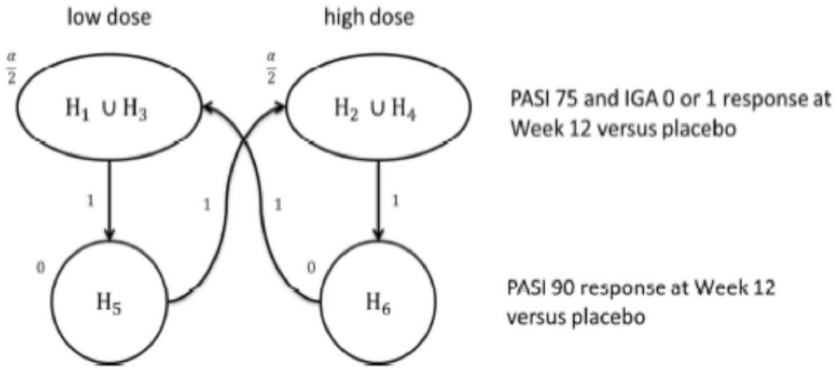
The protocol-specified primary analysis population for testing the superiority against placebo was the FAS (ITT population). Following the intent-to-treat principle, subjects were analyzed according to the treatment assigned to at randomization. The protocol specified that analysis of the primary endpoints (PASI 75 and IGA response at Week 12) is to be carried out using an exact logistic regression model with treatment group, baseline body weight stratum, age stratum and baseline PASI score as explanatory variables. Odds ratios were to be computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. Confidence intervals for risk difference were derived based on the exact method. According to the clinical study report, if convergence was not reached, the covariates could be removed from the model one by one until convergence was reached, by starting with continuous covariates (i.e., baseline PASI) and followed by removing categorical covariates (i.e.,

age stratum, body weight stratum). Note that the baseline PASI score as an explanatory variable was removed in the model due to the convergence issue.

The protocol/SAP specified a sequential gatekeeping approach to control the Type I error rate for testing co-primary and secondary efficacy endpoints. The following hypotheses are tested using the testing strategy outlined in Figure 2. Testing StrategyFigure 2.

H1: secuk. low dose is not superior to placebo with respect to PASI 75 response at Week 12
H2: secuk. high dose is not superior to placebo with respect to PASI 75 response at Week 12
H3: secuk. low dose is not superior to placebo with respect to IGA response at Week 12
H4: secuk. high dose is not superior to placebo with respect to IGA response at Week 12
H5: secuk. low dose is not superior to placebo with respect to PASI 90 response at Week 12
H6: secuk. high dose is not superior to placebo with respect to PASI 90 response at Week 12

Figure 2. Testing Strategy



Source: the 52-week clinical report file (ain457a2310wk52p01--legacy-clinical-study-report.pdf)

Within each pair of hypotheses (H1 or H3) and (H2 or H4), each hypothesis is tested at $\alpha/2$. Only if both hypotheses of a pair are rejected, the testing sequence will continue. In the next step of the sequence, the null hypotheses corresponding to the PASI 90 comparison of secukinumab versus placebo is tested. H5 and H6 will be tested at $\alpha/2$ (one-sided). If all hypotheses within a set referring to a secukinumab dose regimen have been rejected, i.e., either (H1, H3 and H5) or (H2, H4 and H6), the corresponding Type I error probability can be passed on to the other set of hypotheses, and if needed, hypotheses can be retested at a higher significance level. The level of significance was set to 2.5% one-sided.

The protocol-specified primary imputation method for the handling missing data was multiple imputation (MI) for the response variables based on PASI score and IGA categories and the non-responder imputation was specified as a sensitivity method. As previously noted, the Agency commented in the advice letter of May 24, 2018 that, for consistency with the original application, the missing data should be handled as non-responders.

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

A total of 187 subjects were screened, of which 162 completed the screening phase and were randomized to the four treatment groups in a 1:1:1:1 ratio. Table 4 presents the disposition of subjects. The majority of subjects (96.3% overall) completed the induction period. The discontinuation rates were generally similar across the four treatment arms (1 or 2 subjects per arm).

Table 4. Subject Disposition for the Induction period in Study CAIN457A2310[(1)]

	Secukinumab				
	Low dose (N=40) n (%)	**High dose (N=40) n (%)**	**Placebo (N=41) n (%)**	**Etanercept (N=41) n (%)**	**Total (N=162) n (%)**
Completed	39 (97.5)	38 (95.0)	39 (95.1)	40 (97.6)	156 (96.3)
Discontinued	1 (2.5)	2 (5.0)	2 (4.9)	1 (2.4)	6 (3.7)
Primary reason for discontinuation					
Adverse event	0 (0.0)	1 (2.5)	1 (2.4)	0 (0.0)	2 (1.2)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.6)
Protocol deviation	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.6)
Subject/guardian Decision	1 (2.5)	1 (2.5)	0 (0.0)	0 (0.0)	2 (1.2)

(1) Data presented for the randomized set which is the same as the full analysis set.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

The demographics for Study CAIN457A2310 are presented in Table 5. This study was an international study carried out in 19 countries including Belgium, Colombia, Germany, Egypt, Spain, Estonia, France, United Kingdom, Guatemala, Hungary, Israel, Italy, Japan, Latvia, Poland, Romania, Russian Federation, Switzerland, and United States. The demographics were generally balanced across the treatment arms. Approximately 77% of the subjects were older than 12 years old, and approximately 60% of the subjects were females. Approximately 83% of the subjects were white. Only 12 subjects weighed less than 25 kg.

Table 5. Demographics for Study CAIN457A2310[(1)]

	Secukinumab			
	Low dose (N=40)	**High dose (N=40)**	**Placebo (N=41)**	**Etanercept (N=41)**
Age (years)				
Mean (SD)	13.7 (2.9)	13.2 (3.2)	13.7 (3.3)	13.5 (2.9)
Median	14.5	14.0	15.0	14.0
Range	7 to 17	6 to 17	6 to 17	6 to 17
Categories, n (%)				
<12	8 (20.0)	9 (22.5)	10 (24.4)	10 (24.4)
≤12	32 (80.0)	31 (77.5)	31 (75.6)	31 (75.6)
Sex, n (%)				
Male	13 (32.5)	17 (42.5)	19 (46.3)	16 (39.0)
Female	27 (67.5)	23 (57.5)	22 (53.7)	25 (61.0)
Race, n (%)				
White	34 (85)	34 (85.0)	36 (87.8)	30 (73.2)
Black	1 (2.5)	1 (2.5)	0	0

	Secukinumab			
	Low dose (N=40)	High dose (N=40)	Placebo (N=41)	Etanercept (N=41)
Asian	1 (2.5)	2 (5.0)	1 (2.4)	3 (7.3)
Native American	3 (7.5)	3 (7.5)	3 (7.3)	8 (19.5)
Other	1 (2.5)	0	1 (2.4)	0
Ethnicity, n (%)				
Other	22 (55.0)	27 (67.5)	22 (53.7)	19 (46.3)
Hispanic or Latino	4 (10.0)	4 (10.0)	4 (9.8)	9 (22.0)
East Asiana	1 (2.5)	1 (2.5)	1(2.4)	2 (4.9)
Unknown	4 (10.0)	2 (5.0)	2 (4.9)	2 (4.9)
Not Reported	3 (7.5)	3 (7.5)	5 (12.2)	3 (7.3)
Weight (kg)				
Mean (SD)	52.6 (15.3)	53.6 (20.2)	55.7 (22.3)	52.0 (19.4)
Median	51.5	51.0	50.5	50.0
Range	21 to 85	20.5 to 116	17.6 to 104	20.5 to 105.5
Categories, n (%)				
<25	2 (5.0)	3 (7.5)	3 (7.3)	4 (9.8)
25 - <50	17 (42.5)	15 (37.5)	17 (41.5)	16 (39.0)
≤50	21 (52.5)	22 (55.0)	21 (51.2)	21 (51.2)

(1) Data presented for the randomized set which is the same as the full analysis set.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

Table 6 presents the baseline disease characteristics for Study CAIN457A2310. The baseline disease characteristics were generally balanced across the treatment arms.

Table 6. Baseline Disease Characteristics for Study CAIN457A2310(1)

	Secukinumab			
	Low dose (N=40)	High dose (N=40)	Placebo (N=41)	Etanercept (N=41)
PASI Score				
Mean (SD)	28.0 (8.7)	27.6 (6.9)	28.0 (8.1)	28.4 (9.1)
Median	25.5	25.6	25.8	24.8
Range	17.2 to 58.8	20.2 to 48.0	20.2 to 55.0	20.1 to 59.8
IGA mod 2011				
3 – Moderate	1 (2.5%)	0	0	0
4 – Severe	39 (97.5%)	40 (100%)	41 (100%)	41 (100%)
Total BSA (%)				
Mean (SD)	40.3 (17.6)	37.6 (13.9)	39.0 (17.7)	43.1 (19.6)
Median	36.8	36.7	34.5	37.7
Range	16.0 to 94.0	12.0 to 72.5	17.9 to 77	13.1 to 90.5

Abbreviations: PASI, Psoriasis Area and Severity Index; IGA mod 2011, Investigator's Global Assessment modified 2011; BSA, body surface area
(1) Data presented for the randomized set which is the same as the full analysis set.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

Table 7 presents the proportion of subjects with missing data for the co-primary endpoints by treatment arm at each study visit. Overall, the numbers of subjects with missing data was low, ranging from 1 to 5 except Week 12 with the maximum of 8. Missing data were generally balanced across the treatment arms.

Table 7. Missing Data by Treatment Arm During the Induction Period in Study CAIN457A2310[1]

	Secukinumab		
Week	Low dose (N=40)	High dose (N=40)	Placebo (N=41)
Week 1	2 (5%)	3 (7.5%)	3 (7.3%)
Week 2	3 (7.5%)	3 (7.5%)	3 (7.3%)
Week 3	1 (2.5%)	5 (12.5%)	2 (4.9%)
Week 4	2 (5%)	2 (5%)	1 (2.4%)
Week 8	1 (2.5%)	2 (5%)	3 (7.3%)
Week 12	8 (20%)	4 (10%)	6 (14.6%)

[1] Data presented for the randomized set which is the same as the full analysis set
Source: Statistical Reviewer's Analysis

8.1.4. Efficacy Results of the Co-Primary Endpoints

Table 8 shows the efficacy results for the co-primary endpoints at Week 12 using the multiple imputation (MI) for handling missing data. Both low and high doses of secukinumab were statistically superior to the placebo for both co-primary efficacy endpoints (p-values less than 0.0001) using the multiple testing procedure presented in Error! Reference source not found..

Table 8. Efficacy Results for the Co-Primary Endpoints at Week 12 in Study CAIN457A2310[1]

	Secukinumab		Placebo
Endpoint	Low dose (N=40)	High dose (N=40)	(N=41)
IGA 0/1	28[2] (70.6%)	25[2] (62.0%)	2[2] (5.1%)
Difference (95% CI)[3]	65.4% (48.8%, 82.0%)	56.8% (39.7%, 73.9%)	
P-value[4]	<.0001	<.0001	
PASI 75	32[2] (80.5%)	32[2] (80.5%)	6[2] (15.2%)
Difference (95% CI)[3]	65.3% (48.0%, 82.6%)	65.3% (48.2%, 82.3%)	
P-value[4]	<.0001	<.0001	

Abbreviation: IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index; MI = multiple imputation
[1] Results presented for the randomized set which is the same as the full analysis set (FAS) using MI for handling missing data.
[2] The rounded mean number of responders for 100 imputations for multiple imputation
[3] 95% CI is based on the normal approximation
[4] P-value obtained using an exact logistic regression model with treatment group, baseline body weight stratum, and age stratum as explanatory variables based on Rubin's rule for 100 imputed datasets
Source: Statistical Reviewer's Analysis

Table 7 presents efficacy results of two sensitivity analyses for handling missing along with the multiple imputation results that was specified in the protocol and presented in Table 6. The first sensitivity analysis considers the non-responder imputation (NRI), as this analysis was carried out for adult trials and recommended by the Agency in the advice letter of May 24, 2018 as discussed before, and the second analysis consider the worst-case scenario (i.e., impute missing data as NR for active arm and responder for the placebo arm). It should be noted that as the number of missing data is small (see, Table 2), these sensitivity analyses are not expected to have much impact on the results presented in Table 6.

Table 9. Efficacy Results of the Sensitivity Analyses for Handling Missing Data Along with Multiple Imputation at Week 12 in Study CAIN457A2310[1]

	Secukinumab			Difference with Placebo	
	Low dose (n=40)	High dose (n=40)	Placebo (n=41)	High dose	Low dose
Observed data	32 (80%)	36 (90%)	35 (85%)		
IGA 0/1					
MI	28/40 (70.6%)	25/40 (62.0%)	2/41(5.1%)	56.9%	65.5%
NRI	24/40 (60.0%)	23/40 (57.5%)	2/41(4.9%)	52.6%	55.1%
Worst case[2]	24/40 (60%)	23/40 (57.5%)	8/41 (19.5%)	38.0%	40.5%
PASI75					
MI	32/40 (80.5%)	32/40 (80.5%)	6/41(15.2%)	65.3%	65.3%
NRI	28/40 (70.0%)	30/40 (75.0%)	6/41 (14.6%)	60.4%	55.4%
Worst case[2]	28/40 (70.0%)	30/40 (75.0%)	12/41 (29.3%)	45.7%	40.7%

Abbreviation: IGA, Investigator Global Assessment; PASI, Psoriasis Area and Severity Index; MI, multiple imputation; NRI, non-responder imputation
[1] Results presented for the randomized set which is the same as the full analysis set (FAS).
[2] Worst case indicates non-responder imputation in secukinumab groups and responder imputation in the placebo group for handling missing values.
Source: Statistical Reviewer's Analysis

8.1.5. Results for the Secondary Efficacy Endpoints

Table 10 presents the efficacy results for the key secondary efficacy endpoint. Both secukinumab low and high doses were statistically superior (p-values < 0.001) to placebo for the key secondary endpoint, PASI90, for both the MI and NRI approaches.

Table 10. Efficacy results for the Key Secondary Efficacy Endpoint at Week 12 in Study CAIN457A2310[1]

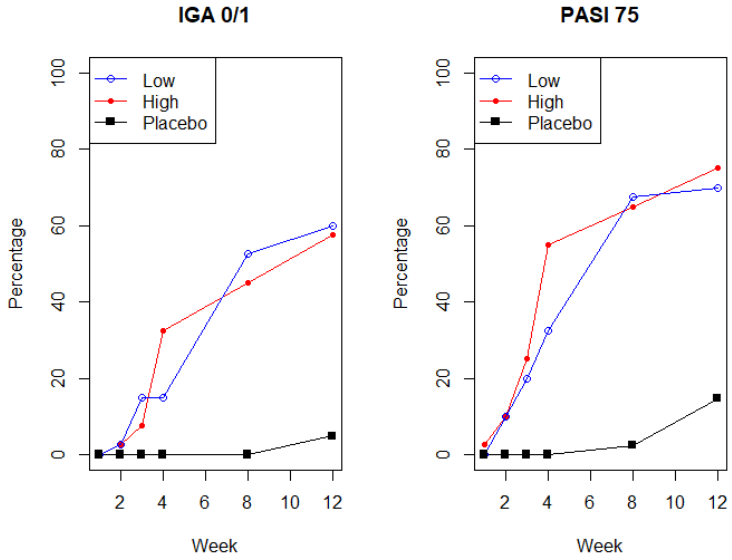
	MI			NRI		
	Secukinumab			Secukinumab		
Endpoint	Low dose (N=40)	High dose (N=40)	Placebo (N=41)	High dose (N=40)	Low dose (N=40)	Placebo (N=41)
PASI 90	29[2] (71.6%)	28[2] (69.8%)	1[2] (2.5%)	26 (65.0%)	26 (65.0%)	1 (2.4%)
Difference (95% CI)[3]	69.1% (53.5%, 84.7%)	67.2% (51.7%, 82.7%)		62.6% (47.0%, 78.1%)	62.6% (47.0%, 78.1%)	
P-value[4]	<.0001	<.0001		<.0001	<.0001	

Abbreviation: FAS, full analysis set (intent-to-treat population set); PASI, Psoriasis Area and Severity Index; MI, multiple imputation; NRI, non-responder imputation
[1] Results presented for the randomized set which is the same as the full analysis set (FAS).
[2] The rounded mean number of responders for 100 imputations for multiple imputation.
[3] 95% CI is based on the normal approximation.
[4] P-value obtained using an exact logistic regression model with treatment group, baseline body weight stratum, and age stratum as explanatory variables based on Rubin's rule for 100 imputed datasets
Source: Statistical Reviewer's Analysis

8.1.6. Efficacy Over Time

For the double-blind treatment period, treatment responses were evaluated using the IGA scale and PASI 75 at Weeks 1, 2, 3, 4, 8, and 12. Figure 3 presents the efficacy results for the co-primary efficacy endpoints during the double-blind treatment period for Study CAIN457A2310.

Figure 3. Efficacy results over time for double blind period for the co-primary endpoints for Study CAIN457A2310(1)



Abbreviation: FAS, full analysis set (intent-to-treat population set); IGA, Investigator Global Assessment; PASI, Psoriasis Area and Severity Index; NRI, non-responder imputation
Source: Statistical Reviewer's Analysis

8.1.7. Findings in Special/Sugroup Populations

8.1.7.1. Sex, Race, Age, and Baseline Disease Severity

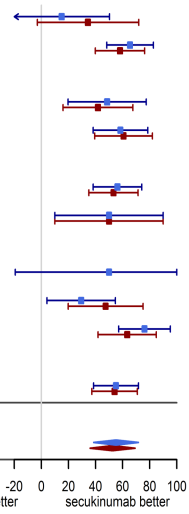
Figure 4 and Figure 5 present the efficacy results for the co-primary endpoints (i.e., IGA response and PASI 75) at Week 12 by sex, race (white vs. non-white), age (≥ 12 years vs. < 12 years), baseline weight (less than 25 kg, 25 kg to 50 kg, greater than 50 kg) and baseline IGA scire for Study CAIN457A2310. The results are based on FAS population using the Agency's recommended method for handling the missing data (i.e., non-responder imputation method). The results (not shown) for the subgroup analyses based on the Applicant's primary method for handling missing data (i.e., multiple imputation) were similar to those using the non-responder imputation.

For both co-primary efficacy endpoints, treatment effects were generally consistent across subgroups with some variability from the smaller subgroups (i.e., subjects younger than 12 years and subjects who weigh less than 25 kg). The observed variability is expected to be due to

chance factor with the small sample sizes for those subcategories. The response rates for PASI 75 were generally higher than those based on IGA, and results for all subgroups in both endpoints showed a positive treatment effect.

Figure 4. Subgroup Efficacy Results for IGA Response at Week 12 in Study CAIN457A2310 (FAS; NRI)

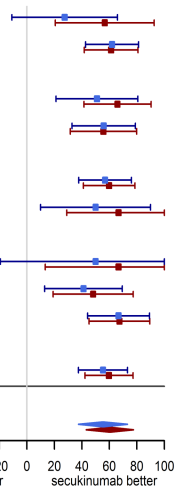
Subgroups (n[low], (n[high], n[p])	Secukinumab low dose (n=40)	Secukinumab high dose (n=40)	Placebo (n=41)	Difference low dose	Difference high dose	Difference (95% CI)
Age (years)						
<12 (8, 9, 10)	25.0%	44.4%	10.0%	15.0%	34.4%	
>=12 (32, 31, 31)	68.8%	61.3%	3.2%	65.5%	58.1%	
Sex						
Males (13, 17,19)	53.9%	47.1%	5.3%	48.6%	41.8%	
Females (27, 23, 22)	63.0%	65.2%	4.6%	58.4%	60.7%	
Race						
White (34, 34, 36)	61.8%	58.8%	5.6%	56.2%	53.3%	
Non-White (6, 6, 5)	50.0%	50.0%	0.0%	50.0%	50.0%	
Weight						
< 25 kg (2, 3, 3)	50.0%	0.0%	0.0%	50.0%	0.0%	
>= 25kg - < 50 kg (17, 15, 17)	35.3%	53.3%	5.9%	29.4%	47.5%	
>= 50 kg (21, 22, 21)	81.0%	68.2%	4.8%	76.2%	63.4%	
Baseline IGA						
4 - Severe (40, 39, 41)	60.0%	59.0%	4.9%	55.1%	54.1%	
Overall	**60.0%**	**57.5%**	**4.9%**	**55.1%**	**52.6%**	



Abbreviation: FAS, full analysis set (intent-to-treat population set); IGA, Investigator Global Assessment; PASI, Psoriasis Area and Severity Index; NRI, non-responder imputation
There is only one subject with baseline IGA 0/1 of the category of 3 (moderate) in secukinumab high dose and as a non-responder.
Source: Statistical Reviewer's Analysis

Figure 5. Subgroup Efficacy Results for on PASI 75 Response at Week 12 in Study CAIN457A2310 (FAS; NRI)

Subgroups (n[low], (n[high], n[p])	Secukinumab low dose (n=40)	Secukinumab high dose (n=40)	Placebo (n=41)	Difference low dose	Difference high dose
Age (years)					
<12 (8, 9, 10)	37.5%	66.7%	10.0%	27.5%	56.7%
>=12 (32, 31, 31)	78.1%	77.4%	16.1%	62.0%	61.3%
Sex					
Males (13, 17,19)	61.5%	76.5%	10.5%	51.0%	65.9%
Females (27, 23, 22)	74.1%	73.9%	18.2%	55.9%	55.7%
Race					
White (34, 34, 36)	73.5%	76.5%	16.7%	56.9%	59.8%
Non-White (6, 6, 5)	50.0%	66.7%	0.0%	50.0%	66.7%
Weight					
< 25 kg (2, 3, 3)	50.0%	66.7%	0.0%	50.0%	66.7%
>= 25kg - < 50 kg (17, 15, 17)	52.9%	60.0%	11.8%	41.2%	48.2%
>= 50 kg (21, 22, 21)	85.7%	86.4%	19.0%	66.7%	67.4%
Baseline IGA					
4 - Severe (40, 39, 41)	70.0%	74.4%	14.6%	55.4%	59.7%
Overall	**70.0%**	**75.0%**	**14.6%**	**55.4%**	**60.4%**

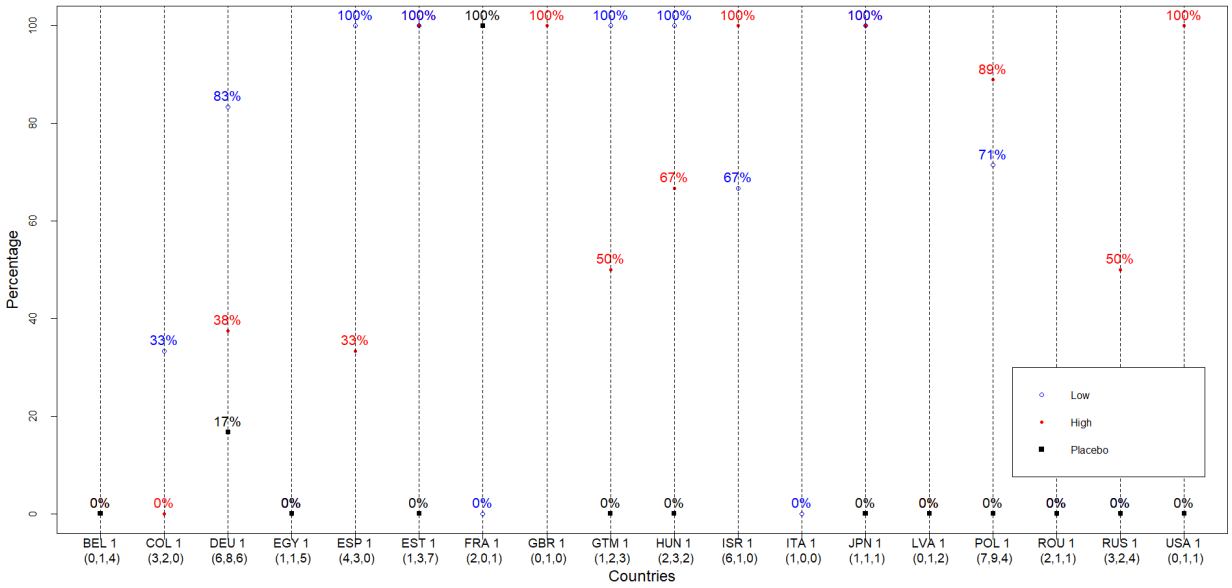


Abbreviation: FAS, full analysis set (intent-to-treat population set); IGA, Investigator Global Assessment; PASI, Psoriasis Area and Severity Index; NRI, non-responder imputation
There is only one subject with base IGA 0/1 of the category of 3 (moderate) in secukinumab high dose and as a non-responder.
Source: Statistical Reviewer's Analysis

8.1.7.2. Geographic Location (Country)

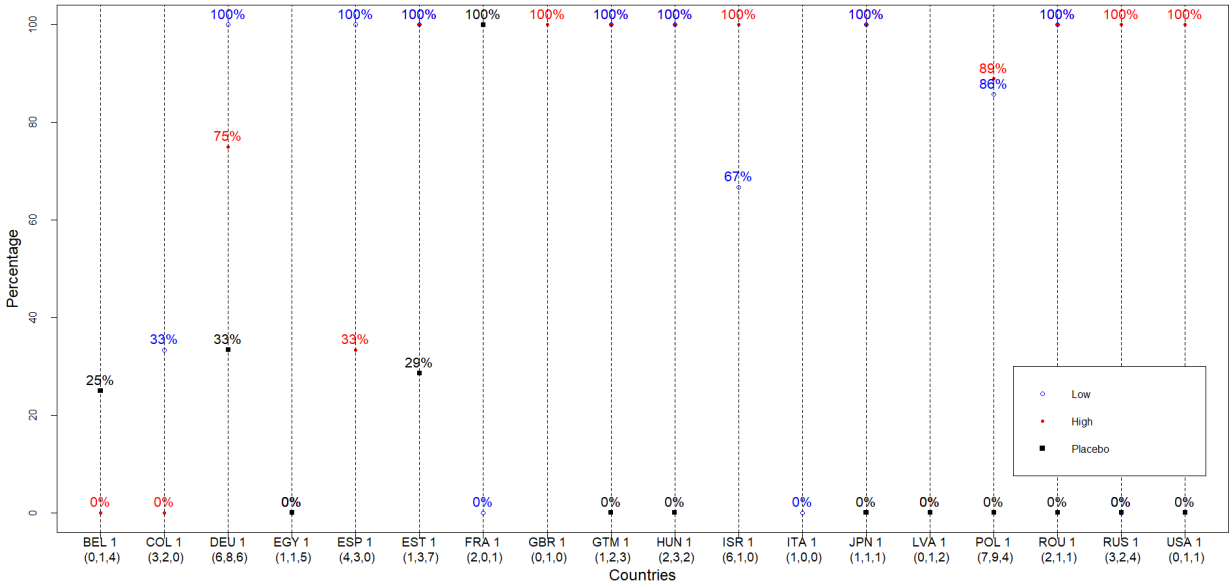
Figure 6 and Figure 7Error! Reference source not found. present the efficacy results for the co-primary endpoints (IGA response and PASI 75) at Week 12 by country for secukinumab high and low doses and placebo for the FAS population using the NRI method for handling the missing data. For both endpoints, there was some variability in treatment effect across the countries; however, this may be due to the relatively small sample sizes across the countries.

Figure 6. Results for IGA Response at Week 12 by Country in Study CAIN457A2310 (FAS; NRI)



Abbreviation: FAS, full analysis set (intent-to-treat population set); IGA, Investigator Global Assessment; NRI, non-responder imputation
Country Code: BEL, Belgium; COL, Colombia; DEU, Germany; EGY, Egypt; ESP, Spain; EST, Estonia; FRA, France; GBR, United Kingdom; GTM, Guatemala; HUN, Hungary; ISR, Israel; ITA, Italy; JPN, Japan; LVA, Latvia; POL, Poland; ROU, Romania; RUS, Russian Federation; USA, United States of America
Source: Statistical Reviewer's Analysis

Figure 7. Results for PASI 75 response at Week 12 by Country for Study CAIN457A2310 (FAS; NRI)



Abbreviation: FAS, full analysis set (intent-to-treat population set); PASI, Psoriasis Area and Severity Index; NRI, non-responder imputation
Country Code: BEL, Belgium; COL, Colombia; DEU, Germany; EGY, Egypt; ESP, Spain; EST, Estonia; FRA, France; GBR, United Kingdom; GTM, Guatemala; HUN, Hungary; ISR, Israel; ITA, Italy; JPN, Japan; LVA, Latvia; POL, Poland; ROU, Romania; RUS, Russian Federation; USA, United States of America
Source: Statistical Reviewer's Analysis

8.1.8. Additional Efficacy Analyses by Baseline Body Weight

The goal of the additional analyses is to explore treatment effect beyond the primary time point i.e., Week 12) as finding from such analysis may help in selecting the dose for this pediatric population, taking into account the small difference in treatment effect between high and low dose for each weight category and the uncertainty about the treatment effect due to the small sample sizes in each weight category. Error! Reference source not found. presents summary of the efficacy results for co-primary endpoints at Week 12 (primary analysis) along with results for Week 24 and Week 52 (key secondary efficacy endpoints) by the baseline weight. It should be noted that the number of subjects in each comparison is relatively small to make a meaningful conclusion, however, the results show that the 300 mg does not offer meaningful benefits over the 150 mg dose for the ≥ 50kg weight group and that 150 mg dose appears to provide a slightly higher efficacy than the 75 mg for the ≥ 25kg, < 50kg weight group at Week 12. However, the results for key secondary endpoint at Week 24 and Week 52 do not support 150 mg dose over the 75 mg this age group. Overall, the results of the analyses support use of the 75 mg for the ≥ 25kg, < 50kg weight category. Table 12 summarizes the efficacy results for [redacted] (b) (4) doses by weight categories.

Table 11. Efficacy Results by Baseline Body Weight at Week 12, Week 24, and Week 52 in Study CAIN457A2310 (FAS; NRI)[1]

		< 25kg	≥ 25kg, < 50kg		≥ 50kg	
		Secukinumab	Secukinumab		Secukinumab	
		75 mg	75 mg	150 mg	150 mg	300 mg
		N=5	N=17	N=15	N=21	N=22
Primary Time Point (Week 12)	**IGA 0/1**	1 (20.0%)	6 (35.3%)	8 (53.3%)	17 (81.0%)	15 (68.2%)
	PASI75	3 (60.0%)	9 (52.9%)	9 (60.0%)	18 (85.7%)	19 (86.4%)
	PASI90	1 (20.0%)	8 (47.1%)	8 (53.3%)	17 (81.0%)	18 (81.8%)
Week 24						
	IGA 0/1	4 (80.0%)	15 (88.2%)	9 (60.0%)	18 (85.7%)	19 (86.4%)
	PASI75	4 (80.0%)	16 (94.1%)	11 (73.3%)	19 (90.5%)	22 (100.0%)
	PASI90	3 (60.0%)	14 (82.4%)	9 (60.0%)	17 (81.0%)	21 (95.5%)
Week 52						
	IGA 0/1	4 (80.0%)	13 (76.5%)	9 (60.0%)	14 (66.7%)	19 (86.4%)
	PASI75	3 (60.0%)	15 (88.2%)	12 (80.0%)	18 (85.7%)	22 (100.0%)
	PASI90	3 (60.0%)	13 (76.5%)	10 (66.7%)	15 (71.4%)	21 (95.5%)

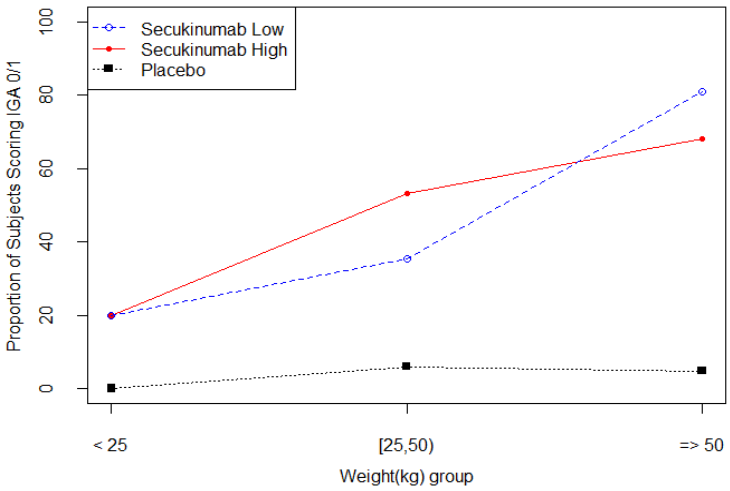
Abbreviation: FAS, full analysis set (intent-to-treat population set); IGA, Investigator Global Assessment; NRI = non-responder imputation
[1] There are no results for placebo because PASI 75 non-responders in the placebo group were switched to either secukinumab low dose or secukinumab high dose treatment group at the start of the maintenance period (see *Figure 1*).
Source: Statistical Reviewer's Analysis

Table 12. Summary of efficacy results for the recommended doses by weight category at Week 12 in Study CAIN457A2310

	Body Weight < 50kg		**Body Weight ≥ 50kg**	
	COSENTYX 75 mg (N=22) n (%)	**Placebo (N=20) n (%)**	**COSENTYX 150 mg (N=21) n (%)**	**Placebo (N=21) n (%)**
IGA 0/1	7 (32)	1 (5)	17 (81)	1 (5)
PASI 75	12 (55)	2 (10)	18 (86)	4 (19)
PASI 90	9 (41)	1 (5)	17 (81)	0 (0)

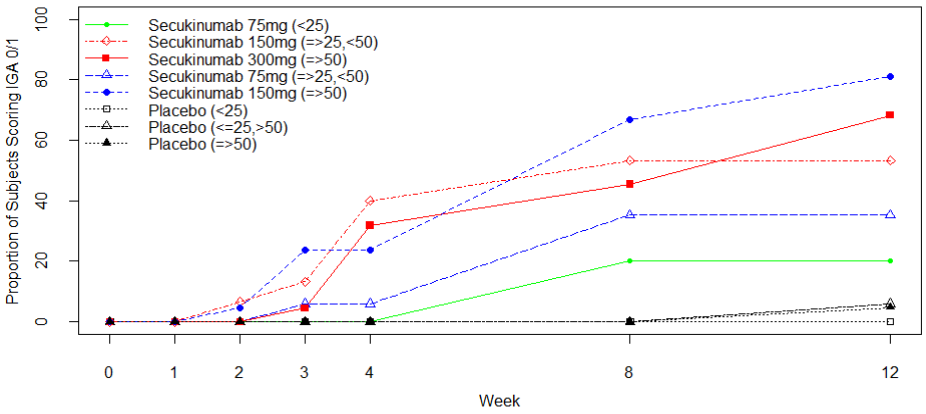
Figure 8 presents the IGA response at Week 12 by baseline body weight category. Error! Reference source not found. presents IGA response over time.

Figure 8. Efficacy Results for IGA Response at Week 12 by Baseline Body Weight in Study CAIN457A2310 (FAS; NRI)



Abbreviation: FAS, full analysis set (intent-to-treat population set); IGA, Investigator Global Assessment; NRI = non-responder imputation
Source: Statistical Reviewer's Analysis

Figure 9. Efficacy Results over time based on response on the IGA by baseline body weight for Study CAIN457A2310 (FAS; NRI)



Abbreviation: FAS, full analysis set (intent-to-treat population set); IGA, Investigator Global Assessment; NRI, non-responder imputation
Source: Statistical Reviewer's Analysis

8.1.9. Comparison with Results for Plaque Posriasis in Adults Subjects

Table 13 presents the efficacy results for the co-primary efficacy endpoints at Week 12 for the two pivotal Phase 3 studies used to approve secukinumab for the treatment of plaque psoriasis in adult subjects (Studies CAIN457A2302 and CAIN457A2303) as well as Study CAIN457A2310 for pediatric subjects.

The results are presented for the ITT population using the NRI method for handling the missing data. The reader is reminded that for pediatric subjects, study CAIN457A2310 evaluated the dose regimen of 75 mg, 150 mg or 300 mg depending on the weight. The secukinumab response rates for both co-primary efficacy endpoints were similar between adult and pediatric subjects. The placebo response rates for both endpoints were higher for pediatric subjects compared to adult subjects (5% and 15% vs 2% to 5%). The statistical reviewer notes that the sample size in Study CAIN457A2310 (pediatric subjects) was much smaller compared to the studies in adult subjects.

Table 13. Comparison of the Efficacy Results for the Co-Primary Endpoints at Week 12 in Adult Studies [CAIN457A2302 and CAIN457A2303] and the Pediatric Study [CAIN457A2310] (ITT*; NRI)

	Secukinumab			Difference from Placebo	
	High dose	Low dose	Placebo	High dose	Low dose
CAIN457A2302[(1)]	N=245	N=245	N=248		
IGA 0/1	160 (65%)	125 (51%)	6 (2%)	63%	49%
PASI 75	200 (82%)	174 (71%)	11 (4%)	78%	67%
CAIN457A2303[(1)]	N=327	N=327	N=326		
IGA 0/1	202 (62%)	167 (51%)	9 (3%)	59%	48%
PASI 75	249 (76%)	219 (67%)	16 (5%)	71%	62%

CAIN457A2310[(2)]	N=40	N=40	N=41		
IGA 0/1	23 (58%)	24 (60%)	2 (5%)	53%	55%
PASI 75	30 (75%)	28 (70%)	6 (15%)	60%	55%

Abbreviation: IGA, Investigator Global Assessment; PASI, Psoriasis Area and Severity Index; NRI, non-responder imputation
* ITT population is defined as all randomized subjects. Missing data imputed using NRI
(1) For Studies CAIN457A2302 and CAIN457A2303, the approved secukinumab dose regimens were 150 mg (low dose) and 300 mg (high dose).
(2) For Study CAIN457A2310, the secukinumab dose regimen is 75 mg, 150 mg or 300 mg depending on the weight.
Source: Label for BLA 125504 and Statistical Reviewer's Analysis

8.2. Review of Safety

8.2.1. Safety Review Approach

To support the indication for treatment of moderate to severe plaque psoriasis in pediatric patients 6 years of age and older, the totality of the data includes two pediatric clinical studies [Study A2310 (in severe disease) and Study A2311 (in moderate to severe disease)], complemented by extrapolation of the data from the adult clinical studies in moderate to severe disease (A2302, A2303, A2308 and A2309). Refer to Section 7.1, Table of Clinical Studies, for further details.

Pediatric Study A2310 and the adult studies were double blind, placebo-controlled studies. Pediatric Study A2311 was open label, did not have a control arm (relying on historical placebo data from adult studies), and was the only study that contributed to the pool of the pediatric moderate disease population. Despite these differences, the primary safety database is comprised of data from each individual pediatric study (A2310 and A2311), as well as pooled data from both of these studies given that the drug product, doses, and frequency were the same. In supportive safety analyses, the Applicant compared the results from studies A2310 and A2311 to pooled data from the pivotal studies in adults with psoriasis.

The safety review will mainly focus on the data through Week 52 from Study A2310 and data through Week 24 from Study A2311. All safety analyses were based on the Safety set, which includes all subjects who took at least one dose of study drug during the treatment periods.

The following types of individual and pooled data were analyzed to assess the safety profile of secukinumab in pediatric subjects ≥ 6 years of age: exposure, demographics, baseline characteristics, treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, adverse events of special interest (AESIs), vital signs, findings from physical examinations, ECGs, laboratory studies, immunogenicity, and pregnancy testing.

Analyses by pediatric weight group was underscored by this reviewer throughout this review because 1) the proposed subcutaneous doses are based on body weight; 2) body weight is a significant intrinsic factor for clearance as secukinumab clearance increases with increasing body weight; and 3) pediatric C_{trough} values obtained from the group weighing ≥50 kg on 300 mg

were noticeably and inexplicably higher at certain time points than Ctrough values from adults on 300 mg dose.

Safety comparisons between study drug, active comparator, and placebo arms were overall consistent through the primary endpoint time point of 12 weeks and appear so in the available longer term assessments as well. Due to the differing sample sizes between the secukinumab arms and other treatment arms, as well as differing durations of therapy for many subjects as time progressed, a direct comparison could not be made. Although not without limitations, safety beyond 12 weeks was compared across treatment arms using exposure-adjusted incidence rates (EAIR) per 100 patient-years given the different durations of therapy between the treatment arms as time progressed (e.g., etanercept subjects had to discontinue the study after Week 52 making their overall exposure lower).

8.2.2. Review of the Safety Database

Overall Exposure

Up to Week 12

A total of 164 subjects from Studies A2310 and A2311 were initially randomized to Any secukinumab dose, representing 37.8 patient-years (PY) of exposure. Forty one subjects were initially randomized to placebo representing 9.5 PY, and 41 subjects were randomized to receive etanercept representing 9.7 PY.

The duration of exposure for the period *Up to Week 12*, as demonstrated by the mean and median patient-days of exposure, was similar between the secukinumab, placebo, and etanercept groups, as well as between the secukinumab treatment groups in pediatric and adult subjects. Table -- presents the extent of exposure through Week 12 for the pooled pediatric studies compared to the pooled pivotal adult studies.

Table 14. Duration of Exposure to Study Treatment, by Population (pediatric and adult) – Up to Week 12 Safety set

	Pediatric Psoriasis			Adult Psoriasis		
	Any secukinumab n=164	Placebo n=41	Etanercept n=41	Any secukinumab n= 1382	Placebo N=694	Etanercept n=323
Exposure ≤ 12 weeks	142 (87%)	35 (85%)	35 (85%)	1066 (77%)	502 (72%)	253 (78%)
Mean days of exposure	84.1	84.6	86.3	83.1	81.8	82.6
Median days of exposure	84.0	84.0	84.0	84.0	84.0	84.0

Source: Modified Sponsor Table S2.1.1upd from Summary of Clinical Safety Appendix 1
Adult pool includes studies A2302, A2303, A2308 and A2309. Pediatric pool includes studies A2310 and A2311.

Up to Week 52

Up to Week 52 data consists of all subjects who completed their Week 52 visit, those who discontinued prior to Week 52, and subjects from Study A2311 who continued in the study but did not reach the Week 52 visit as of the data cut-off (November 14, 2019). At the time of the Week 24 analysis cut-off (November 14, 2019) for Study A2311, most subjects had not yet reached 52 weeks of treatment, so the mean and median duration of exposure to study treatment ≥52 weeks was lower for the *moderate* psoriasis pediatric population compared to the moderate psoriasis adult population.

Table 15 below presents the comparable extent of exposure through Week 52 for the pediatric studies compared to the pivotal adult studies.

Table 15. Duration of Exposure to Study Treatment, by Population (pediatric and adult) – Up to week 52 Safety set

	Pediatric Psoriasis		Adult Psoriasis	
	Any secukinumab n=198 (%)	Etanercept n=41	Any secukinumab n= 1989	Etanercept n=323
Exposure ≤ 52 weeks	73 (37%)	30 (73%)	948 (48%)	223 (69%)
Mean days of exposure	305.3	338.2	321.3	335.3
Median days of exposure	335.0	364.0	363.0	364.0

Source: Modified Sponsor Table S2.1.2upd from Summary of Clinical Safety Appendix 1
Adult pool includes studies A2302, A2303, A2308 and A2309. Pediatric pool includes studies A2310 and A2311.

Entire Treatment Period

Study A2310 recruited subjects over a 3 year span starting with adolescents ages 12 to <18 years then recruited younger subjects ages 6 to <12 years. As of the Week 52 cut-off date (September 18, 2019), 98 (86%) subjects received any dose of secukinumab for ≥52 weeks. The median duration of exposure to Any secukinumab was 730.5 days equivalent to a cumulative exposure of 228.10 PY.

Study A2311 recruited subjects over 9 months. As of the Week 24 cut-off date (November 14, 2019), 15 (18%) subjects received Any secukinumab for ≥52 weeks. The median duration of exposure was 244.0 days equivalent to a cumulative exposure of 59.25 PYs.

During the Entire Treatment Period, the median duration of exposure to secukinumab by body weight was generally comparable to the median exposure to etanercept by weight as presented in Table 16 below.

Table 16. Duration of Exposure to Study Treatment in Pediatric Population (A2310 and A2311) by weight group – Entire treatment period, Safety set

	<25 kg		≥ 25 kg and < 50 kg		≥ 50 kg	
	Any secukinumab n= 16	Etanercept n=4	Any Secukinumab n= 71	Etanercept n=16	Any Secukinumab n=111	Etanercept n=21
Median days of exposure	281.5	366.0	365.0	370.5	461.0	442.0

The overall extent of exposure of pediatric subjects is reasonable to inform safety. Worth highlighting is that the cumulative exposure for adolescents in Study A2310 is anticipated to be more sizable compared to that of younger subjects due to the stepwise recruitment scheme. Additionally, although the duration of exposure for subjects in Study A2311 is relatively limited, it is considered adequate in combination with Study A2310 to help determine risk/benefit for the pediatric population.

Adequacy of the safety database:

The safety database is adequate for this pediatric supplement.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of secukinumab for the treatment of moderate to severe plaque psoriasis in pediatric patients ≥ 6 years of age.

Categorization of Adverse Events

The Applicant organized adverse events (AEs) by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 for Study A2310 and version 22.1 for Study A2311. AEs were also evaluated according to severity (mild, moderate, and severe), as well as possible relationship to study drug.

Safety data for the pooled pediatric studies was evaluated by treatment periods:

- Induction period: includes data from all subjects until their Week 12 visit or early discontinuation visit
- Up to Week 24: includes data from all subjects until their Week 24 visit or early discontinuation visit
- Up to Week 52: includes data from all subjects until their Week 52 visit or early discontinuation visit (for Study A2311, Week 52 data up to the cut-off date of November

14, 2019 are included)
- Entire treatment period: included all safety data up to the cut-off date of September 18, 2019 for Study A2310 and November 14, 2019 for Study A2311

For adult studies (A2302, A2303, A2308 and A2309), data from the Induction period, up to Week 24 and up to Week 52 were considered for safety analysis.

The Applicant also organized the safety pool by treatment groups and made side-by-side comparisons as appropriate:

For the pediatric pool:
- Up to Week 12 (placebo-controlled Induction period): secukinumab Low dose, secukinumab High dose,
  Any secukinumab, placebo and etanercept.
- Up to Week 24: Any secukinumab Low dose, Any secukinumab High dose, Any secukinumab, etanercept.
- Up to Week 52: Any secukinumab Low dose, Any secukinumab High dose, Any secukinumab and etanercept.
- Entire treatment period: Any secukinumab Low dose, Any secukinumab High dose, Any secukinumab, etanercept, and placebo (for the treatment emergent AEs)

For the adult pool:
- Induction period (up to Week 12): secukinumab 150 mg, secukinumab 300 mg, Any secukinumab, placebo, and etanercept.
- Up to Week 24: Any secukinumab 150 mg, Any secukinumab 300 mg, Any Secukinumab, and etanercept.
- Up to Week 52: Any secukinumab 150 mg, Any secukinumab 300 mg, Any secukinumab, and etanercept.

The Applicant presented adverse events as absolute incidence for each treatment period with comparison of absolute incidence rates versus placebo being limited to the Induction period of pediatric studies. AEs were also expressed as incidence rate per 100 PY of exposure (calculated as the number of AEs divided by the PY in the treatment group x 100). EAIR was calculated for the long-term safety summary to adjust for patient exposure.

Routine Clinical Tests

Routine safety monitoring included vital signs, physical examinations, concomitant medications, clinical laboratory evaluations (chemistry and hematology), immunogenicity assessments, and ECGs. The clinical evaluations conducted are reasonably applicable to assess the safety of secukinumab in the pediatric population.

8.2.4. Safety Results

Deaths

There were no deaths during the pediatric development program for secukinumab.

Serious Adverse Events

Following administration of Any secukinumab dose, 21 serious adverse events (SAEs) were reported in 13 subjects within the pediatric pool--all 21 were documented as resolved/recovered. Most of these 21 SAEs belonged to the Infections and infestations SOC (10, 45%), and the majority of them occurred in the ≥ 50 kg weight group who received (high dose) secukinumab 300 mg (although one subject, A2310 (b) (6), accounted for six of the 8 SAEs in this subgroup).

Up to Week 12
During the placebo-controlled period (Up to Week 12 in Study A2310), two (1%) subjects, one in each secukinumab group, had serious adverse events (SAEs) compared to four (10%) in the etanercept arm and none in the placebo group.

- Subject A2310 (b) (6): toxic shock syndrome
  The subject, a 6-year-old female with severe plaque psoriasis, weighed **≥25** kg to <50kg and received secukinumab 150 mg (high dose).
  She developed pyrexia on Day 16 and was diagnosed with toxic shock syndrome (TSS) requiring hospitalization and IV antibiotics. Study drug was permanently discontinued. Thirteen days after the last dose of study drug, the patient discharged from the hospital. The following day, a right leg ultrasound revealed a calf phlegmon. Methicillin resistant Staphylococcus aureus (MRSA) was isolated from the phlegmonous material and it was reported that the subject's TSS was due to MRSA in the setting of immunosuppression. Nine days later, a "mild" right calf abscess was diagnosed requiring multiple antibiotics. Thirty-five days after the last dose of study medication, toxic shock syndrome and her limb abscess resolved.
  - *Given the temporal relationship between drug administration and development of TSS in this subject without other comorbidities, a role for secukinumab in this serious infection cannot be excluded.*

- Subject A2310- (b) (6): increased ALT
  The subject, a 15-year-old female with severe plaque psoriasis who was taking concomitant oral contraceptive medication, weighed **≥** 50 kg and received secukinumab 150 mg (low dose).
  On Days 7 and 14, she developed moderate abdominal pain that resolved the same day after ibuprofen administration. On Day 59, the subject was diagnosed with viral gastroenteritis that resolved on Day 73 without intervention. On an unspecified date, liver enzymes were increased: ALT of 177 U/L (range < 35 U/L), AST of 78 U/L (range < 35 U/L),

and GGT U/L (range < 39 U/L). On Day 78 she was hospitalized for mild ALT elevation and discharged the next day. On an unknown date, Hepatitis A, B, D and E serology was negative. On Day 87, the subject completed the placebo-controlled period and entered the next treatment period. On Day 101, increased ALT and AST resolved; bilirubin levels were never elevated. The subject continued on treatment beyond 52 weeks; study treatment was permanently discontinued due to lack of efficacy on Day 463.

- *Given the rise of liver enzymes following a viral gastroenteritis and normalization of the liver enzymes in the setting of uninterrupted secukinumab treatment it is unlikely that this event was related to study drug.*

Beyond Week 12, 19 more SAEs were reported in 11 subjects. The AEs are described by dose (low or high) and indicated the corresponding weight group.

- Low dose:

- Subject A2310-(b) (6): testicular torsion
  The subject, an 8-year-old male, weighed < 25 kg and received placebo-secukinumab 75 mg (low dose).
  He received placebo until Day 88 then was randomized to secukinumab 75 mg for the next treatment period. On Day 300, he was hospitalized and underwent surgery for testicular torsion. The subject fully recovered on Day 307.
  - *This event was unlikely to be related to secukinumab treatment.*

- Subject A2310-(b) (6): suicidal ideation, major depression
  The subject weighed **≥25** kg to <50kg and received placebo-secukinumab 75 mg (low dose). She was a 12-year-old female with a 5-year history of plaque psoriasis and no prior psychiatric history, who entered the *Up to Week 24* treatment period on Day 85 in the setting of her parents divorcing, moving to a new home, and attending a new school. On Day 169, she was assessed as a PASI 75 responder but 5% of her head and neck were affected by psoriasis and her DLQI questionnaire reflected that she "was troubled quite a lot" because of psoriasis. On Day 185, the subject was diagnosed with moderate depression. On day 253, she required hospitalization for suicidal ideation and major depression. Study drug was permanently discontinued. Sixty-two days after the last study drug dose, signs and symptoms of depression had decreased. One hundred thirty eight (138) days after the last dose of study medication, suicidal ideation and major depression resolved.
  - *Although there were confounding factors, a role for secukinumab in this serious mood disorder cannot be excluded.*

- Subject A2310-(b) (6): reactive arthritis and worsening psoriasis
  The subject, a 17-year-old female with a 5-year history of plaque psoriasis, weighed **≥** 50kg and received placebo-secukinumab 150 mg (low dose).
  She received her first dose of secukinumab 150 mg on Day 85. On Day 88, 13 days after acute bronchitis, the subject developed knee pain and was diagnosed with moderate reactive arthritis. Study drug was permanently discontinued due to reactive arthritis; the

last received dose was on Day 98. On Day 107, she was hospitalized. Twenty two days after last dose of study drug, reactive arthritis resolved; and 87 days after the last dose of study drug, the patient developed severe "aggravated" psoriasis requiring hospitalization. One hundred fourteen days after the last dose of study drug, "aggravated" psoriasis resolved. The Investigator suspected a relationship between reactive arthritis and study drug but did not suspect a relationship between psoriasis and study drug.

- *Development of severe worsening of psoriasis might represent a rebound phenomenon. The event of reactive arthritis may be related to secukinumab treatment.*

- Subject A2311 (b) (6): infectious mononucleosis

The subject, a 14-year-old male with a 3-year-history of plaque psoriasis weighed ≥ 50kg and received secukinumab 150 mg (low dose).
On Day 92, the subject was hospitalized with mild infectious mononucleosis. No action was taken with the study medication. His symptoms lasted eight days. The Investigator did not suspect a relationship between infectious mononucleosis and the study drug.

- *A role for secukinumab in this serious infection cannot be excluded.*

- High Dose:
  - Subject A2310- (b) (6): lymphadenopathy

The subject, an 8-year-old female with a history of plaque psoriasis, atopic dermatitis, asthma, and hypogammaglobulinemia, initially weighed < 25 kg and received secukinumab 75 mg then began receiving 150mg due to an increase of body weight to ≥25 kg to <50kg. Her SAE occurred while receiving secukinumab 75 mg.
The subject developed mild dermatopathic lymphadenopathy and was treated with cephalexin On Day 28. On Day 57, mild cervical lymphadenopathy was present for which cephalexin was again prescribed. No action was taken with the study drug. On Day 79, the subject completed the placebo-controlled period and entered the next treatment period. On Day 91, the subject was hospitalized for severe generalized lymphadenopathy requiring hospitalization and biopsy. Study drug was temporarily stopped due to lymphadenopathy. There was no associated recent infection, fever, discomfort, weight loss, or respiratory symptoms. Ultrasound examination showed adenopathies involving ganglion chains in the neck, thigh, and inguinal regions. Surgical resection of the right thigh ganglion showed dematopathic lymphadenopathy, considered to be due to psoriasis. Ganglion culture showed Staphylococcus aureus sensitive to trimethoprim. On Day 106, cervical lymphadenopathy resolved; the study drug was restarted at the same planned dose.
From Day 113 onwards, the subject started receiving secukinumab 150 mg as per protocol, following a change in her body weight group to ≥25 kg to <50 kg. The subject was permanently discontinued from study drug due to reported lack of efficacy on Day 301; post treatment follow-up period was completed on Day 428.
The Investigator suspected a relationship between lymphadenopathy and the study medication.

- *The lymphadenopathy may be considered related to the subject's chronic skin diseases and also to secukinumab treatment*.

- Subject A2310-(b) (6): Contusion, concussion
  The subject, a 15-year-old female with a 13-year history of plaque psoriasis, weighed **≥25** kg to <50kg and received secukinumab placebo-secukinumab 150 mg (high dose). On Day 528, she required hospitalization for a mild contusion and concussion due to a skiing accident. The contusion resolved on Day 540 and concussion on Day 566. The Investigator did not suspect a relationship between contusion, concussion and the study medication.
  - *This event was not considered related to secukinumab treatment.*

- Subject A2310-(b) (6): bronchitis
  The subject, a 16-year-old female with an 11-year history of plaque psoriasis, weighed **≥** 50kg and received secukinumab 150mg (low dose)- 300 mg (high dose).
  She received secukinumab 150 mg up to Week 12, completing the placebo-controlled period on Day 85. Due to an Interactive Response Technology (IRT) system error, the subject received secukinumab 300 mg at Weeks 13, 14, 15 (Day 92, 99, 108) instead of placebo. On Day 151, the subject required hospitalization for severe bronchitis, which resolved on Day 159. The Investigator suspected a relationship between bronchitis and the study medication.
  - *A role for secukinumab in this serious infection cannot be excluded.*

- Subject A2310(b) (6): thrombophlebitis, pneumonia-two episodes, venous thrombosis limb, lung abscess, infectious pleural effusion, abdominal hernia
  The subject, a 16-year-old overweight male with Down's syndrome, congenital heart disease, selective IgM and CD3/CD4 immunodeficiency, pneumonia, and a 16-year history of plaque-type psoriasis, weighed **≥** 50 kg and received placebo-secukinumab 300 mg (high dose). On Day 85 the subject completed the placebo-controlled period and began receiving high dose secukinumab.
  On Day 122, he required hospitalization for severe pneumonia requiring antimicrobials and severe left lower leg thrombophlebitis. No action was taken with the study medication. Thrombophlebitis resolved on Day 131, and pneumonia improved on Day 141.
  On Day 316, the patient was diagnosed with pneumonia (second episode), left lung abscess, infectious pleural effusion, and venous thrombosis in left lower limb—all severe. On Day 335, he was discharge having documented resolution of these events.
  On Day 498, the subject required hospitalization for a severe abdominal hernia and underwent elective surgery the next day. The Investigator did not suspect a relationship between thrombophlebitis, pneumonia-two episodes, venous thrombosis limb, lung abscess, infectious pleural effusion, abdominal hernia and the study medication stating other possible contributory factor for pneumonia and pulmonary empyema was co-existing immunodeficiency.

- *Although, the subject has a history of prior lower respiratory infections in the setting of an immune compromised setting, a role for secukinumab in these serious infections cannot be excluded. The abdominal hernia event was unlikely to be related to secukinumab treatment.*

- Subject A2310-(b) (6): bacterial enterocolitis
  The subject, a 17-year-old female with a 4-month history of plaque psoriasis and acne, weighed ≥ 50 kg and received secukinumab 300 mg (high dose).
  She completed the placebo-controlled period on Day 85 and entered the next treatment period. Due to an Interactive Response Technology (IRT) system error, the subject continued to receive 300 mg instead of placebo at Visits Week 13, 14, 15 (Day 92, 99, 106). On Day 305, she developed acute severe bacterial enterocolitis requiring hospitalization, anti-diarrheal agents, antibiotics, and intravenous fluids. No action was taken with the study medication. On Day 309, bacterial enterocolitis resolved and the patient was discharged. The Investigator did not suspect a relationship between enterocolitis bacterial and the study
  medication.
  - *A role for secukinumab in this serious infection cannot be excluded.*

- Subject A2310-(b) (6): clavicular fracture
  The subject, a 16-year-old male with a 7-year history of plaque psoriasis, weighed ≥ 50kg and received secukinumab 300 mg (high dose).
  The subject completed the placebo-controlled period on Day 85. Due to an Interactive Response Technology (IRT) system error he continued to receive 300 mg instead of receiving placebo at Visits Wk 13, 14, 15 (Day 92, 99, 106). On Day 258, the subject sustained a clavicular fracture during physical education class.
  The Investigator did not suspect a relationship between the clavicular fracture and the study drug.
  - *This event was considered unlikely to be related to secukinumab treatment.*

- Subject A2310-(b) (6): appendicitis
  The subject, a 17-year-old male with a 17-year history of plaque psoriasis, weighed ≥ 50 kg and received secukinumab 300 mg (high dose) on Day 1. Due to an Interactive Response Technology (IRT) system error, the subject continue to receive 300 mg instead of placebo at Visits Week 13, 14, 15 (Day 91, 98, 105). The patient completed the maintenance period on Day 364 and received his last dose of study drug on Day 506 due to lack of efficacy. Ninety-six days after the last dose of study medication and during the treatment-free follow-up period, the patient was hospitalized due to severe appendicitis and underwent laparoscopic appendectomy. The Investigator did not suspect a relationship between appendicitis and the study medication.
  - *A role for secukinumab in this serious infection cannot be excluded.*

Overall, the EAIR of SAEs was lower in subjects on secukinumab (Any secukinumab dose: 4.4

per 100 PY) compared to the etanercept group (16.1 per 100 PY). The incidence rates of SAEs related to Infections and infestations SOC was 1.4 per 100 PY in the Any secukinumab Low dose group, 2.1 per 100 PY in the Any secukinumab High dose group, and 2.4 per 100 PY in the etanercept group.

Dropouts and/or Discontinuations Due to Adverse Effects

Five subjects who received Any secukinumab dose discontinued treatment due to an AE: two subjects belonged to the ≥ 50kg weight group and three weighed ≥25 kg to <50kg. No subject in weight group < 25 kg discontinued study drug due to an AE.

The following AEs led to discontinuation of treatment:

Weight group **≥25** kg to <50kg:

- Subject A2310-(b) (6): suicidal ideation, major depression
  This subject who received placebo-secukinumab 75 mg (low dose) was previously discussed under SAEs.

- Subject A2310-(b) (6): toxic shock syndrome
  This subject who received secukinumab 150 mg (high dose) was previously discussed under SAEs.

- Subject A2311-(b) (6): increased ALT and AST
  The subject is an 11-year-old female with a 2-year-history of plaque psoriasis who received secukinumab 150 mg (high dose). ALT and AST were recorded as elevated at 62 U/L (range 5-30) and 106 U/L (range <37) prior to administration of the first secukinumab dose. After a single dose, ALT rose to 73 U/L and AST increased to 116 U/L. Study drug was interrupted on Day 8 and never resumed. No treatment intervention was reported. The liver enzymes normalized by Day 57.

Weight group **≥** 50kg:

- Subject A2310-(b) (6): reactive arthritis and worsening psoriasis
  This subject who received placebo-secukinumab 150 mg (low dose) was previously discussed under SAEs.
- Subject A2311-(b) (6) hemorrhagic diarrhea
  The subject, a 14-year-old female with a 4-year history of plaque psoriasis requiring methotrexate, weighed ≥ 50kg and received secukinumab 300 mg (high dose). On Day 98, the subject developed mild hemorrhagic diarrhea that was treated with metronidazole. Study drug was temporarily interrupted due to this event. On Day 147, the patient permanently discontinued secukinumab due to hemorrhagic diarrhea and transitioned to the treatment-free follow-up period. On Day 177, the hemorrhagic diarrhea event ended. On Day 267, the patient completed treatment-free follow-up and terminated the study. The

Investigator suspected a relationship between hemorrhagic diarrhea and the study medication.

Significant Adverse Events

Safety considerations that arose from prior experience with secukinumab include: infections, hypersensitivity, neutropenia, inflammatory bowel disease (IBD), suicidal ideation and behavior (SIB), as well as malignancy, major adverse cardiovascular events (MACE), Hepatitis B reactivation, and interaction with live vaccines. Within the pediatric pool, there were no reports of the latter four adverse events of special interest (AESIs).

- Infections

The most frequent AEs were reported in the Infections and infestations SOC with the majority of events documented as mild to moderate intensity; almost all severe events (83%) reported in the secukinumab group. Twelve infections were classified as severe: 7 (58%) in the secukinumab High dose group; 3 (25%) in subjects who received secukinumab Low dose; and 2 (17%) in the etanercept group. There were no severe or serious infections reported in subjects who received placebo.

As previously noted, nearly half of the 21 SAEs following administration of Any secukinumab dose belonged to the Infections and infestations SOC (10, 45%), and the majority of them occurred in the ≥ 50 kg weight group who received (high dose) secukinumab 300 mg (although one subject, A2310-(b) (6), accounted for six of the 8 SAEs in this subgroup).

Up to Week 12
During the placebo-controlled period (Study A2310), 75 infection-related AEs were reported [24 (32%) in the placebo group; 15 (20%) in those who received etanercept; 16 (21%) in the secukinumab Low dose group, and 20 (27%) in the secukinumab High dose group]. All AEs except one were mild to moderate. Although the Applicant stated that "none of the infection-related AEs were serious or led to the discontinuation of the study drug during this period," subject A2310-1500-005, who received secukinumab 150 mg (high dose) developed a serious infection of MRSA TSS and a limb abscess during the first 12 weeks of study A2310, and ultimately required discontinuation of study drug.

Entire Treatment Period
The exposure-adjusted incidence rates (EAIR) for infection-related AEs was lower in the Any secukinumab dose (95.9 per 100 PY) compared to etanercept group (118.5 per 100 PY). EAIR of infection AEs was higher in the Any secukinumab Low dose group (100.8 per 100 PY) than in the Any secukinumab High dose group (91.3 per 100 PY).

- Hypersensitivity

Up to Week 12

Hypersensitivity AEs during this study period included eczema, injection site hypersensitivity, allergic rhinitis, allergic conjunctivitis, and urticaria which were reported in 3 (3.7%) subjects in the secukinumab Low dose group, 2 (2.4%) subjects in the secukinumab High dose group, 1 (2.4%) subject in the placebo, and 2 (4.9%) subjects in the etanercept group. All of these events were reported in one subject for each event. Allergic conjunctivitis was the only hypersensitivity AE that occurred in 2 (4.9%) subjects who received etanercept.

Entire Treatment Period
The EAIR for hypersensitivity was lower in the Any secukinumab Low dose group (5.4 per 100 PY) compared to the Any secukinumab High dose group (10.1 per 100 PY); however, the EAIR was lower in the Any secukinumab group (7.8 per 100 PY) compared to the etanercept group (13.4 per 100 PY).

- Neutropenia

Up to Week 12
During the placebo-controlled period which included a total of 80 subjects treated with secukinumab and 41 subjects treated with placebo up to 12 weeks, neutropenia (≥ CTCAE Grade 2) was reported in 3 (3.75%) of the subjects treated with secukinumab compared with no subjects treated with placebo.

Entire Treatment Period
In the pediatric safety pool (198/287.4 patient years), 22 (11%) subjects reported neutropenia (≥ CTCAE Grade 2) followed out to Week 116. Fourteen of the 90 (15.6%) subjects treated with the recommended dose of secukinumab (i.e., 75 mg for a body weight <50 kg and 150 mg for a body weight ≥ 50 kg) were reported to have neutropenia (≥ CTCAE Grade 2).

One subject within the pediatric pool experienced Grade 3 neutropenia as described below.

- Subject A2310-(b) (6): Grade 3 neutropenia
  An 8-year-old female who weighed ≥25 kg to <50kg and received secukinumab 75 mg (low dose) had a normal neutrophil count at baseline, developed Grade 2 neutropenia during the first 12 weeks of Study A2310, then on Day 127, presented with a viral upper respiratory tract infection followed by a worsening neutrophil count (0.84 x 10^9/L (Grade 3) on Day 141 (Week 20 visit). The event was suspected to be related to the study drug; no action was taken with the study drug.

  Neutropenia is a known AE from the adult studies and from post-marketing experience; however, it is only described in the Prescribing Information (PI) in Adverse Reactions (6.1). Given the totality of data in which neutropenia was associated with fatal infections in post-marketing and an 11% rate of Grade 2 neutropenia was seen in the pediatric studies, it is reasonable to convey a warning for neutropenia in section 5 of the labeling, as well as communicate dose interruption instructions in section 2. Given that laboratory testing is not

routinely performed in pediatric patients, and because it is not unusual (especially if a patient is not regularly monitored) that infection/sepsis may be the presenting symptom of neutropenia, informing prescribers of a risk that can be mitigated with appropriate monitoring provides for a favorable benefit/risk when considering expanding the use of secukinumab into the pediatric population.

- Inflammatory Bowel Disease and Suicidal ideation and behavior

Up to Week 12
There were no reports of inflammatory bowel disease (IBD) or suicidal ideation and behavior (SIB) AEs during the period up to Week 12.

Entire Treatment Period
The EAIRs for IBD and SIB were both 0.3 per 100 PY in the Any secukinumab dose group compared to none in etanercept group. The incidence rates of IBD and SIB were not higher in the pediatric population compared to the adult population.

Inflammatory Bowel disease
There was a single report of "acute bacterial enterocolitis" that the Applicant classified as IBD. Subject A2310-(b) (6) was a 17-year-old female who weighed ≥ 50 kg and received secukinumab 300 mg (high dose) though Week 52. She was previously discussed under SAEs.
Of note, one subject, A2311-(b) (6), previously discussed under "discontinuations secondary to AEs" developed hemorrhagic diarrhea. An etiology was unspecified; however, the Applicant considered the diarrhea as non-inflammatory due to the absence of fecal calprotectin.

Suicidal ideation and behavior
One subject, A2310(b) (6), in the secukinumab Low dose group experienced suicidal ideation; she was previously discussed under Serious AEs, as well as Discontinuations due to AEs.

Treatment Emergent Adverse Events and Adverse Reactions

Up to Week 12

The overall incidence of TEAEs was comparable between the secukinumab Low dose (51%), High dose (54 %) and placebo groups (54 %), while the incidence of TEAEs was higher in the etanercept group (61 %).

Common Adverse Events
In all treatment groups, AEs were most commonly reported in the Infections and infestations SOC. Overall, nasopharyngitis, pharyngitis, and abdominal pain were the three most commonly

reported preferred terms (PTs). None of these events were serious and none resulted in treatment discontinuation. The most commonly reported TEAEs during the placebo-controlled period are presented in Table 17.

Table 17. Most frequent **(≥4%** in any treatment group) treatment emergent AEs by (PT) in pediatric pool (Study A2310 and Study A2311) – Up to Week 12 (Safety set)

Preferred term	**secukinumab Low Dose N=82 n (%)**	**secukinumab High Dose N=82 n (%)**	**Any secukinumab N=164 n (%)**	**Placebo N=41 n (%)**	**Etanercept N=41 n (%)**
Any preferred term	42 (51.2)	44 (53.7)	86 (52.4)	22 (53.7)	25 (61.0)
Nasopharyngitis	13 (15.9)	10 (12.2)	23 (14.0)	1 (2.4)	4 (9.8)
Pharyngitis	3 (3.7)	3 (3.7)	6 (3.7)	4 (9.8)	0 (0.0)
Abdominal pain	3 (3.7)	2 (2.4)	5 (3.0)	0 (0.0)	3 (7.3)
Headache	2 (2.4)	3 (3.7)	5 (3.0)	4 (9.8)	1 (2.4)
Upper respiratory tract infection	2 (2.4)	3 (3.7)	5 (3.0)	3 (7.3)	1 (2.4)
Abdominal pain upper	0 (0.0)	4 (4.9)	4 (2.4)	2 (4.9)	2 (4.9)
Aspartate aminotransferase increased	1 (1.2)	2 (2.4)	3 (1.8)	0 (0.0)	2 (4.9)
Nausea [d]	0 (0.0)	2 (2.4)	2 (1.2)	2 (4.9)	3 (7.3)
Oral herpes	0 (0.0)	2 (2.4)	2 (1.2)	1 (2.4)	2 (4.9)
Rhinitis	0 (0.0)	2 (2.4)	2 (1.2)	4 (9.8)	1 (2.4)
Arthralgia	1 (1.2)	0 (0.0)	1 (0.6)	1 (2.4)	2 (4.9)
Gastrointestinal infection	1 (1.2)	0 (0.0)	1 (0.6)	2 (4.9)	0 (0.0)
Influenza	1 (1.2)	0 (0.0)	1 (0.6)	3 (7.3)	1 (2.4)
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)
Conjunctivitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)

- Preferred terms are sorted in descending order of frequency in the "Any secukinumab Dose" column.
- MedDRA version 22.1 was used for reporting.
- Source: Modified Applicant's Table SCS Appendix 1-Table S10.1.1

Per the approved label, nasopharyngitis, diarrhea, and upper respiratory tract infection were the top three most commonly reported adverse reactions during the placebo-controlled period in the adult psoriasis program.

The incidence of TEAEs in pediatric and adult subjects with *severe* psoriasis who received secukinumab was comparable (58 % and 54 % respectively); however, the incidence of TEAEs in the pediatric population with *moderate* psoriasis was notably lower relative to the adult population with moderate disease (44% and 60 % respectively).
Due to the large disparity in total number of pediatric subjects with moderate psoriasis (64) and adult subjects with moderate psoriasis (991), no meaningful conclusions could be drawn regarding the difference between these populations.

Entire Treatment Period

After adjusting for exposure, the overall incidence rate of TEAEs was lower in the secukinumab groups (Any Low dose: 177.8 and Any High dose: 175.7 per 100 PY) relative to etanercept

(253.4 per 100 PY) and the placebo groups (391.0 per 100 PY).

Common Adverse Events

The most commonly affected SOC was Infections and infestation with the EAIRs higher in the etanercept group (118.5 per 100 PY) than the Any secukinumab Low dose group (100.7 per 100 PY) and the Any High dose group (90.0 per 100 PY). The most frequently reported TEAEs during the Entire treatment period were nasopharyngitis and headache. As shown in Table --, diarrhea, tonsillitis, acne, and rhinitis were more frequently reported in the Any secukinumab group compared to the etanercept group, while abdominal pain and psoriasis were reported with significantly higher frequency in the etanercept group.

Table 18. EAIRs for TEAEs (PTs with **≥5.0** per 100 PY in any of the secukinumab treatment groups (Low or High) in pediatric pool (Study A2310 and Study A2311) – Entire Treatment Period (Safety set)

Preferred term	Secukinumab Low Dose N=98 n/EX (IR)	Secukinumab High Dose N=100 n/EX (IR)	Secukinumab Any Dose N=198 n/EX (IR)	Etanercept N=41 n/EX (IR)
Any preferred term	74/0.42 (177.8)	74/0.42 (175.7)	148/0.84 (176.7)	34/0.13 (253.4)
Nasopharyngitis	22/1.07 (20.6)	30/1.00 (29.9)	52/2.07 (25.1)	11/0.35 (31.1)
Headache	11/1.21 (9.1)	13/1.30 (10.0)	24/2.51 (9.6)	4/0.39 (10.2)
Pharyngitis	11/1.20 (9.2)	7/1.32 (5.3)	18/2.52 (7.1)	3/0.40 (7.5)
Diarrhea	6/1.31 (4.6)	9/1.38 (6.5)	15/2.69 (5.6)	1/0.40 (2.5)
Tonsillitis	7/1.30 (5.4)	8/1.38 (5.8)	15/2.68 (5.6)	1/0.41 (2.5)
Acne	9/1.31 (6.9)	5/1.40 (3.6)	14/2.71 (5.2)	0/0.41 (0.0)
Cough	5/1.33 (3.8)	9/1.36 (6.6)	14/2.68 (5.2)	2/0.40 (5.0)
Upper respiratory tract infection	7/1.26 (5.5)	6/1.40 (4.3)	13/2.66 (4.9)	3/0.39 (7.8)
Rhinitis	4/1.33 (3.0)	8/1.34 (6.0)	12/2.67 (4.5)	1/0.41 (2.5)
Abdominal pain	5/1.35 (3.7)	7/1.38 (5.1)	12/2.73 (4.4)	5/0.37 (13.4)
Abdominal pain upper	4/1.33 (3.0)	7/1.36 (5.1)	11/2.70 (4.1)	4/0.39 (10.2)
Oropharyngeal pain	4/1.34 (3.0)	7/1.35 (5.2)	11/2.69 (4.1)	1/0.41 (2.5)
Gastroenteritis	7/1.31 (5.4)	2/1.45 (1.4)	9/2.75 (3.3)	1/0.40 (2.5)
Influenza	7/1.31 (5.3)	1/1.47 (0.7)	8/2.78 (2.9)	3/0.40 (7.6)
Psoriasis	7/1.35 (5.2)	1/1.46 (0.7)	8/2.81 (2.8)	4/0.40 (9.9)

- Preferred terms are sorted in descending order of IR in the "Any secukinumab Dose" column.
- EX = exposure in 100 patient years. IR=incidence rate per 100 patient years.
- Source: Modified Applicant's Table SCS Appendix 1-Table S10.1.5

Laboratory Findings

Markedly Abnormal Hematology Changes:

Up to Week 12

There were no reports of markedly abnormal (≥ CTCAE Grade 3) hematology values during the placebo-controlled period. The most commonly reported hematology abnormalities in the secukinumab groups were Grade 1 leukopenia and Grade 2 neutropenia.

Entire Treatment Period
One secukinumab treated subject experienced Grade 3 neutropenia. See neutropenia events under "Significant Adverse Events" for clinically significant laboratory discussion.

Markedly Abnormal Chemistry Changes:
Up to Week 12
One secukinumab treated subject aged ≥ 12 years, weighing ≥50 kg with severe psoriasis received 300 mg (high dose) and experienced Grade 3 increase in AST which resolved.

Entire Treatment Period
Beyond Week 12, one additional subject who received secukinumab experienced Grade 3 AST. This subject was also ≥ 12 years, weighed ≥50 kg, and had severe psoriasis.

Vital Signs

Vital signs (heart rate and blood pressure) were comparable between treatment groups during the study.

Electrocardiograms (ECGs)

Overall, no clinically meaningful differences were reported between the treatment groups.

QT

Up to Week 12
No subject had QTcF >450 ms. QTcF change from baseline of >30 ms occurred in 5 (3.2%) subjects on secukinumab compared to 3 (8.1%) in the etanercept group.

Entire Treatment Period
Overall, during the Entire treatment period, 1 (0.5%) subject on Any secukinumab High dose group had QTcF >450 ms. Ten (5.1%) patients on secukinumab and 5 (12.2%) patients on etanercept group had QTcF change from baseline of >30 ms.

Large monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study was not necessary to conduct for this supplement.

Immunogenicity

Potential risks based on class of drug (anti-cytokine) and of the drug substance (foreign protein) were considered. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, injection site/infusion reactions and immunogenicity.

Only two samples were anti-drug antibody (ADA) positive with low titers as described below,

hence modification of the current product labeling for COSENTYX which states that <1% of subjects treated with COSENTYX developed anti-drug antibodies (ADA) is not recommended.

1) One subject in the etanercept group from Study A2310 was ADA-positive (titer 1:1) at baseline.
2) One subject in 300 mg treatment group from Study A2311 was ADA-positive (titer of 1: 7.98) at baseline.

Immunogenicity to COSENTYX did not impact the overall safety profile including reported hypersensitivity and injection site reactions.

8.2.5. Analysis of Submission-Specific Safety Issues

In Study A2310, an Interactive Response Technology (IRT) error occurred after the primary endpoint assessment (Week 12) that led to additional dosing of 36 subjects in the ≥ 12 age group. Sixteen subjects who were initially randomized to the Low dose group and 20 subjects who were in the High dose group were mistakenly dispensed active medication at Week 13, 14, 15 visits instead of placebo. At these visits, the subjects were expected to receive placebo medication to maintain the blind.

- Five subjects in the High dose group (≥25 kg to <50kg - 150 mg dose) were dispensed secukinumab 150 mg at these visits;
- 16 subjects in the Low dose group (≥50 kg - 150 mg dose) were dispensed secukinumab 300 mg at these visits; and
- 15 subjects in the High dose group (≥50 kg - 300 mg dose) received 300 mg at these visits

Although no new safety signals were identified, the incidence of AEs in the Low dose group between Weeks 13 and 52 who were affected by the dosing error was higher than that in subjects who were not affected by it (14/16, 88% compared to 17/24, 71%) and comparable in the High dose group (17/20, 85% vs 16/20, 80%). The most commonly affected SOC was Infections and infestations with similar incidences in the groups affected by the error and those who were not.

The 2 most commonly reported AEs were nasopharyngitis and headache, both of which occurred at a higher rate in the subjects affected by the error:

Nasopharyngitis:
- secukinumab low dose: affected: 6 subjects (38%) vs not-affected: 3 subjects (13%)
- secukinumab high dose: affected: 8 subjects (40%) vs not-affected: 6 subjects (30%)

Headache:
- secukinumab low dose: affected: 3 subjects (19%) vs not-affected: 2 subjects (8%)
- secukinumab high dose: affected 3 subjects (15%) vs not-affected 2 subjects (10%)

Two subjects were reported with severe AEs:

Subject A2310(b) (6): 16-year-old female who weighed ≥ 50 kg, initially randomized to the Low dose group and received additional doses of 300 mg in error, developed severe bronchitis requiring concomitant medication. The AE was documented as resolved.

Subject A2310-(b) (6): 17-year-old female who weighed ≥ 50 kg, initially randomized to the High dose group and received additional doses of 300 mg in error, was reported with severe acute bacterial enterocolitis requiring concomitant medication. The AE was documented as resolved.

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

There were no COA analyses informing safety/tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

Age

During the placebo-controlled period, in the <12 years subgroup, the incidence of AEs was similar between placebo (40%) and the secukinumab dose groups (Low dose: 40%, High dose: 48%) and highest in the etanercept group (70%). The incidence of AEs in the Any secukinumab dose group was lower in <12 years compared to the ≥ 12 years subgroup (44% and 56%, respectively) and was comparable with the results seen with the placebo or etanercept group. The EAIR during the Entire treatment period was similar between the two age strata (175.4 and 177.2 per 100 PY in Any secukinumab groups).

Weight
The incidence of TEAEs Up to Week 12 in subjects who received Any secukinumab dose was lowest in the < 25 kg subgroup (46 %) compared to the ≥ 25 kg - < 50 kg (49 %) and the ≥ 50 kg body weight subgroups (55%). The incidence of SAEs during the placebo-controlled period or up to Weeks 24 and 52 were comparable between the weight subgroups and no clinically meaningful differences were seen between the secukinumab and the etanercept groups.

The overall EAIRs of TEAEs (per 100 PY) in secukinumab treated subjects in different weight subgroups were comparable: 191 in <25 kg, 174 in ≥ 25 kg - < 50kg group, and 177 in ≥50 kg group

Gender
No gender specific trends were observed in the overall frequency of AEs for the pooled pediatric population. The EAIR of AEs during the Entire treatment period was 200.5 per 100 PY in female subjects and 152.4 per 100 PY in male subjects.

Race and ethnicity
No specific trends were observed in subgroup analysis by race and ethnicity.

8.2.8. Specific Safety Studies/Clinical Trials

There were no specific safety studies conducted by the Applicant for this submission.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignancies were reported during the pediatric development program up to the specified cut-off dates of September 18, 2019 for Study A2310 and November 14, 2019 for Study A2311. This is not unexpected given the duration of the studies and the likelihood of a long latency for the onset of malignancy.

From the approved COSENTYX label:

> 13 NONCLINICAL TOXICOLOGY
> 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
> Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of COSENTYX. Some published literature suggests that IL-17A directly promotes cancer cell invasion in vitro, whereas other reports indicate IL17A promotes T-cell mediated tumor rejection. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

The original approval letter included a post-marketing requirement (PMR 2848-2) to conduct a postmarketing prospective, long-term, observational study to assess a signal of a serious risk of malignancy which occurs infrequently and/or has a long latency compared to other therapies used in the treatment of *adults* with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy in a real world clinical setting.

Human Reproduction and Pregnancy

Three cases of pregnancy were reported, one in the etanercept group and two in the secukinumab Low dose group:

Subject A2310-(b) (6): Pregnancy was reported in this 16-year-old female who received secukinumab 150 mg (Low dose) during the period beyond 52 weeks (i.e., Extension period). The study drug was discontinued on Day 540 due to pregnancy, and the subject was discontinued from the treatment period on Day 557. Based on the pregnancy follow-up information, the subject had a normal vaginal delivery of a newborn with normal height and weight and without any congenital anomalies. Two days after birth, the

neonate was diagnosed with jaundice (treated with phototherapy) and pneumonia (treated with antibiotics). By the sixth day after birth, these events had resolved.

Subject A2310 (b) (6): Pregnancy was reported in this 15-year-old female who received secukinumab 150 mg (Low dose) during the period beyond 52 weeks (i.e., Extension period). The study drug was discontinued on Day 504 due to pregnancy. The patient underwent elective termination of pregnancy on Day 554 and was discontinued from the Extension period on Day 567.

The approved label does not advise a pregnancy registry that monitors pregnancy outcomes in female patients exposed to secukinumab during pregnancy.

Pediatrics and Assessment of Effects on Growth

The safety and efficacy of secukinumab in patients ≥ 6 years of age is discussed throughout this review. The pediatric study requirement for ages 0 to less than 6 years was waived because necessary studies are impossible or highly impracticable; the number of pediatric patients under the age of 6 years with psoriasis is so small.

The Applicant evaluated physical development and maturation by summarizing measurements as well as growth percentiles for height, weight, and BMI. There were no reported clinically meaningful differences between treatment groups in the changes of physical development and maturation endpoints over time.
Due to the limited number of evaluable patients <12 years (n=3) in the treatment period beyond Week 52 in Study A2310, the impact of secukinumab on physical development beyond 1 year of treatment cannot be assessed at this point in this <12 years subgroup.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reports of overdose during the pediatric development program. During Study A2310, an IRT error led to extra dosing with secukinumab in 36 subjects. Refer to the previous discussion under 7.4.5. Analysis of Submission-Specific Safety Issues for a synoptic accounting of pertinent safety issues in subjects affected by this additional exposure.

There is no information suggesting addiction or abuse potential with secukinumab.

Rebound was defined as a worsening of PASI of > 125% of the value from baseline, or occurrence of rebound psoriasis or pustular, or erythrodermic or more inflammatory psoriasis occurring within 8 weeks of stopping therapy.

In Study A2310, one patient each in the secukinumab High, placebo, and etanercept group had events matching the definition of rebound. The potential for risk for rebound with the treatment of secukinumab appears low.

- Subject A2310-[redacted](b) (6) in the secukinumab High dose group reported erythrodermic psoriasis during the Follow up Period, 34 days after the last secukinumab dose.

In Study A2311, no subjects reported events corresponding to the definition of rebound as of data cutoff.

Additional Submission/Safety Issues
The cut-off dates for safety data included in the original sBLA submission were September 18, 2019 for Study A2310 and November 14, 2019 for Study A2311.
A 120-day Safety Update was submitted on November 18, 2020 summarizing new safety information reported to the Novartis global safety ARGUS database since the cutoff dates – specifically, September 18, 2019 to September 15, 2020 for the ongoing study A2310 and November 14, 2019 to September 15, 2020 for the ongoing study A2311.
The safety update also included the most recent Development safety update report (DSUR) from June 26, 2019 to June 25, 2020, as well as information from Study A2311 up to the cut-off date of May 28, 2020 for the Week 52 analysis.

Safety updates for both pediatric psoriasis studies, followed by a summary of the 52-week analysis of the open-label study A2311, then discussion of relevant data from the DSUR will be addresed in more detail below.

➢ A2310 and A2311
In the safety update for studies A2310 and A2311 there were no deaths reported; however, five new non-fatal SAEs were listed:

- facial cellulitis requiring hospitalization and metronidazole plus amoxicillin+clavulanic acid 738 days after first dose of study drug in a 14-year-old male with a prior dental infection who was receiving Low dose secukinumab. No change was made to study treatment and complete recovery was documented.
- acute appendicitis requiring hospitalization, appendectomy, and cefuroxime 229 days after first receiving high dose secukinumab in a 10-year-old female. No change was made to study treatment and complete recovery was documented.

- tonsillitis requiring hospitalization, ceftriaxone, and amoxicillin 436 days after first dose of study treatment in a 17-year-old female who was receiving high dose secukinumab. No change was made to study treatment and complete recovery was documented.
- intentional self-injury (superficial cuts on wrist) in a 14-year-old female with known anxiety and depression prior to study entry was reported to occur 307 days after first dose of low dose secukinumab. Study treatment was discontinued and complete recovery was documented.
- lactose intolerance

These five additional SAEs did not show new or unexpected signals and are consisitent with the known safety profile for secukinumab.

- Study A2311

In the initial sBLA S-043 submission, data up to the Week 24 cut-off date (November 14, 2019) for Study A2311 were included. The safety update report includes all safey data accrued until the last subject reached the Week 52 visit (May 28, 2020), therefore data beyond Week 52 for most subjects were submitted and based on 97.8 subject-years of exposure to any secukinumab dose.

Table 19. Duration of exposure to study treatment – Entire treatment period (A2311 Safety set)

	Low Dose secukinumab n=42	High Dose secukinumab n=42	Any secukinumab n= 84
Exposure ≥ 52 weeks	40 (95%)	37 (88%)	77 (92%)
Mean days of exposure	442	409	425
Median days of exposure	449	431	448

Source: Modified Sponsor Table 2-3 from 120 day safety update

As of the Week 52 cut-off date, 77/84 (92%) of the enrolled subjects remained in the study. Two subjects from the high dose group (A2311[(b) (6)] with mild ALT and AST elevations and A2311-[(b) (6)] with mild hemorrhagic diarrhea) discontinued study treatment. No subject from the low dose group discontinued treatment due to an AE.

There did not appear to be dose-response relationships for the incidence of overall AEs, SAEs, AEs leading to study treatment discontinuation or AESIs of hypersensitivity, neutropenia, and infections. As previously noted, there was one report of mild hemorrhagic diarrhea that led to study treatment discontinuation, although a diagnosis of Crohn's disease or ulcerative colits was not made, as well as a single report of a new SAE of suicidal behavior.

DSUR

The DSUR includes safety information collected from all Novartis sponsored global and local interventional trials of which 5 trials are completed and 25 trials are still ongoing.
During the reporting period, 362 SAEs were initially reported in 283 cases. Out of these, 41 SAEs from 37 cases were listed as being possibly related to secukinumab.
Additionally, 1 death [(b) (6)]) was received as a medically relevant follow-up during the current reporting period.

Subject [(b) (6)] was a 74-year-old man who participated in ongoing Study

CAIN457ADE08 titled "A randomized, multicenter 28 week study to compare the efficacy and safety of combining Cosentyx (secukinumab) (4-weekly, 300 mg s.c.) with a lifestyle intervention to Cosentyx therapy alone in adult patients with moderate to severe plaque-type psoriasis and concomitant metabolic syndrome, followed by a 28 week extension period." At 8 Months, 3 Weeks, 2 Days following first dose, the subject was recorded as permanently discontinuing study treatment with an ultimate outcome of death from metastatic malignant melanoma.

A pertinent listing follows with select narrative insight (if provided) for 120 day safety update/ product specific safety issues:

Ongoing psoriasis studies
Infections: 2 new serious infections were received during the reporting interval

- 1 SAE case of acute appendicitis occurred in the pediatric psoriasis program (A2311)
- 1 device-related Staphylococcus aureus infection (right knee prosthesis) was reported in a 56-year-old male while enrolled in a plaque psoriasis study (A2325) who received first blinded dose of study drug 5 months prior.

According to the DSUR, SAEs for other identified and potential risks (neutropenia, hypersensitivity, malignancy, MACE, IBD, and Suicidal Behavior) were not received during the reporting period for ongoing psoriasis studies.

Ongoing studies across all other indications:
Infections:

- 1 event of Staphylococcal aureus septic arthritis affecting the left shoulder was reported in a 78-year-old type 2 diabetic, hypertensive, dyslipidemic male enrolled in phase 2 study to assess secukinumab in patients wih giant cell arteritis. The subject received blinded study medication plus prednisolone 3 months prior to developing a septic joint.
- 1 SAE of varicella was documented in a 61-year-old male enrolled in a randomized, double-blind study to evaluate the efficacy of secukinumab monotherapy compared with adalimumab monotherapy In patients with active psoriatic arthritis. The subject had come into close contact with a family member with chicken pox.
- A 19-year-old male with underlying ankylosing spondylitis developed an anal abscess approximately 4 months after starting secukinumab (unknown dose).
- A 36-year-old male with underlying ankylosing spondylitis developed pneumonia approximately 7 months after starting secukinumab (unknown dose) requiring hospitalization.
- A 56-year-old female with hidradenitis suppurativa was diagnosed with acute bacterial meningitis 1 month after the first dose of blinded study medication
- A 27-year-old female with with hidradenitis suppurativa was diagnosed with covid 19 infection 1 month after the first dose of blinded study medication

- A 39-year-old female with hidradenitis suppurativa and discoid lupus erythematosus developed right submandibular abscess secondary to actinomycosis 6 months after receiving blinded study medication for hidradenitis suppurativa.

MACE events:

One event each of "acute" myocardial infarction, myocardial infarction, and cerebrovascular accident were listed within the tabulation of subjects in all trials who were administered secukinumab. Other cardiac events reported were single events of cardiac arrest, cardiogenic shock, and ventricular fibrillation.

Inflammatory bowel disease:

- A 29-year-old male was diagnosed with ulcerative colitis 2 years after being started on blinded study medication during run-in phase then on an unknown date began open label secukinumab for treatment of axial spondyloarthritis.
- A 53-year-old male with underlying ankylosing spondylitis was diagnosed with ulcerative colitis 4 months after receiving first dose of secukinumab (unknown dose).
- A 50-year-old female with underlying ankylosing spondylitis was diagnosed with ulcerative colitis approximately 2 months after receiving first dose of secukinumab (unknown dose).
- A 48-year-old female with hidradenitis suppurativa developed inflammatory bowel disease within approximately 2.5 months after the start of blinded study medication.
- A 43-year-old male with hidradenitis suppurativa developed ulcerative colitis 21 days after starting blinded study medication.

Gastrointestinal events:

- A 72-year-old male developed a duodenal ulcer hemorrhage within one and half months after the start of secukinumab (unknown dose) while concomitantly taking clopidogrel and celecoxib for prior stroke and arthritis.
- A 52-year-old female with underlying ankylosing spondylitis and Crohn's disease on methotrexate was diagnosed with a "t-colon" perforation (large intestinal perforation) 1 year after the first dose of secukinumab.
- A 28-year-old male with underlying ankylosing spondylitis taking concomitant celecoxib and methylprednisolone developed an ileal ulcer approximately 1 year after the first dose of secukinumab.
- 51-year-old with underlying ankylosing spondylitis and ulcerative colitis was documented to have multiple rectal ulcers after approximately 1 year after receiving secukinumab.
- A drug-induced liver injury event was listed for a subject who received secukinumab although details were not provided.

Malignancy:

- One event each of acute myeloid leukemia, breast cancer, hepatic cancer, pancreatic cancer, squamous cell lung cancer, as well as two malignant melanoma events were

listed within the tabulation of subjects in all trials who were administered secukinumab.
- Narrative was provided for a 75-year-old male enrolled in an ankylosing spondylitis study (CAIN457FUS06) who was diagnosed with hepatic adenocarcinoma 11 months following first dose of study medication.

The information provided in the update did not change the risk-benefit assessment for use of secukinumab for treatment of pediatric patients with moderate to severe plaque psoriasis. No new adverse drug reactions were identified in the analyses for the 120-Day Safety Update. However, many ongoing studies were blinded at the time of the analyses for the update limiting the conclusions that may be drawn from the data.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Within the most recent Periodic Adverse Drug Experience Report (PADER) for BLA 125504 covering 2019-2020 that was submitted on March 2, 2021, the Applicant stated 21,159 patients and healthy individuals have received secukinumab in Novartis-sponsored clinical studies. The Applicant established the exposure across all indications from studies with a final or interim analysis Clinical Study Report (CSR) completed prior to December 25 , 2020 to be 20,961 adult subjects, equivalent to 34,907.50 subject-years. To date, the COSENTYX cumulative patient exposure since the International Birth Date (December 26, 2014), is over (b) (4) patient-treatment years (PTY) with evaluation of COSENTYX in 100+ studies.
Safety considerations that arose from prior experience with secukinumab are addressed in the currently approved Risk Management Plan. The Applicant has identified no new safety signals in their postmarket safety surveillance program. However, the Division has identified fatal post-marketing cases of neutopenia and sepsis and intends to modify labeling accordingly.

Expectations on Safety in the Postmarket Setting

The clinical review identified no apparent potentially important differences in how secukinumab was administered and used in the clinical trial versus its expected use in the postmarket setting that could lead to increased risk. However, the review by Center for Devices and Radiological Health (CDRH) identified deficiencies in the Applicant's analyses of the device constituent parts of the combination product. According to the CDRH review, the provided literature studies did not validate the device specifications for activation of the Needle Safety Device (NSD) or for removal of the Rigid Needle Shield (RNS) for pediatric use. Failure to activate needle safety and properly remove the needle cap leads to incomplete injections and needle sticks, especially in a vulnerable population (i.e., pediatric patients).
Based on these listed device deficiencies, an adult caregiver will need to administer COSENTYX pre-filled syringe in pediatric patients.

Post-marketing surveillance is routine and ongoing.

A postmarketing requirement (PMR 2848-2) and commitment (PMC 2848-6) issued at the time of original approval remain outstanding for the plaque psoriasis program:

- PMR 2848-2 requires a postmarketing prospective, long term, observational study to assess the long term safety of secukinumab, with a primary outcome of malignancies, compared to other therapies used in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy in a real world clinical setting.
- PMC 2848-6 commits the Applicant to conduct a clinical study evaluating the treatment effect and safety profile of a higher exposure (e.g., 450 mg) of secukinumab in psoriasis subjects with higher body weight and to explore the option of exposure escalation (e.g., 450 mg) for those who cannot achieve the therapeutic goal at the 300 mg dose.

8.2.11. Integrated Assessment of Safety

The data from pediatric patients 6 years of age and older provided in this supplement revealed a safety profile generally similar to that seen in the adult psoriasis population.
The risk of COSENTYX is consistent with the known safety profiles in other systemic agents used for psoriasis. This includes risks of immunosuppression with serious and in some cases opportunistic or unusual infections, reactivation of latent tuberculosis, neutropenia, inflammatory bowel disease, and hypersensitivity events. Based on the available safety data, the expectation is that the postmarketing safety experience for pediatric patients 6 years of age and older will likely be similar to the experience of those in adults.

8.3. Summary and Conclusions

8.3.1. Statistical Issues

There were no major statistical issues affecting overall conclusions.

8.3.2. Conclusions and Recommendations

The Applicant submitted efficacy and safety results from Study CAIN457A2310 to meet the PREA requirements per the Agency request of the approval letter of secukinumab on January 21, 2015. The study was an international study and enrolled a total of 162 subjects who were randomized in a 1:1:1:1 ratio into one of four treatment groups (etanercept, secukinumab low dose group, secukinumab high dose group, or placebo group). Further, subjects randomized to secukinumab treatment arms were stratified by age (<12 years and ≥12 years) and weight (<25

kg, 25 to <50 kg, and ≥50 kg). Subjects randomized to secukinumab treatment arms (low dose and high dose) received a dose based on the weight category as follows: subjects weighing ≥50 kg received 150 mg (low dose group) and 300 mg (high dose group), subjects weighing 25 to <50 kg received 75 mg (low dose group) and 150 mg (high dose group), and subjects weighing <25 kg received 75 mg for both dose groups. The efficacy results for this study were statistically significant (see Table 8 and Table 10) and were consistent with the results of the adult's trials (see Table 13). Results of subgroup analyses by weight groups for Week 12, Week 24, and Week 56 (see Table 11) indicate, although the number of subjects are small in these subgroups to make a meaningful conclusion, that the 300 mg dose does not offer meaningful benefits over the 150 mg dose for the ≥50 kg weight group. In addition, while 150 mg dose appears to provide only a slightly higher efficacy than the 75 mg for the 25 to < 50kg weight group at Week 12, the efficacy results for Week 24 and Week 52 do not provide support for 150 mg over the 75 mg for this weight group. Thus, we conclude that the 75 mg is the recommended dose for the 25 to < 50 kg weight group.

In addition to demonstration that both low and high doses of secukinumab were statistically superior to the placebo for both co-primary efficacy endpoints (p-values less than 0.0001), comparison of secukinumab Ctrough values between children and adults with plaque psoriasis indicated that most of Ctrough values obtained from the majority of pooled pediatric dosing groups [75 mg for body weight (BW) <25 kg; 75 mg BW ≥25 kg and <50 kg; 150 mg for BW ≥25 kg and <50 kg; and 150 mg for BW ≥50 kg] were within the adult reference range. However, secukinumab Ctrough values in pediatric subjects ≥50 kg on 300 mg were considerably higher than Ctrough values in adults on 300 mg dose. At certain time points, the median/mean secukinumab Ctrough values in this pediatric dosing group were about 2-fold as high as those of adults following 300 mg dose. Additionally, subgroup analyses showed that PASI response rate/improvement from baseline at Week 12 in pediatric subjects who weighed ≥50 kg with severe disease at baseline was numerically similar between 150 mg and 300 mg treatment groups. (b) (4)

The Applicant provided substantial evidence of effectiveness in the treatment of plaque psoriasis for doses 75 mg in pediatric patients weighing <50 kg and 150 mg in pediatric patients weighing ≥50 kg and conducted a comprehensive assessment of the safety of COSENTYX in the target population. The size of the safety database and the safety evaluations were adequate to identify treatment emergent adverse reactions. In this reviewer's opinion, the Applicant provided adequate evidence of safety of COSENTYX, and no safety signals that would preclude an approval were identified.

An approval for BLA 125504/Supplement 43 is recommended. The labeling will be updated to describe COSENTYX treatment for patients 6 years and older with moderate-to-severe plaque psoriasis who are candidates for systemic or phototherapy.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee was not convened for this supplement. No novel or complex regulatory issues were identified that required an open forum discussion for this supplement.

10 Pediatrics

This submission is in response to a PREA PMR.
A Pediatric Review Committee meeting was held on February 16, 2021, to discuss the submitted supplemental clinical study results. The committee agreed with the Division that studies A2310 and A2311 provided adequate pediatric data to be included in labeling and that the Applicant has fulfilled the postmarketing requirement as stated in the approval letter for COSENTYX.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling negotiations with the Applicant were pending as the clinical review was being finalized. Labeling recommendations have been incorporated into the draft label.

Table 20. Summary of Major Labeling Changes

Section	Additional Comments
2 DOSAGE AND ADMINISTRATION	• Binary weight based dosing added for pediatric patients. • 75mg/0.5mL prefilled syringe presentation added with language excluding self-administration by pediatric patients • (b) (4)
5 WARNINGS AND PRECAUTIONS	Language added to strengthen neutropenia risk
6 ADVERSE REACTIONS	The safety profile of the pediatric psoriasis trials are discussed
14 CLINICAL STUDIES	Pediatric plaque psoriasis clinical response is discussed in 14.2
16 HOW SUPPLIED	75 mg/mL pre-filled syringe

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13 Postmarketing Requirements and Commitment

No postmarketing requirements or commitments are recommended based on this supplement.

14 Division Director (DHOT) Comments

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP) Comments

16 Division Director (OB) Comments

17 Division Director (Clinical) Comments

I concur with the review team conclusion that the efficacy and safety data submitted by the Applicant support the approval of extension of the indication to pediatric subjects 6 years of age and older with moderate to severe plaque psoriasis who are candidates for systemic or phototherapy.

(b) (4)

I concur with CDRH review conclusion that identified device deficiencies preclude approval of self-administration of COSENTYX prefilled syringe by pediatric patients. The label will indicate that an adult caregiver will need to administer COSENTYX pre-filled syringe in pediatric patients.

18 Office Director (or designated signatory authority) Comments

19 Appendices

19.1. References

See footnotes for references.

19.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for secukinumab. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were studies CAIN457A2310 and CAIN457A2311, which provided the primary data to establish effectiveness and safety of this product.

The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Covered Clinical Study (Name and/or Number): CAIN457A2310

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 335		
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): 0		
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: _____ 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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): CAIN457A2311

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 80		
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): 0		
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: _____ 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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

19.1. OCP Appendices (Technical documents supporting OCP recommendations)

[Add Text and Figures/Tables Here]

19.2. Additional Clinical Outcome Assessment Analyses

[Add Text and Figures/Tables Here]

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KIMBERLE P SEARCY
05/28/2021 01:26:33 PM

CANDACE GOMEZ-BROUGHTON
05/28/2021 01:37:58 PM

YUNZHAO REN
05/28/2021 01:39:24 PM

CHINMAY SHUKLA
05/28/2021 01:58:52 PM

JIANG LIU
05/28/2021 02:00:43 PM

HYOYOUNG CHOO-WOSOBA
05/28/2021 02:02:09 PM

MATTHEW W GUERRA
05/28/2021 02:03:47 PM

MOHAMED A ALOSH
05/28/2021 02:35:53 PM

MARYJOY G MEJIA
05/28/2021 02:40:03 PM

AMY S WOITACH
05/28/2021 02:42:29 PM

TATIANA OUSSOVA
05/28/2021 03:26:54 PM