NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	sNDA 205437/013
Priority or Standard	Priority
Submit Date(s)	October 25, 2023
Received Date(s)	October 25, 2023
PDUFA Goal Date	April 25, 2024
Division/Office	Division of Dermatology and Dentistry/Office of Immunology and Inflammation
Review Completion Date	
Established/Proper Name	Apremilast
(Proposed) Trade Name	Otezla
Pharmacologic Class	Inhibitor of phosphodiesterase 4 (PDE4)
Code name	CC-10004
Applicant	Amgen, Inc.
Dosage form	Tablets
Applicant proposed Dosing Regimen	30 mg twice daily for adult patients and for pediatric patients (≥ 50 kg) and 20 mg twice daily for pediatric patients (20 kg to <50 kg).
Applicant Proposed Indication(s)/Population(s)	For the treatment of pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	200965009 |Plaque psoriasis (disorder)|
Recommended Dosing Regimen	To reduce the risk of gastrointestinal symptoms, titrate to the recommended dosage according to the titration schedule of the USPI. The recommended dose is 30 mg twice daily for adult patients and for pediatric patients (≥ 50 kg) and 20 mg twice daily for pediatric patients (20 kg to <50 kg).

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Dawn Williams
Nonclinical Reviewer	N/A
Nonclinical Team Leader	N/A
Office of Clinical Pharmacology Reviewer(s)	Satish Sarash
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla
Clinical Reviewer	Hamid Tabatabai
Clinical Team Leader	David Kettl
Statistical Reviewer	Matthew Guerra
Statistical Secondary Reviewer	Kathleen Fritsch
Cross-Disciplinary Team Leader	David Kettl
Division Director (DHOT)	N/A
Division Director (OCP)	N/A
Division Director (OB)	N/A
Division Director (OHOP)	N/A
Office Director (or designated signatory authority)	N/A

Additional Reviewers of Application

OPQ	Afsana Akhter
Microbiology	N/A
OPDP	Montherson Saint Juste
OSI	N/A
OSE/DEPI	N/A
OSE/DMEPA	Amy Bao
OSE/DRISK	N/A
Other	N/A

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

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer			Section:	**Select one:** ___ Authored ___ Approved
	Signature:			
Nonclinical Supervisor			Section:	**Select one:** ___ Authored ___ Approved
	Signature:			
Clinical Pharmacology and Pharmacometrics Reviewer	Satish Sharan, Ph.D.	OCP/DIIP	Section: 6	**Select one:** _X_ Authored ___ Approved
	Signature: Satish Sharan -S Digitally signed by Satish Sharan -S Date: 2024.04.25 15:04:00 -04'00'			
Clinical Pharmacology Team Leader	Chinmay Shukla, Ph.D.	OCP/DIIP	Section: 6	**Select one:** ___ Authored _X_ Approved
	Signature: Chinmay Shukla -S Digitally signed by Chinmay Shukla -S Date: 2024.04.25 15:01:25 -04'00'			
Pharmacometrics Team Leader	Youwei Bi, Ph.D.	OCP/DPM	Section: 6	**Select one:** ___ Authored _X_ Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2024.04.25 15:12:46 -04'00'			
			Section:	**Select one:** ___ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Hamid Tabatabai, MD	OII/DDD	Sections:1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.1-2	**Select one:** _X_ Authored ___ Approved
	Signature: Hamid Tabatabai -S Digitally signed by Hamid Tabatabai -S Date: 2024.04.25 15:09:13 -04'00'			
Clinical Team Leader	David Kettl, MD	OII/DDD	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.1-2	**Select one:** __ Authored _X_ Approved
	Signature: David L. Kettl -S Digitally signed by David L. Kettl -S Date: 2024.04.25 14:22:23 -04'00'			
Division Director (Clinical)	Tatiana Oussova, MD, MPH		Sections: All	**Select one:** __ Authored __X Approved
	Signature:			
Deputy Division Director (Clinical)			Sections:	**Select one:** __ Authored __ Approved
	Signature:			
Statistical Reviewer	Matthew Guerra, PhD	CDER/OTS/OB/DBIII	Sections: 8.1, 8.3	**Select one:** _X_ Authored __ Approved
	Signature: Matthew W. Guerra -S Digitally signed by Matthew W. Guerra -S Date: 2024.04.25 15:18:32 -04'00'			
Statistical Secondary Reviewer	Kathleen Fritsch, PhD	CDER/OTS/OB/DBIII	Sections: 8.1, 8.3	**Select one:** __ Authored _X_ Approved
	Signature: Kathleen S. Fritsch -S Digitally signed by Kathleen S. Fritsch -S Date: 2024.04.25 15:23:03 -04'00'			

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
MI	multiple imputation
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

OTEZLA (apremilast) is a Phosphodiesterase 4 (PDE-4) inhibitor approved by the FDA for the indications of treatment of the following:

- Adult patients with active psoriatic arthritis
- Adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy
- Adult patients with oral ulcers associated with Behçet's Disease

The Applicant submitted Prior Approval Efficacy Supplement-13 under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act to add the indication of treatment of pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy to the OTEZLA label.

The Applicant proposes to add to the currently approved psoriasis indication of "[indicated for the treatment of] adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy" the following: "[indicated for the treatment of] pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy" in labeling upon approval of this supplement.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Trial CC-10004-PPSO-003, supporting efficacy supplement-13, was conducted in pediatric subjects (ages 6 to 17 years, inclusive) with a weight of ≥20 kg, with moderate to severe plaque psoriasis (defined as affected BSA ≥10%, sPGA ≥3, and PASI ≥12) of ≥6-month duration at the screening visit, inadequately controlled by or inappropriate for topical therapy for psoriasis who were eligible for systemic therapy or phototherapy. This trial had a 16-week placebo-controlled period followed by a 36-week apremilast-extension period. Subjects between 20 kg to <50 kg received dose titration to 20 mg BID, and subjects ≥50 kg received dose titration to 30 mg BID at the start of their treatment with apremilast.

The primary efficacy endpoint for this trial was the proportion of subjects achieving sPGA response (sPGA score of 0 (clear) or 1 (almost clear) with ≥2-grade reduction from baseline) at Week 16. The major secondary efficacy endpoints (pre-specified and controlled for multiplicity, for which the Applicant seeks labeling claims) was the proportion of subjects achieving ≥75% reduction in Psoriasis Area Severity Index (PASI-75) from baseline at Week 16.

Substantial evidence of efficacy (SEE) was demonstrated based on one adequate and well-controlled clinical investigation supported by confirmatory evidence (approval of the drug product for adult patients with moderate to severe psoriasis in 2014) from the analysis of the

results of the primary efficacy endpoint. Analysis of the results of the key secondary efficacy endpoint was supportive of efficacy.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk profile of apremilast for the treatment of moderate to severe plaque psoriasis in pediatric subjects (between 6 to 17 years of age, inclusive; and a weight of ≥20 kg) is favorable, based on data from one adequate and well-controlled clinical trial, CC-10004-PPSO-003 (N=245).

- Efficacy: Apremilast was statistically superior to the placebo for the primary and the key secondary efficacy endpoint (prespecified in the protocol and controlled for multiplicity), for the ITT population at Week 16:
  i. For the primary efficacy endpoint of sPGA response (sPGA score =0 or 1 with ≥2-grade reduction from baseline), the apremilast group achieved a response of 33.1%, compared to 10.8% for the placebo group, an adjusted difference of 22.3% (2-sided 95% CI: [12.2%, 32.4%], p-value<0.001).
  ii. For the key secondary efficacy endpoint of PASI-75 Response, the apremilast group achieved a response of 45.7%, compared to 16.0% for the placebo group (an adjusted difference of 29.7% (2-sided 95% CI: [17.9%, 41.6%], p-value<0.001).
- Safety: Analysis of the primary safety database for trial CC-10004-PPSO-003 did not identify any new safety signals, was qualitatively similar to safety data from clinical trials for apremilast conducted for adult subjects with moderate to severe plaque psoriasis and was adequate to characterize the safety profile of apremilast for the treatment of moderate to severe plaque psoriasis in pediatric subjects. Adverse Reactions reported through Week 16 in ≥5% of subjects treated with apremilast (and ≥1% more frequently than subjects receiving placebo) compared to subjects treated with placebo included diarrhea (19.6% vs. 10.0%), abdominal pain (19.6% vs. 10.0%), nausea (19.6% vs. 2.5%), vomiting (17.8% vs. 2.5%), dyspepsia (6.1% vs. 0), headache (10.4% vs. 5.0%), nasopharyngitis (6.1% vs. 3.8%), and pyrexia (6.1% vs. 1.3%).

The available results support expansion of the indication of "treatment of adult patients with plaque psoriasis" to include pediatric patients with moderate to severe plaque psoriasis in the "Indications and Usage Section" of the label, and inclusion of the efficacy and safety data from trial CC-10004-PPSO-003 in Sections 14 and 6 of the OTEZLA label. Apremilast offers an alternative treatment option to a number of FDA-approved products with an acceptable benefit-risk profile for this target population. None of the FDA-approved treatments provides a permanent cure or universal response, and all are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is still a need for additional therapeutic options for this subgroup of patients with plaque psoriasis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Psoriasis is a common, chronic, inflammatory multi-system disorder, which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the US is approximately 2-3%, of which an estimated 80 percent have mild to moderate disease, while 20 percent have moderate to severe psoriasis affecting more than 5 percent of the body surface area. One third of patients have concomitant arthritis. Other comorbidities include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome.[1]	Plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and comorbidities.
Current Treatment Options	Available FDA-approved systemic treatment options for pediatric patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy include Tumor Necrosis Factor Inhibitor (e.g., Etanercept), IL-12/IL-23 blocker (e.g., ustekinumab), and IL-17 A blockers (e.g., secukinumab, ixekizumab).	There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of pediatric patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. None of these treatments provides a permanent cure or universal response and all of these products are associated with one or more potential risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.

[1] Menter A et al. Guidelines of care for the management of psoriasis and psoriatic arthritis Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008; 58:826-50.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The primary efficacy endpoint for sPGA response (sPGA score =0 or 1 with ≥2-grade reduction from baseline) at Week 16 for ITT population was achieved in 33.1% of subjects in apremilast group compared to 10.8% of subjects in placebo group in trial CC-10004-PPSO-003 (an adjusted difference of 22.3%). The major secondary efficacy endpoints of PASI-75 at Week 16 for ITT population were achieved in 45.7% of subjects in apremilast group compared to 16.0% of subjects in placebo group in trial CC-10004-PPSO-003 (an adjusted difference of 29.7%).	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trial CC-10004-PPSO-003 was adequate and well-controlled. The results are persuasive. Achievement of clear or almost-clear skin is an intrinsically meaningful outcome for a cutaneous disease such as psoriasis. The data suggest that a pediatric patient with moderate to severe plaque psoriasis treated with apremilast 20 mg or 30 mg BID (according to their baseline weight category) is likely to achieve clear or almost clear skin by Week 16.
Risk and Risk Management	Hypersensitivity, diarrhea, nausea, vomiting, depression, and weight decrease are labeled risks of treatment in the OTEZLA label.	The safety profile of apremilast has been adequately characterized by the premarket and Postmarket safety data for psoriasis, psoriatic arthritis, and oral ulcers of Behcet's disease. Prescription labeling, patient labeling (b) (4) (b) (4) and routine pharmacovigilance are adequate to manage the potential risks of the product.

1.4. Patient Experience Data

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

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	CDLQI
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	sPGA, BSA, PASI
		☐	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		
	x	Patient-focused drug development or other stakeholder meeting summary reports		Patient-focused drug development meeting for psoriasis held by the FDA on 3/17/2016
	☐	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

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution.[2] Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines which trigger and perpetuate the inflammatory cascade.[3]

In the U.S. and Canada, prevalence as high as 4.7% have been reported (Feldman, 2015). It is estimated that approximately 7.5 million people in the United States have psoriasis. Approximately 80 percent of those affected with psoriasis have mild to moderate disease, while 20 percent have moderate to severe psoriasis affecting more than 5 percent of the body surface area. The most common form of psoriasis is plaque psoriasis, affecting about 80 to 90 percent of patients with psoriasis.[4]

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35–50%, it is before the age of 20 years. The average age of onset is earlier in women than in men (Feldman, 2015).

The natural history of psoriasis is chronic with intermittent remissions. Although plaque psoriasis is the most common presentation, other forms of psoriasis include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, most frequently in association with psoriatic arthritis. A diagnosis of psoriasis can be made by history and physical examination in most cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, and nummular eczema. Occasionally, a skin biopsy is performed to rule out other conditions (Feldman, 2015).

The presentation of psoriasis in the pediatric population can be different from that in adults. Psoriasis in infants often presents with involvement of the diaper area. Infants with diaper-area

[2] Feldman, Steven R., MD. PhD; Epidemiology, Clinical Manifestations, and Diagnosis of Psoriasis; UpToDate.com; updated December 9, 2015

[3] Blauvelt, Andrew and Ehst, Benjamin D, Pathophysiology of Psoriasis; UpToDate.com; updated July 8, 2015

[4] Menter A, Gottlieb A, Feldman SR, Van Voorhees AS et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008 May; 58 (5):826-50.

involvement typically develop symmetrical, well-demarcated erythematous patches with little scale. Maceration may be present. Unlike irritant diaper dermatitis, the inguinal folds are usually involved. Affected infants may also have psoriatic plaques in other body areas. These plaques are often smaller and thinner than the psoriatic plaques in adult patients. In children, scalp involvement is a common and often initial presentation of chronic plaque psoriasis. In addition, children with chronic plaque psoriasis are more likely to have facial involvement than adults (Feldman, 2015).

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and suicidal ideation; neurotic, stress-related, or somatoform disorders; and personality and behavioral disorders.[5]

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development (PFDD) Meeting for psoriasis held by the Agency on March 17, 2016. Patients who attended the meeting described severe physical, social, and emotional impact including depression, anxiety, limitations on activities, embarrassment, stigma, and social discrimination. Patients shared their experiences with currently available therapies, and they described varying degrees of success in managing symptoms with these therapies. Patients stressed need to enlarge the treatment armamentarium, given current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments.

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected patients. At the PFDD meeting, patients discussed current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments. Therefore, development of additional safe and effective therapies continues to be an important goal. This is especially true for certain subgroups of patients with psoriasis, such as women during pregnancy and pediatric patients.

2.2. Analysis of Current Treatment Options

In clinical practice,[6] treatment options for patients with (mild to moderate) plaque psoriasis include targeted phototherapy (e.g., excimer light therapy with UVB at a wavelength of 308 nm), off-label use of topical calcineurin inhibitors tacrolimus or pimecrolimus (topical

[5] Korman, Neil; Comorbid Disease in Psoriasis; UpToDate.com; updated March 24, 2017.

[6] Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. *JAMA.* 2020;323 (19):1945–1960. doi:10.1001/jama.2020.4006

calcineurin inhibitors are not FDA-approved for topical treatment of psoriasis); and FDA-approved topical treatments including multiple classes/strengths/formulations of topical corticosteroids (TCS) approved for the indication of "treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (CSRD)", Vitamin D analogues, Keratolytic/Retinoid (tazarotene), Combination topical therapies [TCS/Vitamin D analogue, and TCS/Retinoid], Aryl hydrocarbon receptor (AhR) modulating agonist, and PDE-4 Inhibitors (e.g., roflumilast cream).

The FDA-approved systemic products for the treatment of (moderate to severe) plaque psoriasis belong to multiple categories, including Antimetabolite/Immunosuppressant (e.g., methotrexate), Tumor Necrosis Factor Inhibitor (e.g., infliximab, adalimumab, etanercept, certolizumab), Interleukin (IL) inhibitors: IL-12/IL-23 Inhibitor (e.g., ustekinumab), IL-17A Inhibitor (e.g., secukinumab, ixekizumab), IL-17A receptor antagonist (e.g., brodalumab), IL-17A and F antagonist (e.g., bimekizumab), IL-23 Inhibitor (e.g., guselkumab, tildrakizumab, risankizumab); T-Cell Inhibitor/ Immunosuppressant (e.g., cyclosporine), Retinoid (e.g., acitretin), PDE-4 Inhibitors (e.g., apremilast), tyrosine kinase 2 (TYK2) enzyme inhibitor (e.g., deucravacitinib), and phototherapy.

The proposed additional population (under supplement-013) for treatment with apremilast are pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Table 1 lists the systemic treatment options for moderate to severe plaque psoriasis which have received FDA-approval for use in pediatric patients.

Table 1. Summary of Systemic Treatment Armamentarium for Moderate to Severe Plaque Psoriasis (FDA-Approved for Pediatric Patients)

Product(s) Name/ Year Approved/ Minimum Age of Approval	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Tumor Necrosis Factor Inhibitors					
Etanercept (Enbrel) 2004, 2016 Approved for patients 4 years of age and older	Chronic moderate to severe psoriasis, candidates for photo-therapy or systemic therapy; 11/2016- approved for patients 4 years of age and older	50 mg SC twice weekly for 3 months, followed by 50 mg once weekly; <63 kg (138 lb)- 0.8 mg/kg SC weekly	From the label: 2 R, DB, PC5 trials PASI75 at 3 months 1-Etan-47% vs. 4% placebo 2-Etan-46% vs. 3% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies Warnings: demyelinating disease, worsen CHF, pancytopenia, malignancy, Hep B reactivation	Pregnancy: Available studies with use of etanercept during pregnancy do not reliably support an association between etanercept and major birth defects.
IL-12 and IL-23 Blocker					
Ustekinumab (Stelara) 2009 Approved for patients 6 years of age and older	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	For patients weighing <100 kg:45 mg SC initially and 4 weeks later, followed by 45 mg SC every 12 weeks For patients weighing >100 kg: 90 mg SC initially and 4 weeks later, followed by 90 mg SC every 12 weeks	From the label: 2 R, DB, PC trials PASI75 at week 12 1-uste (90 mg)-66% vs. uste (45 mg)-67% vs. 3% placebo 2-uste (90 mg)-76% vs. uste(45 mg)-67% vs. 4% placebo	Warnings and Precautions (W&Ps): Infections (serious bacterial, fungal, and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB.	Pregnancy: Limited data on the use of Ustekinumab in pregnant women are insufficient to inform a drug associated risk

Product(s) Name/ Year Approved/ Minimum Age of Approval	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
IL-17A Blocker					
Secukinumab (Cosentyx) 2015 Approved for patients 6 years of age and older	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	300 mg SC at Weeks 0, 1, 2, 3 and 4 followed by 300 mg SC every 4 weeks. For some patients, a dose of 150 mg may be acceptable	From the label: 4 R, DB, PC trials PASI75 at week 12 1-sec (300 mg)-82% vs. sec (150 mg)-71% vs. 4% placebo 2-sec (300 mg)-76% vs. sec (150 mg)-67% vs. 5% placebo 3-sec (300 mg)-75% vs. sec (150 mg)-69% vs. 0% placebo 4-sec (300 mg)-87% vs. sec (150 mg)-70% vs. 3% placebo	W&Ps: Infections (serious bacterial, fungal, and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment eval for TB.	Pregnancy: Limited available human data with secukinumab in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes.
Ixekizumab (Taltz) 2016 Approved for patients 6 years of age and older	Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	160 mg (two 80 mg injections) SC at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks	From the label: 3 R, DB, PC trials PASI75 at Week 12 1: Ixe (80 mg q2wk) 89% vs. 4% placebo 2: Ixe (80 mg q2wk) 90% vs. 2% placebo 3: Ixe (160 mg x 1, then 80 mg q2wk) 87% vs. 7% placebo	W&Ps: Infections (Upper respiratory tract, oral candidiasis, conjunctivitis, and tinea infections; Inflammatory Bowel Disease (Crohn's disease and ulcerative colitis); hypersensitivity reactions; pretreatment eval for TB.	Pregnancy: Available data from the published literature and the pharmacovigilance database with TALTZ use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

Source: adapted from Reviewer's Table 1 in BLA 761151 (Bimzelx, bimekizumab-bkzx) Multi-disciplinary Review and Evaluation (May 11, 2022) by Kevin Clark, MD.
Abbreviations: BW, Boxed Warning; CHF, congestive heart failure; DB, double-blind; Etan, etanercept; Hep B, hepatitis B; IL, interleukin; Ixe, ixekizumab; PC, placebo-controlled; q2wk, every 2 weeks; R, randomized; SC, subcutaneous; Sec, secukinumab; TB, tuberculosis; Uste, ustekinumab

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

OTEZLA (apremilast) was developed under IND 070270, submitted on September 21, 2013, and was approved by the Agency on March 21, 2014, for the treatment of adult subjects with active psoriatic arthritis (NDA 205437) and on September 23, 2014, for the treatment of subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy (NDA 206088, administratively closed on October 7, 2014). The following efficacy supplements have subsequently been approved by the Division of Dermatology and Dentistry (DDD) for the indication of plaque psoriasis:

- In April 2020, sNDA 205437-**008** Prior Approval Efficacy Supplement was approved to support the inclusion of psoriasis of the scalp efficacy claims in Section 14.2, and safety data in Section 6.1 of the prescribing information for the treatment of subjects with moderate to severe plaque psoriasis of the scalp.
- In December 2021, sNDA 205437-**011** Prior Approval Efficacy Supplement was approved to support the inclusion of efficacy claims for subjects with mild to moderate plaque psoriasis in Section 14.3 of the prescribing information, and to expand the indication from moderate to severe plaque psoriasis to plaque psoriasis (mild to severe).
- In July 2023, sNDA 205437-**012** Prior Approval Efficacy Supplement was approved to support the inclusion of efficacy claims for subjects with moderate to severe plaque psoriasis of the genital area in Sections 14.2 of the prescribing information.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed apremilast for the treatment of moderate to severe plaque psoriasis under the 505(b)(1) regulatory pathway. The Applicant conducted and submitted the results of the following two clinical studies issued as PREA PMRs and Written Requests (WR), following the initial approval in 2014 of NDA 205437 (initially NDA 206088) for the indication of plaque psoriasis, to broaden the patient population of plaque psoriasis included in the "INDICATION AND USAGE" section of the prescribing information for OTEZLA to include pediatric patients (between 6 to 17 years of age, inclusive; weight of ≥20 kg) with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

- A phase 2, open-label, PK/safety clinical study (CC-10004-PPSO-001) under PREA-PMR 2791-1, WR 1.
- A phase 3, randomized, double-blind (weeks 0-16), placebo-controlled clinical trial (CC-10004-PPSO-003) under PREA PMR 2791-2, WR 2.

Milestone interactions with the Applicant were the following:

- August 19, 2015: FDA Advice letter related to the design of study PPSO-001.
- June 27, 2018: Type C (pre-phase 3) meeting related to the dosing, study design, and SAP for trial PPSO-003.
- October 7, 2019: Type C meeting (WRO) related to study design for the long-term extension study PPSO-004.
- December 7, 2021: FDA Advice letter related to study PPSO-003 Amendment to change the target sample size.
- April 24, 2023: Type B (pre-sNDA) meeting (cancelled)- preliminary comments conveyed.

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

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate.

- For trial CC-10004-PPSO-003, the by-site efficacy results for Study CC-10004-PPSO-003 for the primary (sPGA success) and the key secondary efficacy endpoints (PASI-75) were generated by the statistical reviewer for this sNDA (Matthew Guerra, PhD). Considering the results of sensitivity analyses by site, magnitude of treatment effect and after removal of larger sites in Russia, conducted by Dr. Guerra which showed that efficacy results remained statistically significant; and the marketing history of apremilast (initial approval 2014), the Clinical and Statistical reviewers did not request a clinical study site inspection from the Office of Scientific Investigations.
- For Study CC-10004-PPSO-001, the Clinical Pharmacology review team requested bioanalytical site inspection by OSIS. The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the analytical site (b) (4) where bioanalysis of PK samples was conducted. The rationale for not conducting inspection was that OSIS had conducted a Remote regulatory Assessment (RRA) for the site (b) (4) (b) (4) and concluded that the data from the reviewed studies were reliable.

5 Nonclinical Pharmacology/Toxicology

Not applicable for this efficacy supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Apremilast tablets (OTEZLA) were approved in March 2014 under NDA 205437 for the treatment of active psoriatic arthritis in adults. In September 2014, apremilast tablets were approved for moderate to severe plaque psoriasis in adults under NDA 206088. NDA 206088 was administratively closed and merged with original NDA 205437 (see communication in DARRTS dated October 7, 2014, under NDA 206088).

At the time of original approval of NDA 206088, Studies in pediatric subjects 6 to 17 years were deferred and the following post marketing requirements (PMRs) were issued.

- 2791-1: A dose finding, pharmacokinetics and safety trial in subjects with moderate to severe plaque psoriasis between the ages of 6 to 17 years.
- 2791-2: A safety and efficacy trial in pediatric subjects with moderate to severe plaque psoriasis between the ages of 6 to 17 years.

A dose finding, pharmacokinetics and safety trial in subjects with moderate to severe plaque psoriasis between the ages of 6 to 17 years to fulfill PMR 2791-1 was previously submitted by the sponsor and was deemed to be adequate to fulfil PMR 2791-1 (NDA 205437, DAARTS review dated May 14, 2021).

In the current submission, the Applicant has submitted Phase 3 efficacy and safety report CC-10004-PPSO-003 and report 157167: CC-10004-PPSO-003 which contains population PK /exposure-response analyses report to fulfil PMR 2791-2. Study CC-10004-PPSO-003 had an exploratory objective to characterize apremilast pharmacokinetics and to explore the relationship between apremilast exposure and efficacy. Sparse PK blood samples were collected at Weeks 4, 8, 16, and 24 for measurement of apremilast in plasma. In addition, a population PK analysis and an exposure-response analysis for the primary efficacy endpoint (sPGA response) and key secondary efficacy endpoint (PASI-75 response) were conducted. Dosing regimen in pediatric patients with severe renal impairment was recommended based on modeling and simulation.

Recommendation

From a Clinical Pharmacology perspective, NDA 205437/S-013 is approvable. The Applicant has fulfilled PMR 2791-2 from a Clinical Pharmacology perspective.

6.2. General Dosing and Therapeutic Individualization

General Dosing

Pediatric Patients ≥6 Years with Moderate to Severe Plaque Psoriasis

- For patients ≥50 kg: Recommended dosage is 30 mg twice daily following the initial titration schedule.
- For patients 20 to <50 kg: Recommended dosage is 20 mg twice daily following the initial titration schedule.

Therapeutic Individualization

Pediatric Patients with Moderate to Severe Plaque Psoriasis

In pediatric patients 6 years of age and older with severe renal impairment (CLcr of less than 30 mL per minute estimated by the Cockcroft–Gault equation), the OTEZLA dosage should be reduced to 30 mg once daily for pediatric patients who weigh at least 50 kg and to 20 mg once daily for pediatric patients who weigh 20 kg to less than 50 kg. For initial dosage titration in these groups, it is recommended that OTEZLA be titrated using only the AM schedule listed in Table 2 for the appropriate body weight category and the PM doses be skipped.

Table 2. Dosage Titration Schedule for Pediatric Patients 6 Years of Age and Older With Moderate to Severe Plaque Psoriasis

Body Weight	Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & Thereafter	
	AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
50 kg or more	10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg
20 to less than 50 kg	10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg

Source: Proposed label; sNDA 205437-013

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

In the current submission, the Applicant has submitted Phase 3 efficacy and safety report CC-10004-PPSO-003 and report 157167: CC-10004-PPSO-003 which contains population PK /exposure-response analyses report to fulfil PMR 2791-2.

Dosage regimens identified from Phase 2 study (CC-10004-PPSO-001) based on body weight (apremilast 20 mg and 30 mg BID in subjects weighing 20 kg to <50 kg, and subjects ≥50 kg, respectively) for subjects 6 to 17 years of age were evaluated in the Phase 3 efficacy and safety trial (PPSO-003).

Study CC-10004-PPSO-003 (20200056) was a phase 3, multicenter, randomized, placebo-controlled, double-blind trial of the efficacy and safety of apremilast in pediatric subjects 6 to 17 years (inclusive) with moderate to severe plaque psoriasis. The double-blind, placebo-controlled phase of the study evaluated subjects randomized in a 2 (apremilast):1 (placebo) ratio for the first 16 weeks. Subjects 20 kg to <50 kg received apremilast 20 mg twice daily (BID) or placebo BID, and subjects ≥50 kg received apremilast 30 mg BID or placebo BID following an initial titration. Treatment assignment was stratified by baseline age group (6 years to 11 years or 12 years to 17 years). Eligible pediatric subjects were age 6 years to 17 years, inclusive, weighing at least 20 kg, with moderate to severe plaque psoriasis defined by PASI score ≥12, BSA ≥10%, and sPGA ≥3. Subjects had a diagnosis of chronic plaque psoriasis ≥6 months before screening. Furthermore, the subjects should have had disease which was inadequately controlled by or inappropriate for topical psoriasis therapy and were candidates for systemic therapy or phototherapy. Blood samples for PK analysis were collected at weeks 4, 8, 16, and 24 of the study. A total of 245 subjects were enrolled (163 subjects were randomized to the apremilast group and 82 subjects were randomized to the placebo group and switched to apremilast at week 16).

Pharmacokinetics

The PK population consisted of all subjects who received at least 1 dose of apremilast and had evaluable PK data. The PK analysis dataset was comprised of 896 plasma apremilast samples from 236 subjects including subjects who received 20 mg BID, 30 mg BID and placebo subjects who switched to apremilast 20 mg or 30 mg BID at week 16. The observed geometric mean trough (predose) concentrations of apremilast measured at weeks 4, 16, and 24 ranged from 51 ng/mL to 92 ng/mL across the 20 mg and 30 mg BID dose groups. The 30-minute postdose geometric mean plasma concentrations of apremilast at week 8 were 159 ng/mL and 137 ng/mL for the 20 mg and 30 mg BID dose groups, respectively.

Table 3. Descriptive Statistics of Apremilast Concentration (ng/mL) Estimates Following BID Oral Administration in Pediatric Subjects From 6 Years Through 17 Years of Age With Moderate to Severe Plaque Psoriasis

Dose	Statistic	Week 4	Week 8	Week 16	Week 24
20 mg BID	N	73	65	67	100
	Mean	159	290	132	145
	SD	162	238	143	145
	Min	0.500	0.500	0.500	0.500
	Median	106	237	111	103
	Max	883	1340	889	860
	CV%	102	82	108	100
	GeoMean	92.4	159	50.6	65.9
30 mg BID	N	71	67	66	95
	Mean	195	272	174	172
	SD	178	218	149	169
	Min	0.500	0.500	0.500	0.500
	Median	162	240	150	126
	Max	746	907	697	874
	CV%	92	80	86	98
	GeoMean	77.5	137	82.6	58.8

BID = twice daily; CV% = coefficient of variation percentage; GeoMean = geometric mean; LLOQ = lower limit of quantification; Min = minimum
Weeks 4, 16 and 24 are pre-dose concentrations, Week 8 is 30-minute postdose concentration.
Descriptive statistics are presented to 3 significant figures except for CV%, which is presented to the nearest integer. Values below the LLOQ were set to 0.5 ng/mL, half the LLOQ (1.00 ng/mL), to calculate GeoMean.
Data shown for week 24 includes pooled data from all subjects including subjects who switched from placebo to apremilast at week 16.
Source: *RIM\Clincal\Study Report Contribution\PK Analysis\PK Analysis.AMG 407 Study 20200056.phxproj*

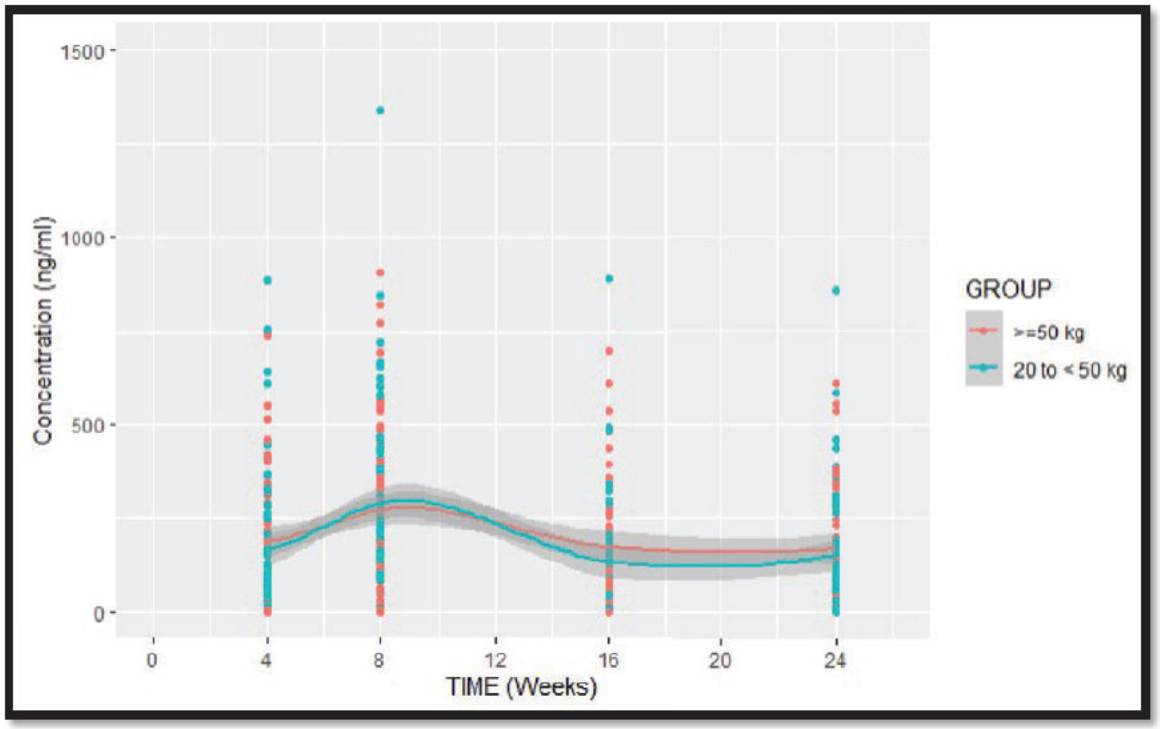
Source: Table 5, Page no. 17, Summary of Clinical Pharmacology (2.7.2)

Table 4. Descriptive Statistics of Apremilast Concentration (ng/mL) Estimates Grouped by Body Weight Following 20 mg or 30 mg BID Oral Administration in Pediatric Subjects With Moderate to Severe Plaque Psoriasis

Group	Time	Mean	Std	Min	Max	Median	CV%	Geo.Mean
≥50 kg	4.00	187.60	171.36	0.50	746.00	162.00	91.34	75.60
≥50 kg	8.00	271.97	217.68	0.50	907.00	240.00	80.04	136.94
≥50 kg	16.00	172.60	149.92	0.50	697.00	146.50	86.86	81.61
≥50 kg	24.00	167.63	141.69	0.50	610.00	136.50	84.52	64.28
20 to <50 kg	4.00	165.61	170.38	0.50	883.00	107.00	102.88	94.64
20 to <50 kg	8.00	289.97	238.24	0.50	1340.00	237.00	82.16	158.76
20 to <50 kg	16.00	133.47	142.91	0.50	889.00	112.00	107.07	51.19
20 to <50 kg	24.00	145.74	149.03	0.50	860.00	109.00	102.25	65.44

Source: Reviewer's analysis, based on ADPC.xpt dataset for study CC-10004-PPSO-003.
Abbreviations: BID, twice daily; CV%, coefficient of variation percentage; Geo.Mean, geometric mean; Std, standard deviation

Figure 1. Apremilast Concentration (ng/mL) Grouped by Body Weight Following 20 mg or 30 mg BID Oral Administration in Pediatric Subjects With Moderate to Severe Plaque Psoriasis



Source: Reviewer's analysis, based on ADPC.xpt dataset for study CC-10004-PPSO-003.
Solid circles are observed apremilast concentrations. Solid lines represent LOESS fit.
Abbreviations: BID, twice daily; LOESS, locally estimated scatterplot smoothing

The observed plasma concentrations by visit (predose concentrations at weeks 4, 16, and 24, and 30-minute postdose concentrations at week 8) were in similar range across treatment groups following dosing at 20 mg or 30 mg BID in subjects weighing ≥20 to <50 kg, and ≥50 kg, respectively.

Population Pharmacokinetics and Exposure-Response Analysis (Study 157167)

Population PK and exposure-response analyses were conducted to confirm the dosages studied in pediatric subjects with moderate to severe plaque psoriasis.

The objectives of the apremilast population PK and exposure-response analysis in adult and pediatric subjects with moderate to severe plaque psoriasis were to:

- Quantitatively characterize apremilast PK in adult and pediatric subjects following BID oral dosing and to quantify the inter-individual and residual variability.
- Evaluate the effects of demographic characteristics and other baseline covariates on PK parameters of apremilast (maximum concentration at steady state [$C_{max,ss}$], minimum concentration at steady state [$C_{min,ss}$], and area under the concentration-time curve from time 0 to 12 hours under steady-state [$AUC_{0-12,ss}$]).

- Characterize the apremilast exposure-response (sPGA and PASI-75) relationship in adults and pediatric subjects with moderate-to-severe plaque psoriasis.

Studies Included in the PPK and ER Analysis

Table 5. Studies Included in the Population Pharmacokinetic and Exposure-Response Analyses of Apremilast

Study	Phase	Study Description	Apremiast Dose	PK Sampling Scheme Frequency	Population (N)
20200164 (CC-10004-PK-001)	1	Double-blind, placebo-controlled ascending single and multiple oral dose, safety and pharmacokinetic study in healthy subjects	10 mg QD, 2 weeks 20 mg QD, 2 weeks 40 mg QD, 2 weeks 80 mg QD, 2 weeks 100 mg QD, 2 weeks	Day 1: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4 , 6, 8, 12, 16, 24 and 36 hr pos-dose Day 3-5: pre AM dose Day 6: pre and 2 h post AM/PM dose Day 7: 0.5, 1, 1.5, 2, 2.5, 3, 4 , 6, 8, 12, 16, 24, 36 and 48 hr post-dose	Healthy subjects PK: 20
20200167 (CC-10004-PK-007)	1	Safety, pharmacokinetics and pharmacodynamics of ascending multiple oral doses in healthy subjects	40 mg QD, 2 weeks 60mg QD, 2 weeks 80 mg QD, 2 weeks 40 mg BID, 2 weeks	Day 1: predose, 0-4, 4-8, 8-12, and 12-24 hr post-dose Day 14: pre-AM dose, 0-4, 4-8, 8-12, 12-16, 16-20, 20-24, 24-36, 36-48-, and 48-60-hours post–AM dose	Healthy subjects PK: 44
20200171 (CC-10004-PPSO-001)	2	Multicenter, open-label study to assess the safety, tolerability and pharmacokinetics of apremilast in pediatric subjects with moderateto severe plaque psoriasis	20 mg BID: ages 12-17 yrs, WT >= 35 kg to < 70 kg 30 mg BID: ages 12-17 yrs, WT >= 70 kg 20 mg BID: ages 6 to 11, WT >= 15kg	Day 1: 2 Day 14: predose, 1, 2, 3, 5, 8, 12, 24	Pediatric subjects with moderateto severe plaque psoriasis PK: 42
Study	**Phase**	**Study Description**	**Apremilast Dose**	**PK Sampling Scheme Frequency**	**Population (N)**
20200184 (CC-10004-PSOR-005-E-LTE)	2	Multicenter, Randomized, Double- Blind, Placebo- Controlled, Dose Ranging, Efficacy and Safety Study in Subjects with Moderate-to-severe Plaque-type Psoriasis	10 mg BID 20 mg BID 30 mg BID	Sparse samples: Weeks 4, 6, 8, 10, 12, 16, 18, 20, and 22 Week 14: predose, 0.5, 1, 2, 3, 4, and 8 hours	Moderate -to -severe plaque-type Psoriasis PK: 67 PK/PD: 335
20200188 (CC-10004-PSOR-011)	2	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy and SafetyStudy of Apremilast in Japanese Subjects with Moderate-to-severe Plaque-type Psoriasis	20 mg BID 30 mg BID	Week 20: predose, 0.5, 1, 2, 3, 4, 8 post AM dose Sparse samples: Weeks 8, 12, 16, 20, 24 within the following time windows: pre dose, 0-3h, 3-5h or 5-8h.	Japanese subjects with moderate -to-severe plaque-type psoriasis PK: 104 PK/PD:254
20200185 (CC-10004-PSOR-008)	3	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Apremilast in subjects with Moderate to-severe plaque-type psoriasis	30 mg BID	Sparse samples: Weeks 24, 32, 36, 40, 44, and 48	Subjects with moderate -to -severe plaque-type psoriasis PK: 166 PK/PD: 844
20200056 (CC-10004-PPSO-003)	3	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Apremilast in pediatric subjects with moderateto severe plaque psoriasis	20 mg BID: WT >= 20 kg to < 50 kg 30 mg BID: WT >= 50 kg	Sparse samples: predose on Week 4, 16 and Week 8: 0.5h	Pediatric subjects with moderate -to -severe plaque psoriasis PK and PK/PD:158

Page 2 of 2

Source: Table 10-1, Page no. 43, Pharmacometrics Report: 157167
Abbreviations: BID, twice daily; h, hour; QD, once daily; PK, pharmacokinetic; PO, oral; WT, weight (kg)

Table 6. Summary Statistics of Subject Level Covariates Included in the Population Pharmacokinetic Analysis by Clinical Study

Characteristic	20200056, N = 158	20200164, N = 30	20200167, N = 44	20200171, N = 42	20200184, N = 67	20200185, N = 165	20200188, N = 105	Overall, N = 611
Age (year)								
Mean (SD)	12 (3)	28 (8)	27 (7)	12 (3)	47 (13)	49 (14)	52 (12)	35 (20)
Median	13 (6-17)	26 (19-47)	25 (18-48)	12 (7-17)	46 (19-80)	50 (19-75)	50 (25-78)	34 (6-80)
(Min-Max)								
Weight (kg)								
Mean (SD)	52 (21)	76 (10)	76 (9)	53 (24)	96 (21)	95 (20)	70 (13)	74 (26)
Median	50	74	76	50	96	92	69	73
(Min-Max)	(20-145)	(60-94)	(58-99)	(21-126)	(61-166)	(51-170)	(46-102)	(20-170)
Disease								
Healthy	0 / 158 (0%)	30 / 30 (100%)	44 / 44 (100%)	0 / 42 (0%)	0 / 67 (0%)	0 / 165 (0%)	0 / 105 (0%)	74 / 611 (12%)
Psoriasis	158 / 158 (100%)	0 / 30 (0%)	0 / 44 (0%)	42 / 42 (100%)	67 / 67 (100%)	165 / 165 (100%)	105 / 105 (100%)	537 / 611 (88%)
Creatinine CL (mL/min)								
Mean (SD)	125 (32)	109 (14)	137 (27)	151 (41)	102 (31)	98 (30)	104 (30)	113 (35)
Median	122	108	138	143	101	98	106	111
(Min-Max)	(70-223)	(82-142)	(91-229)	(85-235)	(29-199)	(34-210)	(38-168)	(29-235)
Sex								
Male	72 / 158 (46%)	30 / 30 (100%)	44 / 44 (100%)	19 / 42 (45%)	42 / 67 (63%)	113 / 165 (68%)	78 / 105 (74%)	398 / 611 (65%)
Female	86 / 158 (54%)	0 / 30 (0%)	0 / 44 (0%)	23 / 42 (55%)	25 / 67 (37%)	52 / 165 (32%)	27 / 105 (26%)	213 / 611 (35%)
Race								
Others	2 / 158 (1.3%)	0 / 30 (0%)	0 / 44 (0%)	4 / 42 (9.5%)	0 / 67 (0%)	2 / 165 (1.2%)	0 / 105 (0%)	8 / 611 (1.3%)
Asian	5 / 158 (3.2%)	0 / 30 (0%)	0 / 44 (0%)	4 / 42 (9.5%)	0 / 67 (0%)	5 / 165 (3.0%)	105 / 105 (100%)	119 / 611 (19%)
Black	4 / 158 (2.5%)	0 / 30 (0%)	0 / 44 (0%)	2 / 42 (4.8%)	0 / 67 (0%)	4 / 165 (2.4%)	0 / 105 (0%)	10 / 611 (1.6%)
White	137 / 158 (87%)	30 / 30 (100%)	44 / 44 (100%)	32 / 42 (76%)	66 / 67 (99%)	154 / 165 (93%)	0 / 105 (0%)	463 / 611 (76%)
Missing	10 / 158 (6.3%)	0 / 30 (0%)	0 / 44 (0%)	0 / 42 (0%)	1 / 67 (1.5%)	0 / 165 (0%)	0 / 105 (0%)	11 / 611 (1.8%)

Source: Table 10-2, Page no. 44, Pharmacometrics Report: 157167
Abbreviations: CL, clearance; max, maximum; min, minimum; SD, standard deviation

Population PK Model

Plasma concentration-time profiles of apremilast in adult subjects with psoriasis were described with a one- compartment model with first order absorption and linear clearance. The population PK model consisted of:

- Structural model describing the relationships between plasma concentration and time.
- A variance component characterizing between-subject variability (BSV) in model parameters.
- Residual unexplained variability modeled using additive and proportional models.

Table 7. Fixed Effects Population Parameter Estimates for the Base and Final PK Model

	Base Model		Final Model	
Parameter (units)	Estimate	RSE(%)	Estimate	RSE(%)
CL (L/hr)	9.47	2.29	11.4	4.72
VC (L)	111	6.11	70.1	4.77
KA (1/h)	0.927	6.33	0.93	6.23
Proportional error (ng/mL)	26.5	5.72	26.5	5.69
Additive error (%)	61.7	10	61.5	9.99
BW on VC			0.901	11.6
SEX on CL			-0.186	23.5
Disease on CL			-0.123	45.3
BW on CL			0.246	22.1
Disease on VC			0.689	12.1

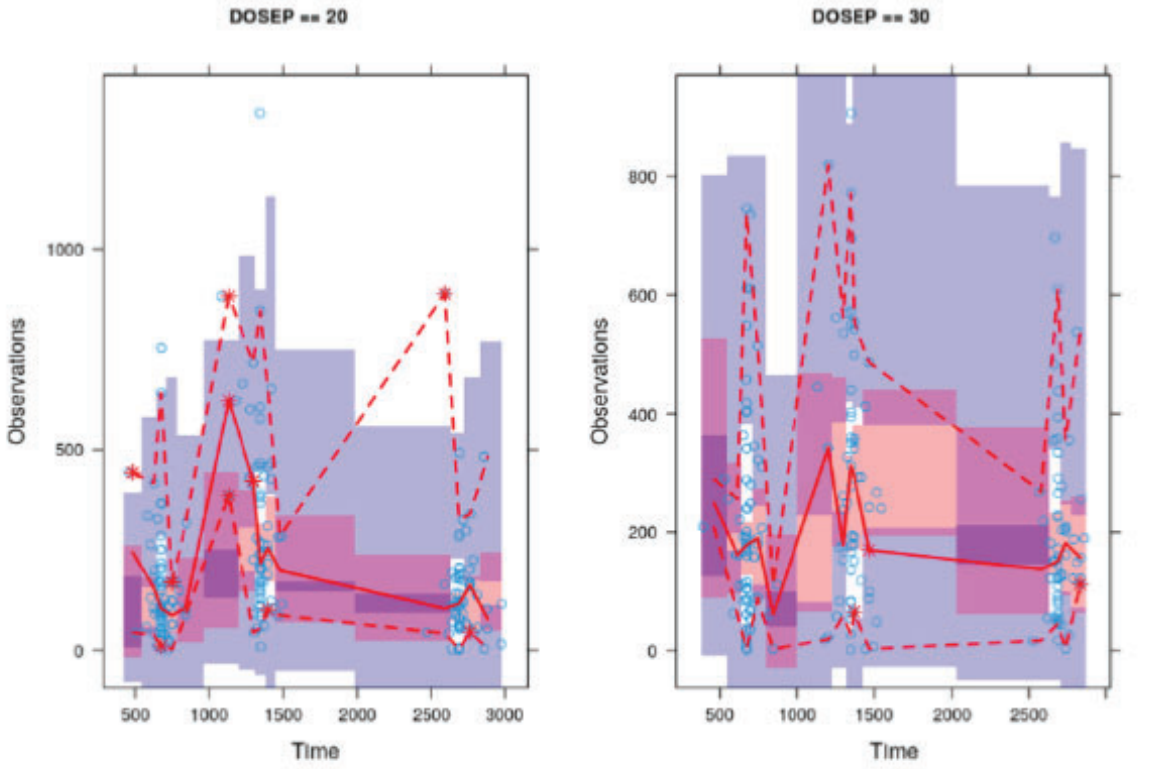
Source: Table 10-4, Page no. 46, Pharmacometrics Report: 157167
RSE = (SE/PE)*100
Abbreviations: CL, clearance from central compartment; KA, 1st order rate absorption into the central compartment; PE, parameter estimate; PK, pharmacokinetic; RSE, relative standard error; SE, standard error; VC, volume of central compartment

Table 8. Random Effects Population Parameter Estimates for the Base and Final PK Model

	Base Model		Final Model	
Parameter	Estimate	RSE(%)	Estimate	RSE(%)
ETA - CL	0.448	4.26	0.429	3.99
ETA - VC	0.627	8.9	0.448	9.76
ETA - KA	0.618	16.7	0.717	15.7

Source: Table 10-4, Page no. 46, Pharmacometrics Report: 157167
RSE = (SE/PE)*100
Abbreviations: CL, clearance from central compartment; KA, 1st order rate absorption into the central compartment; PE, parameter estimate; PK, pharmacokinetic; RSE, relative standard error; SE, standard error; VC, volume of central compartment

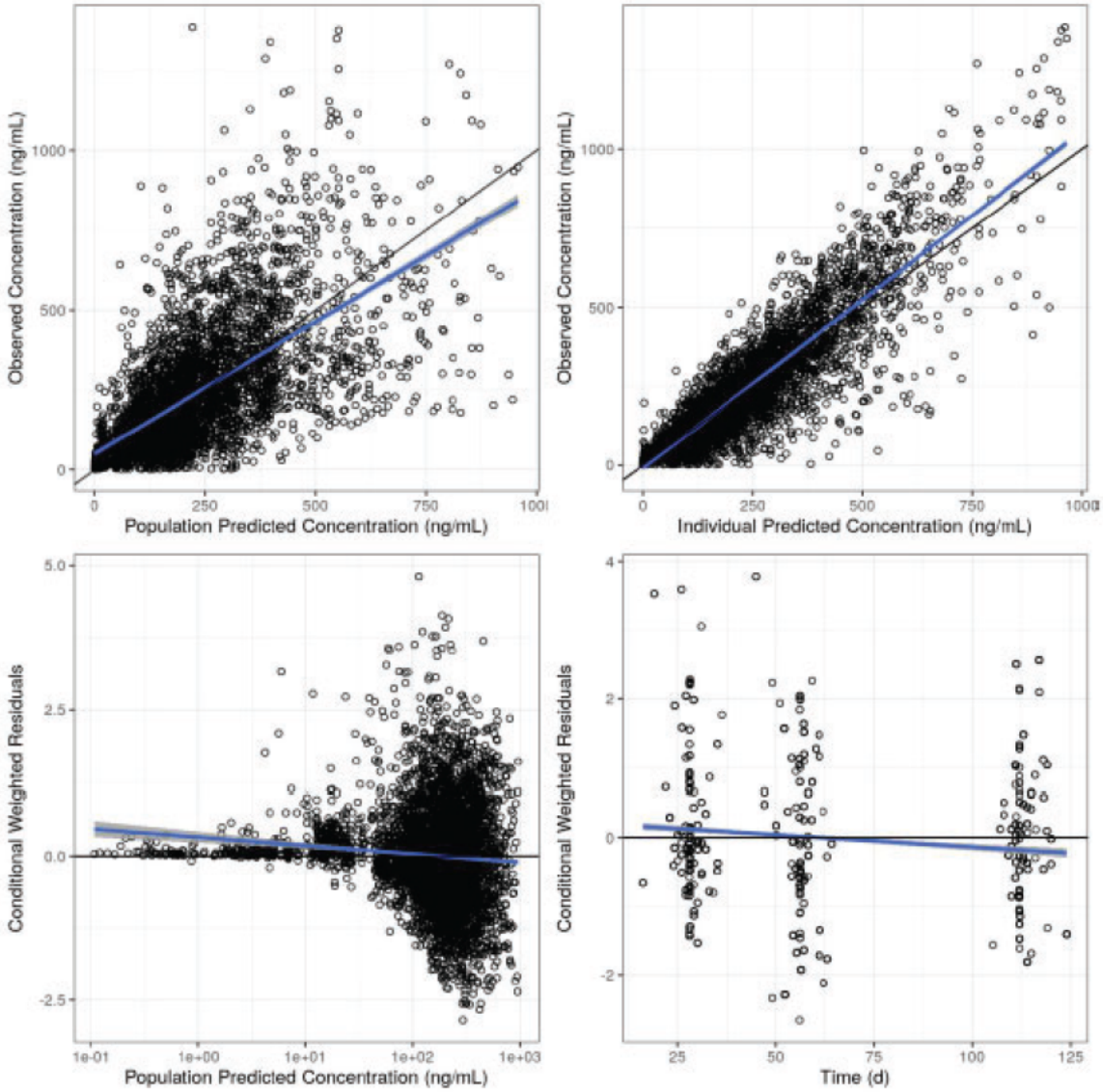
Figure 2. Prediction Corrected Visual Predictive Check for the Final Apremilast PK Model Stratified for Study 20200056 and Dose Level



Lines represent prediction corrected observed data (solid red: median, dashed red: 5th and 95th percentiles, blue: observed proportion) and shaded areas (5th, 50th, 95th, or proportion) represent 90%PI of prediction corrected simulated metrics. Observed and predicted concentrations are plotted as prediction corrected concentration and time is in hours.

Source: Figure 11-12, Page no. 72, Pharmacometrics Report: 157167
Abbreviations: PI, prediction interval; PK, pharmacokinetic

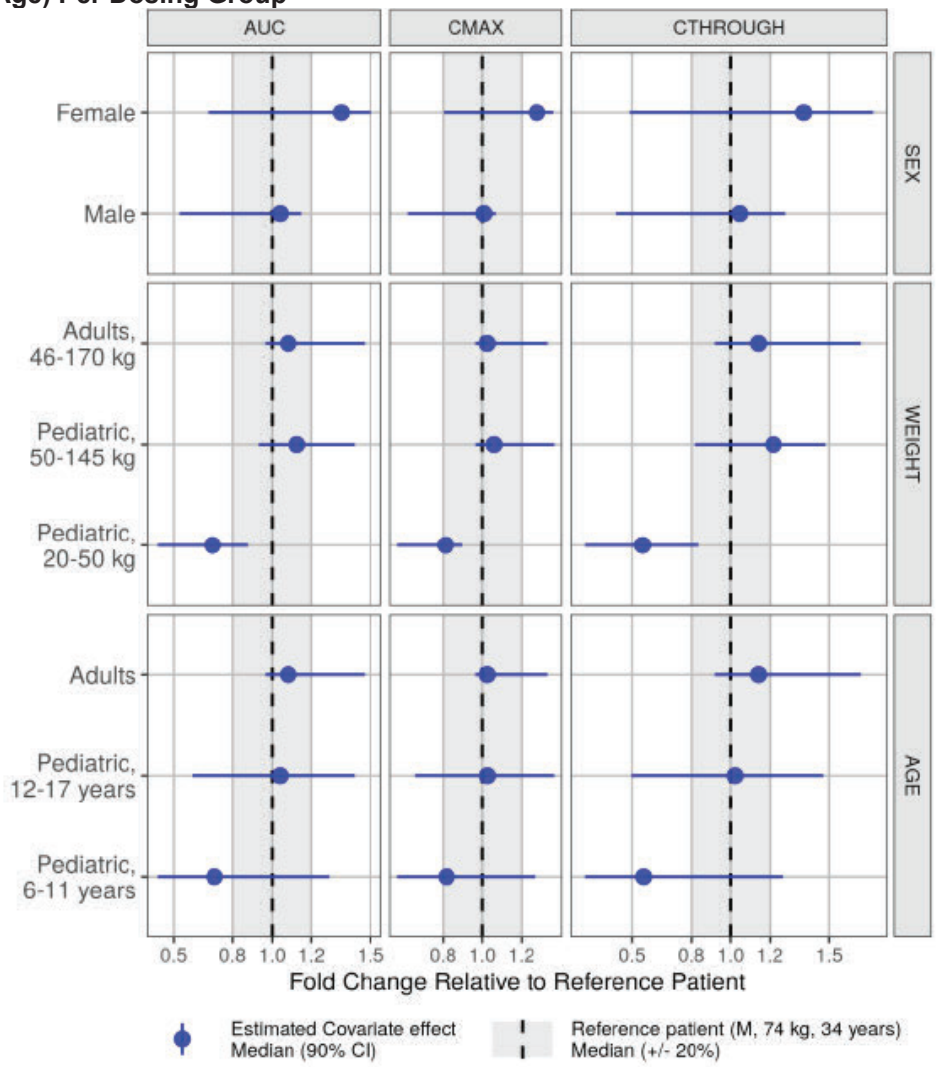
Figure 3. Goodness-of-Fit Plots for the Final PK Model



The blue line is the linear regression trend line. The black dashed line is the reference line for fitting.

Source: Table 10-4, Page no. 46, Pharmacometrics Report: 157167
Abbreviations: d, day(s); PK, pharmacokinetic

Figure 4. Predicted Exposure Fold Change by Final PK Model Covariates (Body Weight, Sex, and Age) Per Dosing Group



Source: Figure 11-22, Page no. 82, Pharmacometrics Report: 157167
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; CMAX, maximum plasma concentration; CTROUGH, trough plasma concentration; PK, pharmacokinetic

Conclusion

Apremilast PK in pediatric patients was adequately described by one-compartment model with first order absorption and linear elimination. The developed model included psoriasis disease status, sex, and weight effect on CL/F and body weight and psoriasis disease status effect on V/F. The age effect on CL/F was also evaluated by evaluating for possible nonlinear relationships between KA, V/F and CL/F vs age to describe the maturation of apremilast clearance. The final covariate model included body weight psoriasis disease status and sex effects on CL/F and body weight and psoriasis disease effect on V/F. The addition of these terms did not improve the objective function value. The final PK model parameters are reasonable and consistent with those previously submitted.

Exposure-Response Model

Exposure- response models were developed to assess changes in PASI-75, and sPGA responses over time. Data collected from four Phase 2/3 studies of apremilast in subjects with moderate-to-severe plaque type psoriasis (20200184, 20200185, 20200188, 20200056) were used in the exposure-efficacy (PASI-75: 1566 subjects; sPGA: 1574 subjects) analysis. Placebo subjects were included in the exposure-efficacy population. For the sPGA response dataset, median body weight for the analysis population was 85 kg (range: 20 kg to 186 kg). The overall population median age was 42 years (range: 6 years to 82 years), including 181 (11.5%) pediatric subjects and 1393 (88.5%) adult subjects. A total of 1053 (67%) subjects were male. Most subjects, 75%, were Caucasian, 20% were Asian, 2.5% Black, and 1.9% another race or missing. For the PASI-75 response dataset, median bodyweight for the analysis population was 83 kg (range: 20 to 186 kg). The overall population median age was 42 years (range: 6 to 82 years), including 181 (11.6%) pediatric subjects and 1385 (88.4%) adult subjects. A total of 1053 (67%) subjects were male. Most subjects, 75%, were Caucasian, 20% were Asian, 2.5% Black, and 1.9% another race or missing.

Table 9. Summary Statistics of Subject Level Covariates Included in the sPGA Exposure-Response Analysis Stratified by Clinical Study

	20200056 N = 181	20200184 N = 305	20200185 N = 834	20200188 N = 254	Overall N = 1,574
Age (year)					
Mean (SD)	12 (3)	44 (14)	46 (13)	51 (12)	42 (17)
Median (Min-Max)	13 (6-17)	44 (18-77)	46 (18-82)	50 (23-80)	44 (6-82)
Weight (kg)					
Mean (SD)	53 (23)	93 (22)	93 (22)	70 (13)	85 (25)
Median (Min-Max)	52 (20-145)	90 (46-178)	91 (45-186)	69 (41-109)	83 (20-186)
Sex					
Male	92 / 181 (51%)	199 / 305 (65%)	564 / 834 (68%)	202 / 254 (80%)	1,057 / 1,574 (67%)
Female	89 / 181 (49%)	106 / 305 (35%)	270 / 834 (32%)	52 / 254 (20%)	517 / 1,574 (33%)
Race					
Others	1 / 181 (0.6%)	5 / 305 (1.6%)	15 / 834 (1.8%)	0 / 254 (0%)	21 / 1,574 (1.3%)
Asian	7 / 181 (3.9%)	12 / 305 (3.9%)	44 / 834 (5.3%)	254 / 254 (100%)	317 / 1,574 (20%)
Black	7 / 181 (3.9%)	5 / 305 (1.6%)	28 / 834 (3.4%)	0 / 254 (0%)	40 / 1,574 (2.5%)
White	157 / 181 (87%)	283 / 305 (93%)	747 / 834 (90%)	0 / 254 (0%)	1,187 / 1,574 (75%)
Missing	9 / 181 (5.0%)	0 / 305 (0%)	0 / 834 (0%)	0 / 254 (0%)	9 / 1,574 (0.6%)

Source: Table 10-3, Page no. 45, Pharmacometrics Report: 157167
Abbreviations: max, maximum; min, minimum; SD, standard deviation; sPGA, static Physician's Global Assessment

Table 10. Summary Statistics of Subject Level Covariates Included in the PASI-75 Exposure-Response Analysis Stratified by Clinical Study

	20200056 N = 181	20200184 N = 297	20200185 N = 834	20200188 N = 254	Overall N = 1,566
Age (year)					
Mean (SD)	12 (3)	44 (13)	46 (13)	51 (12)	42 (17)
Median (Min-Max)	13 (6-17)	44 (18-77)	46 (18-82)	50 (23-80)	44 (6-82)
Weight (kg)					
Mean (SD)	53 (23)	93 (22)	93 (22)	70 (13)	85 (25)
Median (Min-Max)	52 (20-145)	90 (46-178)	91 (45-186)	69 (41-109)	83 (20-186)
Sex					
Male	92 / 181 (51%)	195 / 297 (66%)	564 / 834 (68%)	202 / 254 (80%)	1,053 / 1,566 (67%)
Female	89 / 181 (49%)	102 / 297 (34%)	270 / 834 (32%)	52 / 254 (20%)	513 / 1,566 (33%)
Race					
Others	1 / 181 (0.6%)	5 / 297 (1.7%)	15 / 834 (1.8%)	0 / 254 (0%)	21 / 1,566 (1.3%)
Asian	7 / 181 (3.9%)	12 / 297 (4.0%)	44 / 834 (5.3%)	254 / 254 (100%)	317 / 1,566 (20%)
Black	7 / 181 (3.9%)	4 / 297 (1.3%)	28 / 834 (3.4%)	0 / 254 (0%)	39 / 1,566 (2.5%)
White	157 / 181 (87%)	276 / 297 (93%)	747 / 834 (90%)	0 / 254 (0%)	1,180 / 1,566 (75%)
Missing	9 / 181 (5.0%)	0 / 297 (0%)	0 / 834 (0%)	0 / 254 (0%)	9 / 1,566 (0.6%)

Source: Table 10-4, Page no. 46, Pharmacometrics Report: 157167
Abbreviations: max, maximum; min, minimum; PASI, Psoriasis Area and Severity Index; SD, standard deviation

Table 11. Observed sPGA Response in Apremilast Clinical Trials b Stud and Treatment Arm

	20200056 20mg BID N = 48	20200056 30mg BID N = 57	20200056 Placebo N = 78	20200184 30mg BID N = 54	20200184 Placebo N = 70	20200185 30mg BID N = 562	20200185 Placebo N = 282	20200188 30mg BID N = 85	20200188 Placebo N = 84
sPGA Response rate	21 / 48 (44%)	10 / 57 (18%)	8 / 78 (10%)	21 / 54 (39%)	10 / 70 (14%)	122 / 562 (22%)	11 / 282 (3.9%)	28 / 85 (33%)	13 / 84 (15%)

Statistics presented: n / N (%)

Source: Table 10-5, Page no. 46, Pharmacometrics Report: 157167
Abbreviations: BID, twice daily; sPGA, static Physician's Global Assessment

Table 12. Observed PASI-75 Response in Apremilast Clinical Trials by Study and Treatment Arm

	20200056 20mg BID N = 48	20200056 30mg BID N = 58	20200056 Placebo N = 78	20200184 30mg BID N = 58	20200184 Placebo N = 72	20200185 30mg BID N = 562	20200185 Placebo N = 282	20200188 30mg BID N = 85	20200188 Placebo N = 84
PASI-75 Response rate	23 / 48 (48%)	20 / 58 (34%)	11 / 78 (14%)	25 / 58 (43%)	5 / 72 (6.9%)	186 / 562 (33%)	15 / 282 (5.3%)	24 / 85 (28%)	6 / 84 (7.1%)

Statistics presented: n / N (%)

Source: Table 10-6, Page no. 46, Pharmacometrics Report: 157167
Abbreviations: BID, twice daily; PASI, Psoriasis Area and Severity Index

Exposure-response analysis was conducted in sequential steps. Individual apremilast exposure estimates ($AUC_{\tau,ss}$ at steady state) were generated based on the final population PK model. For subjects with available PK measurements, $AUC_{\tau,ss}$ was calculated from simulations of individual-level model parameters, which account for both subject level covariate effects and individually fitted random effects. For subjects without any available PK measurements, $AUC_{\tau,ss}$ was calculated from simulations including their own subject level covariate effects and random

effects sampled from the model distributions. The calculated exposures were linked to response variables using logistic regression.

The PK/PD model included a logit function to characterize the probability of sPGA and PASI-75 responses driven by the extent exposure and/or time of exposure of apremilast. The models included a saturating Emax-type drug effect and placebo effect with an exponential delay component, and time-fixed as well as time-varying effects.

The model structure is described as follows:

$$P = f_{Placebo} + f_{DrugEffect}$$

$$f_{Placebo} = Intercept + Plb_0\left(1 - e^{-k_{plb}t}\right)$$

$$f_{DrugEffect} = \left(\frac{E_{max} AUC_{0-12h,ss}}{E_{50} + AUC_{0-12h,ss}}\right)$$

Age, body weight, and sex were included as covariates in both sPGA and PASI-75 exposure-response models.

Table 13. Fixed Effects Population Parameter Estimates for the Base and Final sPGA Exposure-Response Model

	Base Model		Final Model	
Parameter (Units)	Estimate	RSE(%)	Estimate	RSE(%)
S0 (logit)	3.96	4.55	3.93	4.63
Kplb (1/ week)	0.0847	17.2	0.103	17.9
Emax	1.37	20.1	1.66	11.7
EC50 (ng.h/mL)	321	168	1800	47.4
Intercept	-5.08	5.87	-5.38	6.43
SEX on EC50			-3.98	38.9
Age on EC50			-2.85	29.1
BW on Intercept			-1.2	18.7

Source: Table 10-11, Page no. 51, Pharmacometrics Report: 157167
RSE = (SE/PE)*100
Intercept: A value in logit space chosen to represent 0% incidence
Abbreviations: BW, body weight (kg); EC50, parameter denotes the apremilast concentration corresponding to the 50% maximal drug effect; Emax, maximal drug effect attainable in logit space; kpbl, 1st order rate on the placebo effect; RSE, relative standard error; S0, final placebo effect; sPGA, static Physician's Global Assessment

In the sPGA model, increasing body weight was associated with a lower regression intercept leading to lower response rates, while younger subjects had greater sensitivity (lower EC50). Females had greater sensitivity to apremilast exposure in the sPGA model compared to males.

Table 14. Fixed Effects Population Parameter Estimates for the Base and Final PASI-75 Exposure-Response Model

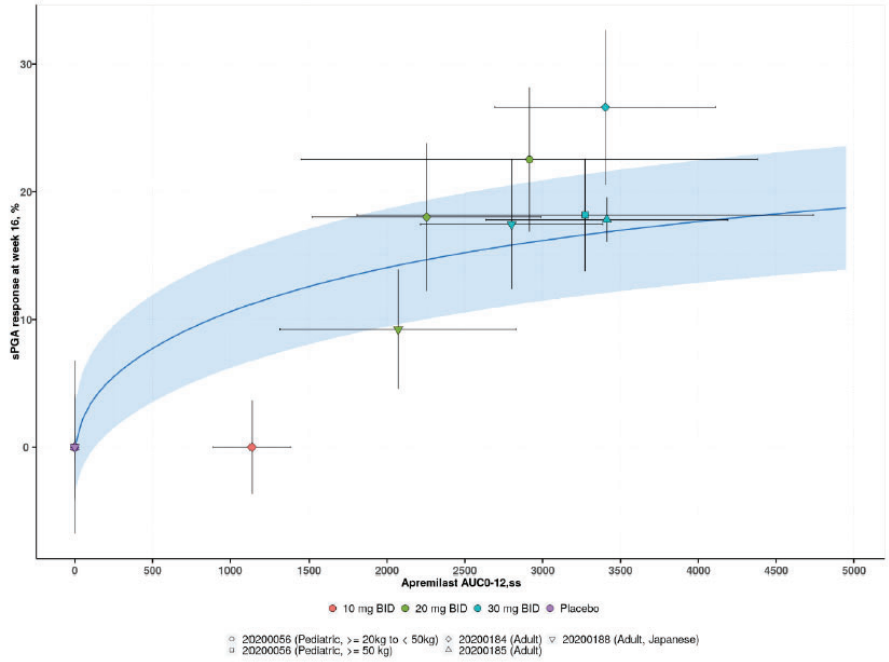
	Base Model		Final Model	
Parameter (Units)	Estimate	RSE(%)	Estimate	RSE(%)
S0 (logit)	5.6	9.87	6.31	10.6
Kplb (1/week)	0.219	14.6	0.243	12.8
Emax	1.91	12	2.07	10.9
EC50 (ng.h/mL)	160	117	60.5	193
Intercept	-7.94	8.62	-9.26	8.44
Sex on Intercept			0.656	18.7
Age on Intercept			-1.77	30.3
BW on Intercept			-0.727	31.2
Age on Emax			0.378	57
Age on S0			0.249	45.3

Source: Table 10-12, Page no. 51, Pharmacometrics Report: 157167
RSE = (SE/PE)*100
Intercept: A value in logit space chosen to represent 0% incidence
Abbreviations: BW, body weight (kg); EC50, parameter denotes the apremilast concentration corresponding to the 50% maximal drug effect; Emax, maximal drug effect attainable in logit space; kpbl, 1st order rate on the placebo effect; PASI, Psoriasis Area and Severity Index; RSE, relative standard error; S0, final placebo effect

In the PASI-75 model, younger subjects showed lower regression intercepts, lower Emax and higher placebo response rates, and increasing body weight was associated with lower intercept values. Females showed a higher intercept relative to males.

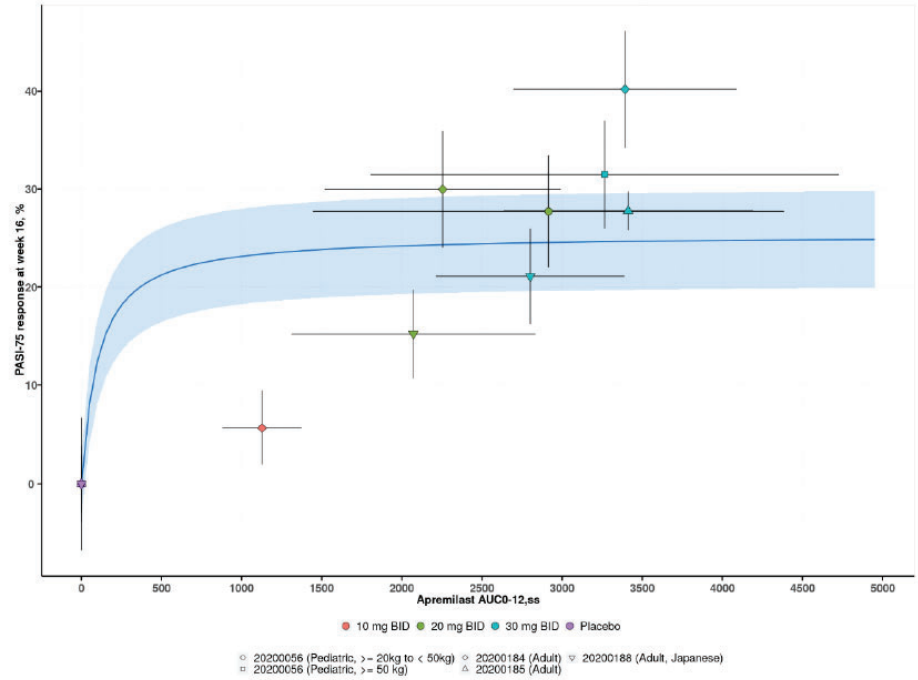
The final model described apremilast response profile for both sPGA and PASI-75 across the four studies and individual subjects.

Figure 5. Placebo-Corrected Exposure-sPGA Response After 16 Weeks of Apremilast Treatment by Study and Dosing Regimen



Source: Figure 11-20, Page no. 80, Pharmacometrics Report: 157167
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; sPGA, static Physician's Global Assessment

Figure 6. Placebo-Corrected Exposure-PASI-75 Response After 16 Weeks of Apremilast Treatment by Study and Dosing Regimen



Source: Figure 11-20, Page no. 80, Pharmacometrics Report: 157167
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; PASI, Psoriasis Area and Severity Index

The exposure-sPGA and -PASI-75 models were used to simulate sPGA and PASI-75 response rates in adult and pediatric subjects with moderate to severe plaque psoriasis. The simulations confirmed that pediatric subjects follow the same placebo-controlled exposure-response profile observed in adults, and that the proposed pediatric dosing regimen results in comparable placebo-corrected response rates as adults.

Apremilast Dosing Recommendations in Subjects with Severe Renal Impairment

Apremilast has previously been evaluated in adult subjects with mild, moderate, or severe renal impairment. Apremilast AUC was 14% lower and 22% higher in adult subjects with mild or moderate renal impairment, respectively, compared to adult subjects with normal renal function (Study CP-029). Apremilast C_{max} central values were similar in subjects with mild (6% difference) or moderate (13% difference) renal impairment compared to subjects with normal renal function. Apremilast was also evaluated in adult subjects with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73m^2 or creatinine clearance (CrCl) <30 mL/min (Study CP-019). Results from this study suggest that apremilast $t_{1/2}$ increased by 2.5 hours and apparent clearance (CL/F) decreased by approximately 47% resulting in an increase in AUC by 88.5% and C_{max} by 142.9%. Based on the results from Studies CP-029 and CP-019 in renally impaired subjects, no dose adjustment is needed when apremilast is administered to adult subjects with mild or moderate renal impairment. However, a dose reduction to 30 mg daily is recommended in adult subjects with severe renal impairment following a modified titration schedule.

To determine the appropriate dosing regimen in pediatric patients with severe renal impairment, Applicant conducted model-based simulations using the median body weight of Study PPSO-003 subjects in each body weight category (20 kg to 50 kg and ≥50 kg) receiving 20 mg or 30 mg BID, respectively, and used a modified titration schedule for subjects with severe renal impairment.

Table 15. Modified Dose Titration Schedule for Pediatric Patients With Severe Renal Impairment

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 and Thereafter
Apremilast 30 mg QD	10 mg	10 mg	10 mg	20 mg	20 mg	30 mg
Apremilast 20 mg QD	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg

Source: Table 8, Page no. 28, Summary of Clinical Pharmacology (2.7.2)
Abbreviations: QD, once daily

The PK model used to perform the simulations was the same as the one developed for Study CC-10004-PPSO-003 (Study 20200056) in pediatric subjects with moderate to severe psoriasis. Estimates of PK parameters for adult subjects with severe renal impairment (CL/F =5.530 L/h; V/F =94.59L) and for healthy adult subjects without renal impairment (CL/F =10.423 L/h; V/F =140.45 L) were obtained from clinical study report CC-10004-CP-019. These values were

used to derive adjustment factors (severe impairment/healthy ratio) to simulate the impact of renal impairment on apremilast PK parameters by multiplying the typical value estimates for pediatric subjects by the severe renal impairment factors derived from adult subjects (CL/F adjustment factor =0.53, V/F adjustment factor =0.67). Typical values of PK parameters in patients with psoriasis derived for pediatric subjects with and without severe renal impairment as well as reference values for adult subjects with and without severe renal impairment are shown in Table 16 below.

Table 16. Summary of Apremilast Pharmacokinetic Parameters for Adult and Pediatric Subjects With and Without Severe Renal Impairment

PK Parameter	Adult subjects[1]		Adjustment factor[2]	Pediatric Subjects	
	Healthy	Severe renal impaired		No renal impairment[3]	Severe renal impaired (derived)
CL/F (L/hr)	10.423	5.530	0.530	11.4	6.04
V/F (L)	140.45	94.59	0.673	70.1	47.18

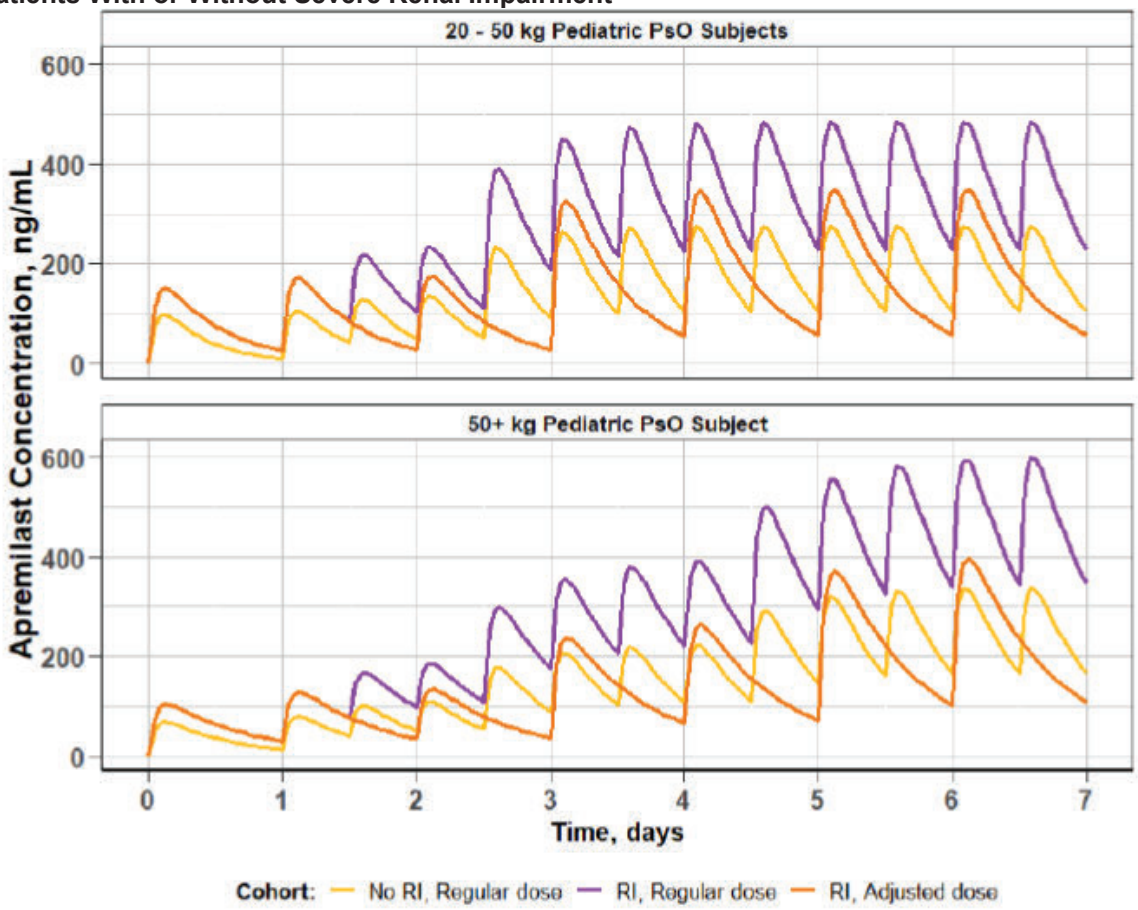
[1] PK Parameters for adult subjects with severe renal impairment and matched healthy adult subjects were taken from clinical study report CC-10004-CP-019.

[2] Adjustment factors were derived as the ratio value for severely renal impaired over the value for healthy subjects for each parameter.

[3] Typical PK parameter estimates for pediatric subjects with moderate to severe psoriasis and without severe renal impairment were taken from study report 157167.

Source: Table 1, Page no. 4, Response to Information Request (April 2, 2024).
Abbreviations: CL/F, clearance from central compartment; PK, pharmacokinetic; V/F, volume of distribution

Figure 7. Simulated Mean Steady-State Apremilast Concentration Vs. Time in Plaque Psoriasis Patients With or Without Severe Renal Impairment

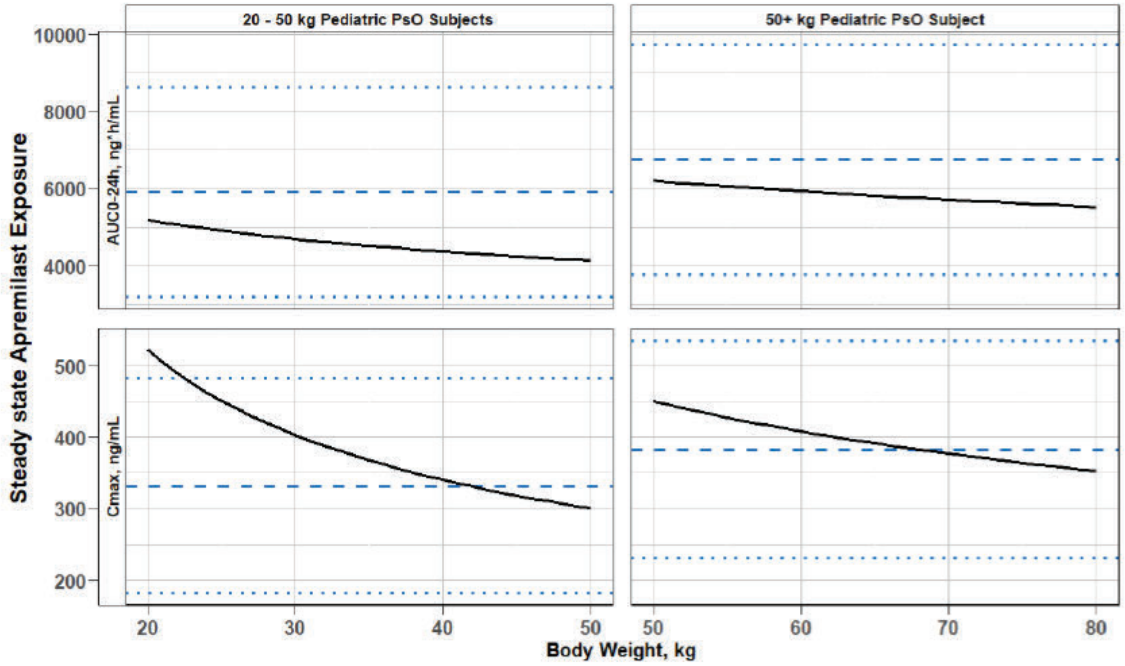


BID = twice daily; PsO = plaque psoriasis; QD = once daily; RI = renal impairment
Figure shows model-predicted apremilast concentration-time curve for the first 7 days of dosing for a typical psoriasis subject in each proposed treatment category, assuming no renal impairment and given regular titration and dose (≥ 20 to < 50 kg and ≥ 50 kg receiving 20 or 30 mg BID, respectively [yellow]), severe renal impairment and given regular titration and dose (≥ 20 to < 50 kg and ≥ 50 kg receiving 20 or 30 mg BID, respectively [purple]), and severe renal impairment given proposed titration and dose (≥ 20 to < 50 kg and ≥ 50 kg receiving 20 or 30 mg QD, respectively [orange])
A typical subject is defined as male with psoriasis weighting 38.4 kg (20 to 50 kg group) or 61.3 kg (50+ kg group). These weights represent the median body weights from each treatment group observed in Study PPSO-003.
Effect of severe renal impairment was estimated by adjusting the clearance and volume parameters in the model by the observed ratio between adult healthy volunteers and adult subjects with severe renal impairment as described in Study CC-10004-CP-019 (CL: 0.530, V: 0.673).

Source: Figure 4, Page no. 29, Summary of Clinical Pharmacology (2.7.2)

The model-predicted proposed doses of 20 mg QD and 30 mg QD in subjects with moderate to severe plaque psoriasis and severe renal impairment are mostly contained within the model-predicted range of exposures in subjects with normal renal function.

Figure 8. Model-Predicted Steady-State Apremilast Exposures in Pediatric Psoriasis Subjects With Severe Renal Impairment by Proposed Treatment



AUC = area under the concentration-time curve; C_{max} = observed maximum plasma concentration
Figure shows model predicted steady-state apremilast exposure metric ($AUC_{0\text{-}24h,ss}$ or $C_{max,ss}$) for psoriasis subjects without renal impairment in each treatment group (≥ 20 to < 50 kg and ≥ 50 kg receiving 20 or 30 mg BID, respectively). Dashed (median) and dotted (standard deviation) blue line represent exposure in the reference population (pediatric psoriasis subjects without renal impairment. Left: 20 to < 50 kg. Right: ≥ 50 kg
Solid black line represents model-predicted steady state apremilast exposures ($AUC_{0\text{-}24h,ss}$ or $C_{max,ss}$) at the proposed daily dose for a subject with severe renal impairment as a function of body weight in each treatment group (≥ 20 to < 50 kg and ≥ 50 kg receiving 20 or 30 mg QD, respectively)

Source: Figure 5, Page no. 30, Summary of Clinical Pharmacology (2.7.2)

The results from the model-predicted simulations for subjects ≥50 kg suggest that the dosage of apremilast 30 mg QD in pediatric subjects with severe renal impairment is comparable and is expected to provide apremilast exposures that are similar to that following a dosing regimen of 30 mg BID in pediatric subjects with normal renal function. Thus, the dosage should be reduced to 30 mg QD in pediatric subjects with severe renal impairment (eGFR <30 mL/min/1.73m^2 or CLcr <30 mL/min) following the modified titration schedule. Similarly, for pediatric subjects ≥20 kg to <50 kg, a dosage of 20 mg QD in subjects with severe renal impairment is expected to result in similar exposures to 20 mg BID dosage in subjects without renal impairment following the modified titration schedule.

Conclusion

Proposed dosing regimen in pediatric subjects with severe renal impairment is supported by PK model-based simulation.

Bioanalytical Method Performance in Study CC-10004-PPSO-003

The overall bioanalytical method was the same as the one used in the original NDA. Incurred sample re-analysis was performed in 10.4% (85/832) of study samples, and 96.5% of the samples met the pre-specified criteria. With the exception of 12 samples, all study samples were analyzed within the established long-term stability of 520 days at -70°C; these data are flagged in the report and presented for informational purposes only.

The accuracy and precision of the standard curve and QCs are below 15%. Analysis of the samples were completed except for 12 samples, within the range of long-term stability of samples established. ISR was also more that 80% showing reproducibility of the method (requirements: sample size -10% reanalysis of the first 1000 samples, and 5% reanalysis of the remaining samples; acceptance criteria - 67% should be ±20% of the mean). Overall, bioanalytical method is acceptable.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the analytical site (b) (4) where bioanalysis of PK samples was conducted. The rationale for not conducting inspection was that OSIS had conducted a Remote regulatory Assessment (RRA) for the site in June 2022 and concluded that the data from the reviewed studies were reliable.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant conducted a phase 2, open-label, PK/safety study (CC-10004-PPSO-001) and a phase 3, R, DB, PC efficacy/safety trial (CC-10004-PPSO-003) in pediatric subjects (between 6 to 17 years of age, inclusive) with moderate to severe plaque psoriasis to provide clinical data pertinent to the evaluation of the efficacy and safety of apremilast in this patient population. Additionally, the Applicant submitted interim safety results of an ongoing phase 3b, open-label, long-term extension study (CC-10004-PPSO-004) for the roll-over subjects who successfully completed trial PPSO-003. A listing of the clinical studies relevant to the efficacy supplement S-013 is presented in Table 17.

Table 17. Listing of Clinical Studies Relevant to NDA 205437-S013

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies To Support Efficacy and Safety								
CC-10004-PPSO-003	03701763	Phase 3, R (2:1), DB, PC trial with apremilast extension period	Tablet, Oral dosing: weight ≥50 kg: apremilast 30 mg BID after 5-day titration or placebo; weight 20 kg to <50 kg: apremilast 20 mg BID after 3-day titration or placebo	Efficacy (at week 16) Primary: sPGA 0/1 Key secondary: PASI75 Other secondary: PASI50, %CFB-PASI, %CFB-BSA, CDLQI 0/1, %CFB-CDLQI Safety TEAE, stool diary, C-SSRS, tanner stage, height, weight, BMI, psoriasis flare/rebound	52 weeks: PC period (weeks 0-16) Apremilast extension period (weeks 16-52) Observational follow-up (weeks 52-66)	245	Pediatric subjects (age 6 to 17 years, inclusive), weight ≥20 kg, with moderate to severe plaque psoriasis (PASI ≥12, BSA ≥10%, sPGA ≥3)	106 sites in Belgium, Canada, Czech Republic, France, Israel, Italy, Netherlands, Russia, Spain, and the United States
Studies To Support Safety								
CC-10004-PPSO-004 Ongoing, database cut-off 3/27/23, snapshot 5/10/23	04175613	Phase 3b, open-label, long-term extension safety study	Tablet, Oral dosing: Weight ≥50 kg: apremilast 30 mg BID Weight 20 kg to <50 kg: apremilast 20 mg BID	Primary safety (TEAE, C-SSRS, tanner stage, growth, height, weight, BMI Secondary (maintenance of effect) sPGA 0/1	208 weeks	160	Roll-over subjects who successfully complete trial PPSO-003	48 sites in Belgium, Canada, Czech Republic, France, Israel, Italy, Russia, Spain, and the United States

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Other Studies Pertinent to the Review of Efficacy or Safety (e.g., Clinical Pharmacological Studies)								
CC-10004-PPSO-001	02576678	Phase 2, open-label PK/safety and tolerability study	Tablet, Oral dosing: Apremilast 20 mg BID: ages 12 to 17 years, weight ≥35 to <70 kg Apremilast 30 mg BID: ages 12 to 17 years, weight ≥70 kg Apremilast 20 mg BID: ages 6 to 11 years, weight ≥15 kg	Primary safety endpoints (TEAE, physical exam, vital signs, clinical laboratory, pregnancy test, ECG, concomitant medications) PK endpoints (C_{max}, T_{max}, AUC_{0-12}, AUC_{0-t}, CL/F, V_{ss}/F, V_z/F, $t_{1/2}$)	50 weeks: PK treatment period (weeks 0-2) Extension treatment period (weeks 2-50) Observational follow-up (at 4, 8, 52 weeks after last dose)	42	Pediatric subjects (age 6 to 17 years, inclusive), with moderate to severe plaque psoriasis (PASI≥12, BSA≥10%, sPGA≥3), weight ≥35 kg (for ages 12 to 17 inclusive) and ≥15 kg (for ages 6 to 11 inclusive)	11 sites in Canada, Germany, Spain, United States

Source: sNDA 205437-013, M 5.2 and individual study CSRs
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; BMI, body mass index; BSA, body surface area; C-SSRS, Columbia Suicide Severity Rating Scale; CDLQI, Children's Dermatology Life Quality Index; CFB, changes from baseline; CL/F, clearance from central compartment; C_{max}, maximum plasma concentration; DB, double-blind; ECG, electrocardiogram; NCT, National Clinical Trial; PC, placebo-controlled; PK, pharmacokinetic; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; $T_{1/2}$, half-life; TEAE, treatment-emergent adverse event; T_{max}, time to reach maximum plasma concentration; V_{ss}/F, steady-state volume of distribution; V_z/F, apparent volume of distribution

7.2. Review Strategy

Data Sources

The Applicant provided CSR and datasets (NDA 205437, SDN 1333 eCTD 0275) by electronic submission at the following network path: \\CDSESUB1\evsprod\NDA205437\0308

Data and Analysis Quality

In general, the data submitted by the Applicant to support the efficacy and safety of apremilast for the treatment of moderate to severe plaque psoriasis in pediatric subjects (6 years of age and older) appeared adequate and the data quality was found to be acceptable by the review team.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design

Trial PPSO-003 was a randomized, multicenter, double-blind, placebo-controlled, parallel-group, Phase 3 trial to evaluate the safety and efficacy of apremilast compared to placebo in pediatric subjects 6 to 17 years of age with moderate to severe plaque psoriasis. For enrollment, the protocol specified the following key inclusion criteria:

- Male or female 6 to 17 years of age (inclusive)
- Weight ≥20 kg
- An age and sex specific body mass index (BMI) value no lower in range than the 5th percentile on the Centers for Disease Control (CDC) growth chart for children and adolescents
- Diagnosis of plaque psoriasis for at least 6 months prior to screening
- Have moderate to severe plaque psoriasis at screening and baseline as defined by:
  - Static Physician Global Assessment (sPGA) score ≥3 (moderate)
  - Psoriasis Area and Severity Index (PASI) score ≥12
  - Body surface area (BSA) ≥10%
- Disease inadequately controlled by or inappropriate for topical therapy for psoriasis
- Candidate for systemic therapy or phototherapy

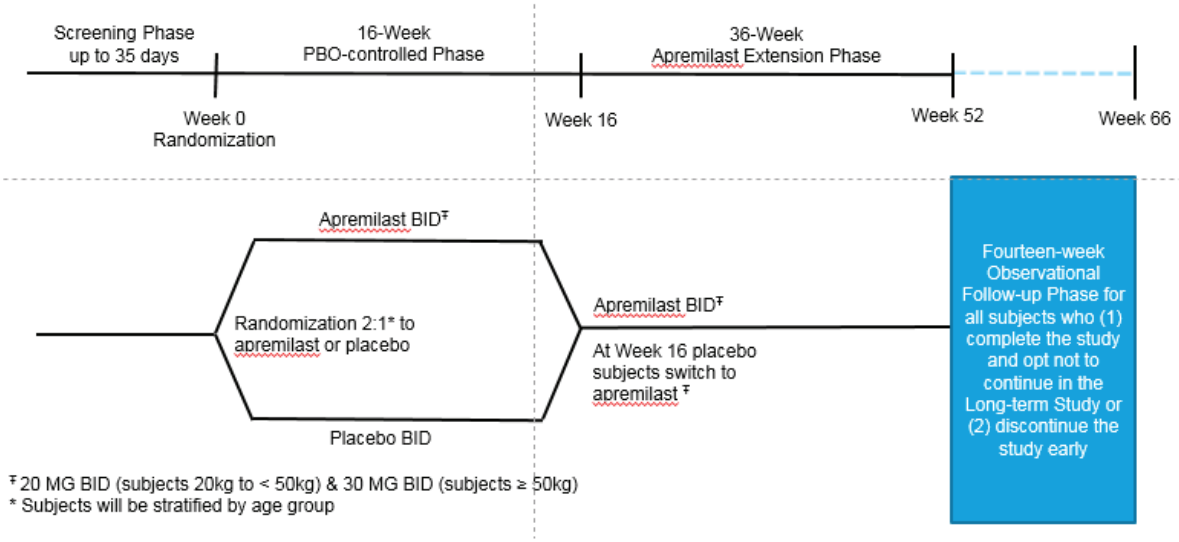
The trial was designed to enroll and randomize approximately 230 subjects in a 2:1 ratio to receive either apremilast tablets or placebo tablets. The protocol specified stratifying the

randomization by baseline age group (6-11 years and 12-17 years). The protocol specified randomizing a minimum of 75 subjects in each age group. Figure 9 presents the trial design schematic for Trial PPSO-003. The trial consisted of the following four phases:

- Screening phase (up to 35 days)
- Double-Blind, Placebo Controlled Phase (Weeks 0 to 16): subjects 20 kg to <50 kg received apremilast 20 mg twice daily (BID) or placebo BID, and subjects ≥50 kg received apremilast 30 mg BID or placebo BID. In addition, a dose titration scheduled was used for the first week, see Table 18. From Week 8 through Week 16, any subjects with a PASI increase ≥50% from baseline was eligible to commence treatment with moderate-to-high potency topical steroid preparations (early escape). These subjects were considered treatment failures in the efficacy analyses.
- Apremilast Extension Phase (Weeks 16 to 52): placebo subjects switched at Week 16 to apremilast 20 mg BID or 30 mg BID, according to baseline weight, and a dose titration schedule was used for the first week, see Table 19. All other subjects continued to receive either apremilast 20 mg BID or apremilast 30 mg BID based on their original dosing assignment.
- Observational Follow-up Phase (14 weeks): all subjects who completed the apremilast extension phase may opt to enroll in a separate long-term study (for up to 4 years or until approval, whichever comes first). Subjects who choose not to participate in the long-term study, or discontinue the study early, were scheduled to return for observational follow-up visits four, eight, and fourteen weeks after the last dose of study drug.

Subjects were scheduled to have the following site visits: screening (up to Day -35), baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 40, 44, 48, and 52. Subjects who choose not to participate in the long-term study, or discontinue the study early, were scheduled to return for observational follow-up visits at 4, 8, and 14 weeks after the last dose of IP.

Figure 9. Trial Design Schematic, Trial PPS0-003



Source: page 29 of the protocol for Trial PPSO-003
Abbreviations: BID, twice daily

Table 18. Treatment Schema for Dose Titration at Baseline (Week 0)

	Week 0											
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6-7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Apremilast 30 mg BID	10 mg A 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg P 20 mg A 30 mg P	20 mg A 30 mg P	20 mg A 30 mg P	20 mg A 30 mg P	20 mg P 30 mg A	30 mg A	30 mg A
Placebo (30 mg)	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	20 mg P 30 mg P	20 mg P 30 mg P	20 mg P 30 mg P	20 mg P 30 mg P	30 mg P	30 mg P
Apremilast 20 mg BID	10 mg A 20 mg P	10 mg P 20 mg P	10 mg A 20 mg P	10 mg A 20 mg P	10 mg A 20 mg P	10 mg P 20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A
Placebo (20 mg)	10 mg P 20 mg P	10 mg P 20 mg P	10 mg P 20 mg P	10 mg P 20 mg P	10 mg P 20 mg P	10 mg P 20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P

Source: page 51 of the protocol for Trial PPSO-003
Abbreviations: A, apremilast; BID, twice daily; P, placebo

Table 19. Treatment Schema for Dose Titration at Week 16

	Week 16											
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6-7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Apremilast 30 mg BID	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	20 mg P 30 mg A	20 mg P 30 mg A	20 mg P 30 mg A	20 mg P 30 mg A	30 mg A	30 mg A
Apremilast 20 mg BID	10 mg P 20 mg A	10 mg P 20 mg A	10 mg P 20 mg A	10 mg P 20 mg A	10 mg P 20 mg A	10 mg P 20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A
Placebo to Apremilast 30 mg BID	10 mg A 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg P 20 mg A 30 mg P	20 mg A 30 mg P	20 mg A 30 mg P	20 mg A 30 mg P	20 mg P 30 mg A	30 mg A	30 mg A
Placebo to Apremilast 20 mg BID	10 mg A 20 mg P	10 mg P 20 mg P	10 mg A 20 mg P	10 mg A 20 mg P	10 mg A 20 mg P	10 mg P 20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A

Source: page 52 of the protocol for Trial PPSO-003
Abbreviations: A, apremilast; BID, twice daily; P, placebo

8.1.2. Endpoints

The protocol-specified primary efficacy endpoint was the proportion of subjects with an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16. The protocol specified a key secondary efficacy endpoint of the proportion of subjects who achieve at least a 75% reduction in PASI (PASI-75) from baseline at Week 16.

The protocol specified five "other" secondary efficacy endpoints; however, the analyses of these endpoints were not controlled for multiplicity. Therefore, these endpoints are not presented in this review.

Table 20. Static Physician Global Assessment

Score	Category	Description
0	Clear	Plaque Elevation =0 (no elevation over normal skin) Scaling =0 (no evidence of scaling) Erythema =0 (except for residual hyperpigmentation/hypopigmentation)
1	Almost Clear	Plaque Elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = ± (surface dryness with some desquamation) Erythema = ± (faint, diffuse pink or slight red coloration)
2	Mild	Plaque Elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions) Erythema = mild (light red coloration)
3	Moderate	Plaque Elevation = marked (marked definite elevation with rough or sloped edges) Scaling = coarser (coarser scale covering most or all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque Elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarser (coarse, non tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)

Source: page 90 of the protocol for Trial PPSO-003

Figure 10. Psoriasis Area and Severit Index PASI

STEP A. Please write in the appropriate number for rows 1 - 3 using the scale below:

0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe

	HEAD	TRUNK	UPPER LIMBS	LOWER LIMBS
1. Erythema				
2. Thickness				
3. Scaling				
4. TOTAL Each Column				

STEP B. Enter the number of hands the psoriasis covers on each body area

	HEAD	TRUNK	UPPER LIMBS	LOWER LIMBS
5. Number of Hands				
6. Area (% of total BSA)	10	30	20	40

STEP C. Calculate % of involvement:

7. % of each region involved **[(Row 5 ÷ Row 6) x 100*]**				
8. TOTAL BSA (sum of # of hands from row 5)				

STEP D. Select Degree of Involvement using value in Row 7:

0 = No involvement

1 = <10%

2 = 10 < 30%

3 = 30 < 50%

4 = 50 < 70%

5 = 70 < 90%

6 = 90 < 100%

9. Degree of Involvement (0-6) of each region				

STEP E. Calculate PASI (Row 4 x Row 6 x Row 9) ÷ 100*

10. PASI for each body region				
11. TOTAL PASI (sum of Row 10 subscores)				

Source: page 91 of the protocol for Trial PPSO-003
* Round all calculations to 1 decimal place
Abbreviations: BSA, body surface area

8.1.3. Statistical Methodology

Analysis Populations

The primary analysis population specified in the protocol and SAP was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocol and SAP also specified conducting sensitivity analyses using the per-protocol (PP) population. The PP population was defined as all subjects included in the ITT population who receive at least one dose of IP, have both baseline and at least one post-treatment sPGA assessment, and have no important protocol deviations which may affect efficacy assessments in the placebo-controlled phase.

Analysis Methods

The protocol and SAP specified analyzing the binary efficacy endpoints using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline age group (i.e., the factor used to stratify the randomization). The protocol and SAP specified calculating the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated two-sided 95% confidence intervals (CIs) using a normal approximation to the weighted average.

Multiplicity Adjustment Plan

To control the Type I error rate, the protocol and SAP specified that the key secondary efficacy endpoint will be tested only if the primary efficacy endpoint is significant with a two-sided p-value less than 0.05. As previously noted, the "other" secondary efficacy endpoints were not included in the multiplicity testing strategy. The protocol and SAP stated that "for the other secondary efficacy endpoints, multiplicity adjustment will not be applied, and statistical significance will not be claimed."

Handling of Intercurrent Events and Missing Data

The protocol and SAP specified that subjects who terminate early due to lack of efficacy or add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16 will be considered treatment failures. These subjects were imputed as non-responders for the primary and key secondary endpoints.

The protocol and SAP specified the primary method for handling missing data to be the multiple imputation (MI) approach. The protocol and SAP specified not including the assessment data in the MI from subjects who terminated early due to lack of efficacy or added moderate-to-severe high potency topical steroid preparations (early escape), or other protocol prohibited medications prior to Week 16.

The protocol and SAP specified the following two-step process for the MI:

- In the first step, missing monotone data will be imputed using the Markov Chain Monte Carlo (MCMC) method. The protocol and SAP specified imputing the missing data 25

times by treatment arm and stratification factor (i.e., baseline age group). In case there are convergence issues, the protocol and SAP specified that a simple model will be used to impute the missing scores by treatment, with further simplification by dropping both treatment and stratification factor in imputation model if necessary. The imputed scores will be rounded to the nearest integer. For sPGA, the minimum and the maximum values for imputation will are 0 and 4. For PASI, the minimum and the maximum values for imputation will are 0 and 72. The protocol and SAP specified using seed =17813721 for this step.

- In the second step, the protocol and SAP specified using the predictive mean matching method to impute the remaining missing data, which will include treatment arm, stratification factor, and values (i.e., sPGA for primary endpoint and PASI for key secondary endpoint) at the scheduled analysis visits. The protocol and SAP specified using seed =55218163 for this step.

After the completion of the imputation, sPGA response at Week 16 and PASI-75 at Week 16 are derived based on both observed and imputed scores. Data from subjects who terminate early due to lack of efficacy or add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16 are added to the 25 imputed datasets as non-responders.

The protocol and SAP specified using the last observation carried forward (LOCF), non-responder imputation (NRI), and the tipping point analysis as sensitivity analyses for the handling of missing data. For the tipping point analysis, the SAP stated:

> "For the tipping point analyses, let M1 and M2 be the total number of subjects with missing data of primary endpoint in Apremilast and Placebo. There are overall (M1+1)*(M2+1) possible ways for imputing missing data as responders or non-responders in statistical analysis, ranging from imputing all missing values as non-responders to imputing all missing values as responders in each of the two arms. For each of the (M1+1)*(M2+1) different imputation patterns, the Chi-square test will be used for testing statistical significance and the output can be plotted in a rectangle for inspection. The staircase region that separates significant and non-significant outcomes forms the tipping-point boundary."

8.1.4. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial PPSO-003 enrolled and randomized a total of 245 subjects (163 to apremilast and 82 to placebo) from 62 centers. Table 21 presents the subject disposition for the placebo-controlled phase of the trial. The discontinuation rate was slightly higher in the placebo group compared to the apremilast group. The demographics and baseline disease characteristics were generally balanced across the two treatment groups and are presented in Table 22.

Table 21. Subject Disposition for the Placebo-Controlled Phase (Weeks 0-16), Trial PPSO-003

Subject Disposition	Apremilast	Placebo	Total
Randomized subjects	163	82	245
Treated subjects	163	80	243
Discontinued, n (%)[1]	14 (9)	10 (12)	24 (10)
Withdrawal by parent/guardian	5 (3)	3 (4)	8 (3)
Adverse events	5 (3)	1 (1)	6 (2)
Withdrawal by subject	3 (2)	2 (2)	5 (2)
Lack of efficacy	0	2 (2)	2 (1)
Other	0	2 (2)	2 (1)
Lost to follow-up	1 (1)	0	1 (<1)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] The percentages were calculated based on the number of subjects that were randomized.

Table 22. Demographics and Baseline Disease Characteristics, ITT Population[1], Trial PPSO-003

Characteristics	Apremilast (N=163)	Placebo (N=82)	Total (N=245)
Age (years)			
Mean (SD)	12.3 (3.3)	12.2 (3.2)	12.2 (3.3)
Median	13.0	13.0	13.0
Min, Max	6.0, 17.0	6.0, 17.0	6.0, 17.0
Categories, n (%)			
6 to 11	67 (41)	34 (41)	101 (41)
12 to 17	96 (59)	48 (59)	144 (59)
Sex, n (%)			
Male	74 (45)	43 (52)	117 (48)
Female	89 (55)	39 (48)	128 (52)
Race, n (%)			
White	140 (86)	73 (89)	213 (87)
Asian	6 (4)	3 (4)	9 (4)
Black or African American	5 (3)	3 (4)	8 (3)
American Indian or Alaska Native	2 (1)	0	2 (1)
Unknown or not collected	10 (6)	3 (4)	13 (5)
Ethnicity, n (%)			
Hispanic or Latino	24 (15)	8 (10)	32 (13)
Not Hispanic or Latino	129 (79)	71 (87)	200 (82)
Unknown or not reported	10 (6)	3 (4)	13 (5)
Weight (kg)			
Mean (SD)	52.0 (21.1)	51.8 (22.2)	52.0 (21.4)
Median	50.0	50.1	50.0
Min, Max	20.0, 145.2	21.8, 135.9	20.0, 145.2
Categories, n (%)			
20 to <50	80 (49)	40 (49)	120 (49)
≥50	83 (51)	42 (51)	125 (51)
Country, n (%)			
United States	38 (23)	20 (24)	58 (24)
Outside United States	125 (77)	62 (76)	187 (76)
Prior conventional systemic therapy, n (%)			
Yes	24 (15)	18 (22)	42 (17)
No	139 (85)	64 (78)	203 (83)
Prior biologic therapy, n (%)			
Yes	9 (6)	5 (6)	14 (6)
No	154 (94)	77 (94)	231 (94)

Characteristics	Apremilast (N=163)	Placebo (N=82)	Total (N=245)
sPGA score, n (%)			
3 – Moderate	122 (75)	63 (77)	185 (76)
4 – Severe	41 (25)	19 (23)	60 (24)
PASI score			
Mean (SD)	20.0 (8.2)	19.5 (7.9)	19.8 (8.1)
Median	17.4	16.5	17.2
Min, Max	12.0, 47.7	12.0, 50.6	12.0, 50.6
Percent BSA			
Mean (SD)	31.9 (18.4)	30.8 (19.0)	31.5 (18.6)
Median	27.0	24.0	26.0
Min, Max	10.0, 92.0	10.0, 88.0	10.0, 92.0

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADBL.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects.
Abbreviations: BSA, body surface area; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician Global Assessment

8.1.5. Intercurrent Events and Remote Visits

Table 23 summarizes the rates of intercurrent events (ICEs) and remote visits during the placebo-controlled phase. In the Applicant's efficacy analyses for the clinical study report (CSR), the Applicant had a total of 6 subjects (3 in the apremilast group and 3 in the placebo group) that had ICEs of added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16. During the review, the Statistical Reviewer identified two additional subjects (i.e., (b) (6)) with ICEs of added concomitant medication of moderate-to-high potency topical steroid prior to Week 16 due to psoriasis exacerbation or worsening. In an Information Request (IR) sent on March 4, 2024, the FDA requested that the Applicant clarify why these 2 subjects were not considered to have an ICE. In addition, the FDA requested that the Applicant provide results of the primary and key secondary efficacy endpoints where these 2 subjects are handled in the same manner as the other 6 subjects (i.e., imputed as non-responders), see Section .1.6 for the results. In the Applicant's response (dated March 14, 2024), the Applicant stated the following as their rationale for not considering these 2 subjects to have an ICE:

- "As described above, Subjects (b) (6) started moderate-to-high potency topical steroid on or after the day that the last efficacy assessment was completed. Because the last efficacy assessments were on or before the dates that the medication was started, these subjects were not flagged as having medication ICEs, and therefore were not imputed as non-responders. Instead, missing values were imputed using the multiple imputation method based on similar subjects who remained in the study, as specified in the SAP."
- "The other 6 subjects referenced by the FDA (i.e., (b) (6) (b) (6)) were imputed as non-responders because these subjects had efficacy visits completed after starting prohibited medication or moderate-to-high potency topical steroid."

A total of 7 visits from 5 subjects had sPGA/PASI assessments conducted remotely during the placebo-controlled period. There were no remote visits at Week 16 (i.e., primary efficacy timepoint) for which sPGA/PASI assessments were conducted.

Table 23. Intercurrent Events and Remote Visits for the Placebo-Controlled Phase (Weeks 0-16), ITT Population[1], Trial PPSO-003

Intercurrent Events (ICEs)	Apremilast (N=163) n (%)	Placebo (N=82) n (%)
ICE 1: terminated early due to lack of efficacy before Week 16	0	2 (2)
ICE 2: added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16		
Applicant's original analysis in CSR	3 (2)	3 (4)
FDA requested analysis	5 (3)	3 (4)
Remote visits		
Baseline	1 (1)	0
Week 4	1 (1)	1 (1)
Week 8	0	2 (2)[1]
Week 12	1 (1)	1 (1)[2]
Week 16	0	0

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADCM.xpt, ADDV.xpt
[1] One of these placebo subjects (b) (6) received protocol prohibited medication (i.e., ustekinumab) at Week 8.
[2] The placebo subject (b) (6) received moderate-to-high potency topical steroid (i.e., triamcinolone) at Week 12. This subject had remote visits at Weeks 4, 8, and 12.

8.1.6. Results for the Primary and Key Efficacy Endpoints

Table 24 presents the results for the primary and key secondary efficacy endpoints regardless of the study visit type in the ITT population. The table includes the results for the Applicant's original analyses contained in the CSR as well as those requested in the IR sent on March 4, 2024 (i.e., 2 additional subjects with ICEs of added concomitant medication of moderate-to-high potency topical steroid prior to Week 16 are imputed as non-responders). For both sets of analyses, apremilast was statistically superior to placebo for the primary and key secondary efficacy endpoints (p-values <0.001). The results were similar between the two sets of analyses (i.e., Applicant's Original Analysis vs. FDA-Requested Analysis). The results in the PP population (not shown) were similar to those obtained using the ITT population. There was a total of 7 subjects (3 in the apremilast group and 4 in the placebo group) that were excluded from the PP population.

Table 24. Results for the Primary and Key Secondary Efficacy Endpoints, ITT Population[1], Trial PPSO-003

	Applicant's Original Analysis in CSR		FDA-Requested Analysis (IR; March 4, 2024) Two Additional Subjects With ICE	
Endpoint	**Apremilast (N=163)**	**Placebo (N=82)**	**Apremilast (N=163)**	**Placebo (N=82)**
Primary Endpoint				
sPGA response[2] at Week 16				
Proportion[3]	33.1%	11.5%	33.1%	10.8%
Unadjusted difference (95% CI)	21.6% (11.2%, 32.0%)		22.3% (12.2%, 32.3%)	
Adjusted difference (95% CI)[4]	21.7% (11.2%, 32.1%)		22.3% (12.2%, 32.4%)	
p-value[4]	<0.001		<0.001	
Key Secondary Endpoint				
PASI-75 at Week 16				
Proportion[3]	45.4%	16.1%	45.7%	16.0%
Unadjusted difference	29.4% (17.8%, 40.9%)		29.7% (17.9%, 41.5%)	
Adjusted difference (95% CI)[4]	29.4% (17.8%, 40.9%)		29.7% (17.9%, 41.6%)	
p-value[4]	<0.001		<0.001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSPGAI.xpt, ADSPGA.xpt, ADP75I.xpt, ADPASI.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who terminated early due to lack of efficacy before Week 16 and subjects who added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications before Week 16 were imputed as non-responders. Missing data was imputed using multiple imputation (MI).
[2] Response was defined as an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[3] The value displayed is the average of the 25 imputed datasets.
[4] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., baseline age group) using CMH weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by baseline age group.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel Haenszel; ICE, intercurrent event; IR, information request; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment

In the Filing Communication letter (sent on December 11, 2023), the FDA requested that the Applicant conduct sensitivity analyses for the primary and key secondary efficacy endpoints where remote visits are treated as missing and imputed based on the primary method for handling the missing data (i.e., MI). In the Applicant's response (dated December 21, 2023), the Applicant provided results for the requested sensitivity analyses; however, the provided results did not follow the protocol/SAP specified approach for handling subjects with ICEs of early termination due to lack of efficacy or ICEs of added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16 (i.e., none of the data for subjects with ICEs should be included in the MI steps). Consequently, the FDA requested (IR sent on March 4, 2024) that the Applicant submit the results for the sensitivity analyses that follow the protocol/SAP. In addition, the FDA requested that the Applicant also consider the two additional subjects with ICEs of added concomitant medication of moderate-to-high potency topical steroid prior to Week 16 (i.e., impute as non-responders). Table 25 presents the results when assessments based on remote visits are treated as missing. The results are similar to those in Table 24 as only a total of 7 visits from 5 subjects had sPGA/PASI assessments conducted remotely, and none of the visits were at Week 16.

Table 25. Results for the Primary and Key Secondary Efficacy Endpoints When Assessments Based on Remote Visits are Treated as Missing, ITT Population[1], Trial PPSO-003

	FDA-Requested Analysis (IR; March 4, 2024) Remote Visits as Missing		FDA-Requested Analysis (IR; March 4, 2024) Remote Visits as Missing AND Two Additional Subjects With ICE	
Endpoint	**Apremilast (N=163)**	**Placebo (N=82)**	**Apremilast (N=163)**	**Placebo (N=82)**
Primary Endpoint				
sPGA response[2] at Week 16				
Proportion[3]	32.9%	11.1%	33.2%	11.0%
Unadjusted difference (95% CI)	21.8% (11.5%, 32.1%)		22.1% (11.9%, 32.3%)	
Adjusted difference (95% CI)[4]	21.9% (11.6%, 32.2%)		22.2% (12.0%, 32.4%)	
p-value[4]	<0.001		<0.001	
Key Secondary Endpoint				
PASI-75 at Week 16				
Proportion[3]	45.2%	16.3%	45.4%	15.7%
Unadjusted difference	28.9% (17.3%, 40.5%)		29.7% (18.3%, 41.2%)	
Adjusted difference (95% CI)[4]	28.9% (17.2%, 40.6%)		29.8% (18.3%, 41.3%)	
p-value[4]	<0.001		<0.001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSPGACV.xpt, ADPASICV.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who terminated early due to lack of efficacy before Week 16 and subjects who added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications before Week 16 were imputed as non-responders. Missing data was imputed using multiple imputation (MI).
[2] Response was defined as an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[3] The value displayed is the average of the 25 imputed datasets.
[4] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., baseline age group) using CMH weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by baseline age group.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel Haenszel; ICE, intercurrent event; IR, information request; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment

Table 26 presents the number of subjects with missing data at Week 16, excluding subjects with an ICE (i.e., subjects who terminated early due to lack of efficacy before Week 16 and subjects with missing data who added moderate-to-high potency topical steroid preparations [early escape] or other protocol prohibited medications before Week 16). Table 26 also presents the results for the primary and key secondary efficacy endpoints across the various prespecified imputation methods for all visit types and when the remote visits are treated as missing. For Table 26, the two additional subjects with ICEs of added concomitant medication of moderate-to-high potency topical steroid prior to Week 16 are imputed as non-responders. The results were similar across the various methods. For NRI, the results were the same between all visits and when remote visits are treated as missing because there were no visits at Week 16 that had sPGA/PASI assessments conducted remotely. For LOCF, the results were the same between all visits and when remote visits are treated as missing because none of the visits that had sPGA/PASI assessments conducted remotely were carried forward (i.e., subjects with remote visits either had an ICE [imputed as non-responders] or an in-person visit at Week 16).

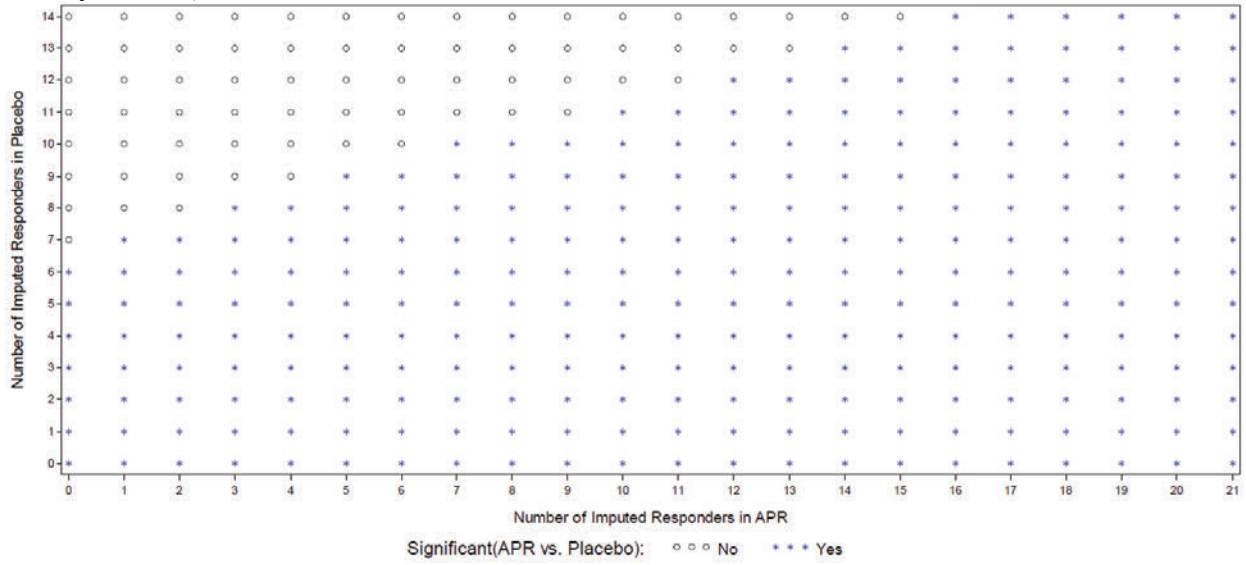
Table 26. Results for the Primary and Key Secondary Efficacy Endpoints by Various Methods to Impute Missing Data, ITT Population[1], Trial PPSO-003

Parameter	Apremilast (N=163)	Placebo (N=82)	Difference (95% CI)[7]
Missing Data[2] at Week 16, n (%)	19 (12)	14 (17)	-
Primary Endpoint: sPGA Response[3] at Week 16			
All visits			
MI (primary)[4]	33.1%	10.8%	22.3% (12.2%, 32.4%)
LOCF[5]	31.3%	11.0%	20.4% (10.5%, 30.3%)
NRI[6]	30.1%	9.8%	20.4% (10.8%, 29.9%)
Remote visits as missing			
MI (primary)[4]	33.2%	11.0%	22.2% (12.0%, 32.4%)
LOCF[5]	31.3%	11.0%	20.4% (10.8%, 29.9%)
NRI[6]	30.1%	9.8%	20.4% (10.5%, 30.3%)
Key Secondary Endpoint: PASI-75 at Week 16			
All visits			
MI (primary)[4]	45.7%	16.0%	29.7% (17.9%, 41.6%)
LOCF[5]	44.2%	14.6%	29.6% (18.7%, 40.4%)
NRI[6]	42.3%	13.4%	28.9% (18.3%, 39.5%)
Remote visits as missing			
MI (primary)[4]	45.4%	15.7%	29.8% (8.3%, 41.3%)
LOCF[5]	44.2%	14.6%	29.6% (18.7%, 40.4%)
NRI[6]	42.3%	13.4%	28.9% (18.3%, 39.5%)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADSPGACV.xpt, ADPASI.xpt, ADPASICV.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who terminated early due to lack of efficacy before Week 16 and subjects who added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications before Week 16 were imputed as non-responders.
[2] Excludes subjects who terminated early due to lack of efficacy before Week 16 and subjects who added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications before Week 16 were imputed as non-responders.
[3] Response was defined as an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[4] Missing data imputed using multiple imputation (MI). Rates displayed are the averages over the 50 imputed datasets.
[5] Missing data imputed using last observation carried forward (LOCF).
[6] Missing data imputed using non-responder imputation (NRI).
[7] Difference and 95% CI based on the weighted average of the treatment differences across the strata (i.e., baseline age group) using CMH weights.
Abbreviations: CI, confidence interval; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment

As specified in the SAP, the Applicant conducted tipping point analyses for the primary and key secondary efficacy endpoints. For the Applicant's analyses, subjects who had ICEs are imputed as non-responders prior to the tipping; however, the two additional subjects identified with ICEs of added concomitant medication of moderate-to-high potency topical steroid prior to Week 16 are not imputed as non-responders. These two subjects (both in the apremilast group) have missing data at Week 16. Therefore, the Applicant's tipping point analyses have 21 subjects in the apremilast arm with missing data instead of the 19 subjects in Table 26. Figure 11 and Figure 12 present the instances when the results tip (i.e., are no longer significant at the two-sided 0.05 level) for the primary and key secondary efficacy endpoints, respectively. For sPGA response, the results tip when 7 out of the 14 subjects with missing data in the placebo group are imputed as responders and all 21 subjects in the apremilast group are imputed as non-responders. For PASI-75, the results tip when 13 out of the 14 subjects with missing data in the placebo group are imputed as responders and all 21 subjects in the apremilast group are imputed as non-responders. These sensitivity analyses support the robustness of the results for the primary and key secondary efficacy endpoints.

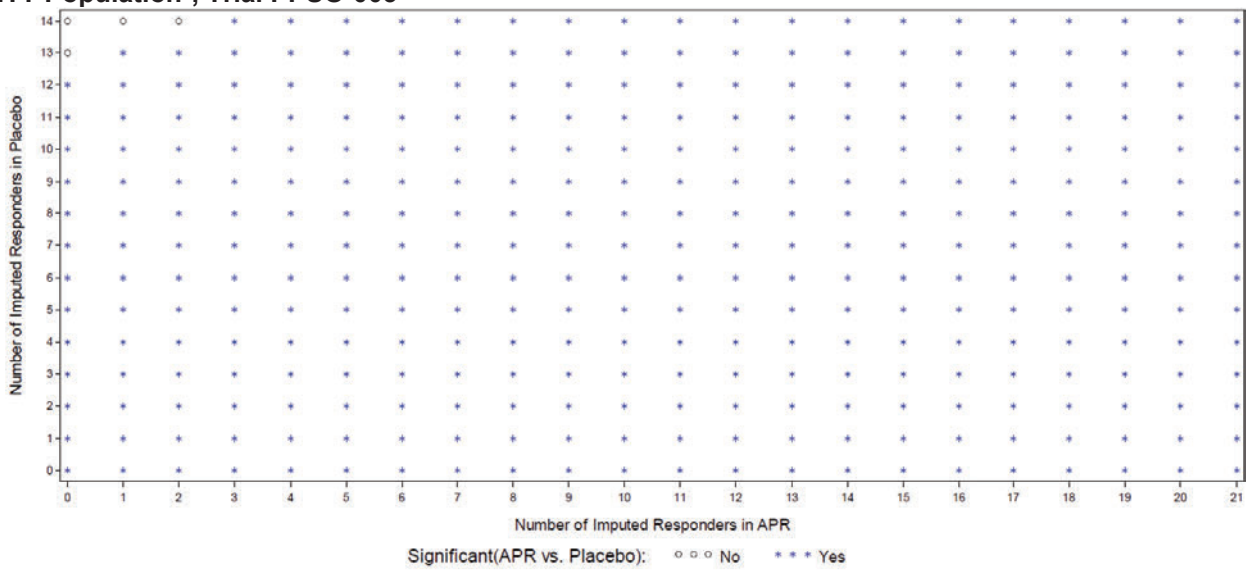
Figure 11. Tipping Point Analysis for the Primary Efficacy Endpoint (sPGA Response[1] at Week 16), ITT Population[2], Trial PPSO-003



The figure presents the matrix for all possible combinations of imputing total numbers of responders for subjects with missing values in the two treatment arms.
For each combination, the chi-square test was used to compare the overall response rates between the two treatment arms (APR vs. Placebo) at the two-sided 0.05 significance level.

Source: Applicant's Figure 14-4.1.3 in clinical study report for Trial PPSO-003
[1] Response was defined as an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[2] Intent-to-treat (ITT) population: all randomized subjects.
Abbreviations: APR, apremilast; sPGA, static Physician Global Assessment

Figure 12. Tipping Point Analysis for the Key Secondary Efficacy Endpoint (PASI-75 at Week 16), ITT Population[1], Trial PPSO-003



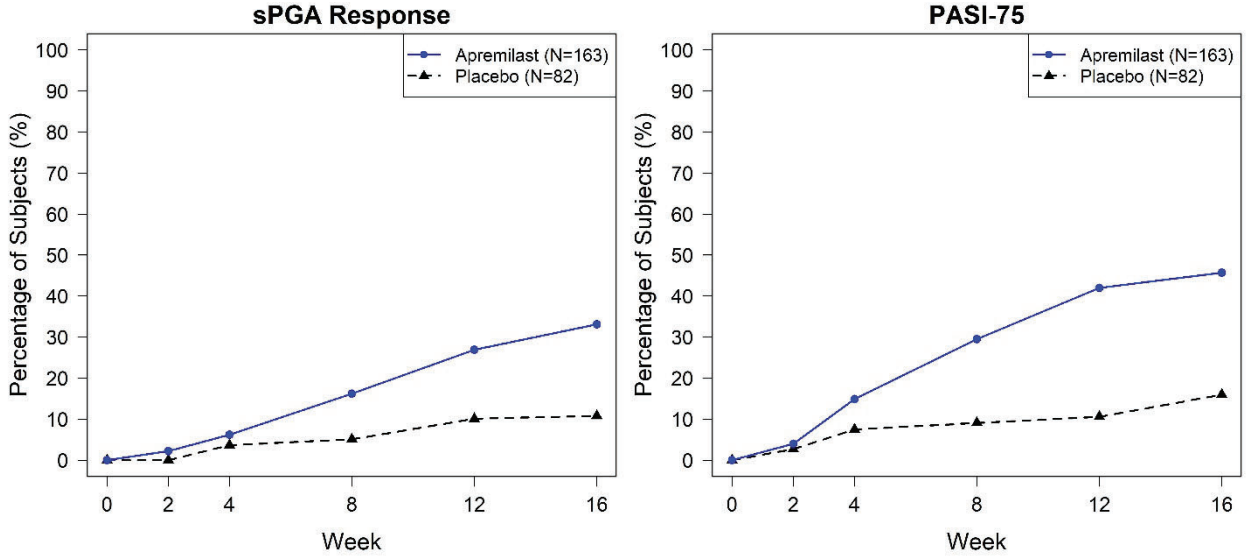
The figure presents the matrix for all possible combinations of imputing total numbers of responders for subjects with missing values in the two treatment arms.
For each combination, the chi-square test was used to compare the overall response rates between the two treatment arms (APR vs. Placebo) at the two-sided 0.05 significance level.

Source: Applicant's Figure 14-4.1.3 in clinical study report for Trial PPSO-003
[1] Intent-to-treat (ITT) population: all randomized subjects.
Abbreviations: APR, apremilast; PASI, Psoriasis Area and Severity Index

8.1.7. Results for Efficacy Over Time

Figure 13 presents the results for sPGA response and PASI-75 by visit. For this figure, the two additional subjects with ICEs of added concomitant medication of moderate-to-high potency topical steroid prior to Week 16 are imputed as non-responders.

Figure 13. Results for sPGA Response[1] and PASI-75 by Visit, ITT Population[2], Trial PPSO-003



Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASI.xpt
[1] Response was defined as an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[2] Intent-to-treat (ITT) population: all randomized subjects. Subjects who terminated early due to lack of efficacy before Week 16 and subjects who added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications before Week 16 were imputed as non-responders. Missing data was imputed using multiple imputation (MI). Rates displayed are the averages over the 25 imputed datasets.
Abbreviations: PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment

8.1.8. Findings in Special/Subgroup Populations

Table 27 and Table 28 present the subgroup analysis results for the primary and key secondary efficacy endpoints, respectively. For this figure, the two additional subjects with ICEs of added concomitant medication of moderate-to-high potency topical steroid prior to Week 16 are imputed as non-responders. The responder rate in the apremilast group was higher than in the placebo group except in the subgroup of subjects that identified as Hispanic or Latino; however, the number of subjects in this subgroup was relatively small (i.e., 24 in the apremilast group and 8 in the placebo group). Therefore, it would be difficult to make reliable conclusions regarding this subgroup comparison.

Table 27. Results for the Primary Efficacy Endpoint (sPGA Response[1] at Week 16) by Subgroups, ITT Population[2], Trial PPSO-003

Subgroups (n[A], n[P])	Apremilast (N=163)	Placebo (N=82)	Difference (95% CI)[3]
Age (years)			
6 to 11 (67, 34)	49.9%	9.8%	40.1% (24.0%, 56.2%)
12 to 17 (96, 48)	21.4%	11.6%	9.8% (-2.6%, 22.2%)

Subgroups (n[A], n[P])	Apremilast (N=163)	Placebo (N=82)	Difference (95% CI)[3]
Sex			
Male (74, 43)	19.9%	6.0%	14.3% (2.0%, 26.7%)
Female (89, 39)	44.0%	16.1%	27.4% (11.8%, 43.0%)
Race			
White (140, 73)	33.6%	10.7%	23.2% (12.3%, 34.1%)
Other races (23, 9)	30.1%	12.0%	15.4% (-11.9%, 42.7%)
Ethnicity			
Hispanic or Latino (24, 8)	23.0%	38.5%	-18.8% (-56.5%, 18.9%)
Not Hispanic or Latino / Not reported or unknown (139, 74)	34.8%	7.8%	27.4% (17.1%, 37.7%)
Weight (kg)			
20 to <50 (80, 40)	47.7%	20.8%	27.0% (9.2%, 44.7%)
≥50 (83, 42)	19.0%	1.3%	17.6% (8.0%, 27.2%)
Country			
United States (38, 20)	27.9%	16.4%	10.8% (-10.4%, 32.1%)
Outside United States (125, 62)	34.7%	9.0%	25.8% (14.1%, 37.5%)
Baseline sPGA score			
3 – Moderate (122, 63)	32.7%	10.3%	23.4% (11.9%, 34.9%)
4 – Severe (41, 19)	34.2%	12.6%	17.3% (-5.1%, 39.7%)
Overall	33.1%	10.8%	22.3% (12.2%, 32.3%)

Source: Statistical Reviewer's Analysis; ADSL.xpt, ADSPGA.xpt
[1] Response was defined as an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[2] Intent-to-treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI).
[3] Difference and 95% CI based on the weighted average of the treatment differences across the strata (i.e., baseline age group) using CMH weights.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel Haenszel; sPGA, static Physician Global Assessment

Table 28. Results for the Key Secondary Efficacy Endpoint (PASI-75 at Week 16) by Subgroups, ITT Population[1], Trial PPSO-003

Subgroups (n[A], n[P])	Apremilast (N=163)	Placebo (N=82)	Difference (95% CI)[2]
Age (years)			
6 to 11 (67, 34)	53.1%	13.9%	39.3% (21.3%, 57.2%)
12 to 17 (96, 48)	40.5%	17.4%	23.0% (7.6%, 38.5%)
Sex			
Male (74, 43)	37.6%	12.0%	25.8% (10.3%, 41.3%)
Female (89, 39)	52.4%	20.3%	31.8% (14.3%, 49.4%)
Race			
White (140, 73)	49.1%	16.3%	32.9% (20.4%, 45.4%)
Other races (23, 9)	24.9%	13.3%	9.4% (-19.0%, 37.8%)
Ethnicity			
Hispanic or Latino (24, 8)	37.7%	40.0%	-1.1% (-42.2%, 40.0%)
Not Hispanic or Latino / Not Reported or Unknown (139, 74)	47.1%	13.4%	33.9% (21.8%, 46.1%)
Weight (kg)			
20 to <50 (80, 40)	52.7%	21.8%	30.7% (13.0%, 48.4%)
≥50 (83, 42)	38.9%	10.4%	28.5% (13.2%, 43.8%)
Country			
United States (38, 20)	44.3%	29.8%	14.1% (-12.9%, 41.1%)
Outside United States (125, 62)	46.1%	11.5%	34.6% (22.2%, 47.1%)
Baseline sPGA score			
3 – Moderate (122, 63)	46.2%	12.7%	33.9% (21.3%, 46.5%)
4 – Severe (41, 19)	44.0%	26.7%	15.0% (-12.9%, 42.9%)

Subgroups (n[A], n[P])	Apremilast (N=163)	Placebo (N=82)	Difference (95% CI)[2]
Overall	45.7%	16.0%	29.7% (17.9%, 41.6%)

Source: Statistical Reviewer's Analysis; ADSL.xpt, ADPASI.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI).
[2] Difference and 95% CI based on the weighted average of the treatment differences across the strata (i.e., baseline age group) using CMH weights.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel Haenszel; sPGA, static Physician Global Assessment

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of apremilast for pediatric subjects (≥6 years of age) with moderate to severe plaque psoriasis relied primarily on safety data from the phase 3, efficacy/safety trial PPSO-003; supported by safety data from the phase 2, PK/safety study PPSO-001, and the interim safety data for the phase 3b, long term safety (LTS) study PPSO-004. Because of different study designs, the Applicant submitted safety data for each study separately and did not pool or integrate safety data (e.g., as an ISS). Safety results reported for the phase 3 trial PPSO-003 will be the main focus of this review.

Trial PPSO-003

The safety analysis population (all randomized subjects who used the study drug at least once) for trial PPSO-003 included 243 subjects randomized (2:1) to treatment with apremilast (n=163) [at doses of 20 mg or 30 mg twice daily (BID) according to their baseline weight group following a 3-day or a 5-day initial dose titration] or placebo (n=80) [2 subjects in the placebo group (of ITT) were not dosed and were excluded from safety population].

A total of 221 subjects who completed the 16-week PC period, including 149/163 (91.4%) subjects in the apremilast group and 72/82 (87.8%) subjects in the placebo group, continued on to treatment with apremilast at doses of 20 mg or 30 mg BID (based on their baseline weights) in the apremilast-extension period (Weeks 16-52). A total of 186/235 (79.1%) subjects exposed to apremilast (in the apremilast exposure period) completed week 52.

Subjects treated with placebo during the PC period received apremilast dose titration (to a dose of 20 mg BID or 30 mg BID, based on their weight at baseline) at Week 16. As randomized at baseline visit (Week 0), 125 subjects (83.9%) in the apremilast group and 61 subjects (84.7%) in the placebo group completed the study.

The apremilast-exposure period (defined as all subjects who received at least 1 dose of apremilast in the PC period, the apremilast-extension period, or both) included a total of 235 subjects, of which 119 subjects received apremilast 30 mg BID and 116 subjects received apremilast 20 mg BID.

Investigators conducted safety assessments at screening, baseline, Weeks 2, 4, 8, 12, and 16 visits during the PC period; at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52 visits during

apremilast-extension period; at Weeks 56, 60, and 66 visits during observational follow-up period; and at unscheduled or early termination visits.

The WARNINGS AND PRECAUTIONS SECTION of the current OTEZLA label includes hypersensitivity, diarrhea, nausea, vomiting, depression, and weight decrease.

To determine the safety profile of apremilast for the treatment of moderate to severe psoriasis in pediatric subjects ≥6 years of age, the review team analyzed the data for exposure, demographics, baseline characteristics, TEAEs, severe TEAEs, serious adverse events (SAEs), TEAEs leading to discontinuation (AELDs), physical examinations, tanner stage, stool diary, clinical laboratory measurements (chemistry, hematology, urinalysis, and serum or urine pregnancy tests for female subjects of child-bearing potential), psoriasis flare/rebound, vital signs (pulse, blood pressure, temperature, respiration rate), height and weight, and psychiatric assessment (by C-SSRS). No Adverse Events of Special Interest (AESIs) were prespecified in the protocol.

8.2.2. Review of the Safety Database

Overall Exposure

Overall exposure to apremilast in terms of frequency, duration and target population was adequate for the evaluation of safety.

Trial PPSO-003

During the PC period (weeks 0-16), the mean duration of exposure to apremilast and placebo were 15.3 (SD 3.0) weeks and 15.2 (SD 2.7) weeks, respectively. A total of 221 subjects, including 149/163 (91.4%) in apremilast group and 72/82 (87.8%) in the placebo group completed the PC period at Week 16. A total of 186 subjects, including 125/163 (83.9%) in apremilast group and 61/82 (84.7%) in the placebo group completed the trial at Week 52. Of the subjects who completed the trial, 98 subjects received treatment with apremilast for 52 weeks.

A total of 235 subjects were exposed to apremilast in the apremilast-exposure period (PC period and/or apremilast-extension period), including 119 subjects treated with apremilast 30 mg BID and 116 subjects treated with apremilast 20 mg BID.

During apremilast-exposure period (weeks 0--52), the mean duration of exposure to apremilast was 41.9 (SD 13.7) weeks.

The Demographic Characteristics of the study population at baseline were well-balanced across treatment groups and representative of the target population. Refer to Section .1 of this review for additional detail related to subject disposition.

Adequacy of the Safety Database

The safety database presented by the Applicant is adequate to characterize the safety profile of apremilast for the treatment of moderate to severe plaque psoriasis in pediatric subjects 6 years of age and older. Safety assessments were reasonable and consistent with known adverse events for apremilast in the target population:

- The size of safety database is adequate.
- The total subject exposure to apremilast during the PC period (weeks 0-16) provides adequate data for the evaluation of safety.
- The demographics of the study population are sufficiently representative of the target population as presented in Table 29.

Table 29. Baseline Demographic Characteristics, ITT Population, Trial PPSO-003

Characteristic	Placebo (n=82)	Apremilast (n=163)	Total (N=245)
Age (years)			
Mean	12.2	12.3	12.2
SD	3.25	3.32	3.29
Median	13.0	13.0	13.0
Minimum to maximum	6, 17	6, 17	6, 17
Age category (years)- n(%)			
6-11	34 (41.5)	67 (41.1)	101 (41.2)
12-17	48 (58.5)	96 (58.9)	144 (58.8)
Sex, n(%)			
Male	43 (52.4)	74 (45.4)	117 (47.8)
Female	39 (47.6)	89 (54.6)	128 (52.2)
Race, n(%)			
American Indian or Alaska native	0	2 (1.2)	2 (0.8)
Asian	3 (3.7)	6 (3.7)	9 (3.7)
Black or African American	3 (3.7)	5 (3.1)	8 (3.3)
Native Hawaiian or other Pacific Islander	0	0	0
White	73 (89.0)	140 (85.9)	213 (86.9)
Unknown/unreported	3 (3.7)	10 (6.1)	13 (5.3)
Ethnicity, n(%)			
Hispanic or Latino	8 (9.8)	24 (14.7)	32 (13.1)
Not Hispanic or Latino	71 (86.6)	129 (79.1)	200 (81.6)
Unknown/unreported	3 (3.7)	10 (6.1)	13 (5.3)
Weight (kg)			
Mean	51.8	52.0	52.0
SD	22.2	21.1	21.4
Median	50.1	50.0	50.0
Minimum to maximum	21.8, 135.9	20.0, 145.2	20.0, 145.2
Baseline weight category- n (%)			
≥20 to <50 kg	40 (48.8)	80 (49.1)	120 (49.0)
≥50 kg	42 (51.2)	83 (50.9)	125 (51.0)

Characteristic	Placebo (n=82)	Apremilast (n=163)	Total (N=245)
Baseline age (years) and weight (kg) categories			
6-11 years and ≥20 to <50 kg	30 (36.6)	58 (35.6)	88 (35.9)
6-11 years and ≥50 kg	4 (4.9)	9 (5.5)	13 (5.3)
12-17 years and ≥20 to <50 kg	10 (12.2)	22 (13.5)	32 (13.1)
12-17 years and ≥50 kg	38 (46.3)	74 (45.4)	112 (45.7)
BMI (kg/m^2)			
Mean	21.3	21.3	21.3
SD	5.6	5.2	5.3
Median	20.5	20.5	20.5
Minimum to maximum	12.7, 46.2	13.2, 46.7	12.7, 46.7

Source: adapted from sNDA 205437-S13, CSR: CC-10004-PPSO-003, Section 14.2, Table 14-2.1 (Page 149-151). Consistent with Clinical Reviewer's Analysis with JMP/JMP Clinical.
Abbreviations: BMI, body mass index; ITT, intent-to-treat; n, number of subjects with observed data, SD, standard deviation

Table 30. Baseline Disease Characteristics, ITT Population, Trial PPSO-003

Characteristic	Placebo (n=82)	Apremilast (n=163)	Total (N=245)
Baseline sPGA			
3 (Moderate)	63 (76.8)	122 (74.8)	185 (75.5)
4 (Severe)	19 (23.2)	41 (25.2)	60 (24.5)
Baseline PASI score			
Mean	19.5	20.0	19.8
SD	7.9	8.2	8.1
Median	16.5	17.4	17.2
Minimum to maximum	12.0, 50.6	12.0, 47.7	12.0, 50.6
Baseline BSA (%) affected			
Mean	30.8	31.9	31.5
SD	19.0	18.5	18.6
Median	24.0	27.0	26.0
Minimum to maximum	10.0, 88.0	10.0, 92.0	10.0, 92.0

Source: adapted from sNDA 205437-S13, CSR: CC-10004-PPSO-003, Section 14.2, Table 14-2.2 (Page 152-156). Consistent with Clinical Reviewer's Analysis with JMP/JMP Clinical.
Abbreviations: BSA, body surface area; ITT, intent-to-treat; n, number of subjects with observed data, PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician Global Assessment

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of apremilast for treatment of moderate to severe psoriasis in subjects ≥6 years of age. The review team discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

An Adverse Event (AE) was defined as any untoward medical occurrence, including illness, sign, symptoms, clinically significant laboratory abnormalities, or disease temporally associated with the use of the drug, in a subject administered the drug product. AEs did not necessarily have a causal relationship to the study drug. AEs were recorded from the time the informed consent

was signed. Treatment Emergent Adverse Events (TEAEs) were AEs that occurred after the first administration of the study drug (TEAE start date no later than 28 days after the last dose of study drug). AEs were documented at each study visit as observed by the investigators or reported by subjects. If the treatment-emergent status of an AE was unclear due to a missing or incomplete start date, it was considered treatment-emergent unless shown otherwise by data.

The investigators categorized AEs by system-organ-class (SOC) and preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 (V. 22.0 for PPSO-001). The Applicant assessed TEAEs by the number of subjects reporting one or more adverse events. Each subject reporting a TEAE was counted once at each level of MedDRA summarization (PT or SOC). Both verbatim terms and preferred terms were included in the data files for trial PPSO-003, and there was good correlation between the verbatim and preferred terms used. No new safety signals emerged from the review of TEAEs.

The investigators categorized AEs for seriousness, causality, event name (diagnosis/signs and symptoms), duration, maximum intensity (severity), action taken regarding the study drug (including any treatment given), and outcome of AEs. Subjects were followed by the Investigators to resolution of the AE (return to normal/baseline or stabilization).

Serious Adverse Events (SAEs) were any AE that resulted in death, was immediately life-threatening, required (or prolonged) hospitalization, resulted in persistent disability or incapacity, resulted in a congenital anomaly or birth defect, or a medically important event that may have required medical or surgical intervention to prevent one of the outcomes listed above.

Severity of AEs were assessed by investigators as mild, moderate, or severe.

Causality of AEs was assessed by investigators as “Suspected” or “Not Suspected”(related or unrelated) based on positive temporal relationship to the study drug, reasonable possibility of association of AE with underlying or concomitant illness or therapy, whether the AE was related to study procedures or lack of efficacy, and existence of a likely alternative etiology.

Adverse Events of Special Interest (AESIs) were not prespecified in the Protocol. However, the Applicant reported the frequency of TEAEs associated with the (identified or potential) key risks of apremilast, including Hypersensitivity, Gastrointestinal AEs (Nausea, vomiting, diarrhea), Depression, Suicidal Ideation and Behaviors (SIB), and Weight decrease.

The Applicant’s assessment of adverse events conducted for the study PPSO-003 appears reasonable and appropriate. The Applicant reported accurate definitions of treatment emergent adverse events, serious adverse events, and severity of adverse events.

Routine Clinical Tests

The Applicant performed clinical laboratory evaluations (chemistry, hematology, and urinalysis) at screening, baseline, and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56 (or ET) visits.

Serum pregnancy tests were performed at screening (and to confirm a positive urine pregnancy tests), and urine pregnancy tests at screening, baseline, and all visit at Week 4 or later.

An abnormal laboratory value was considered to be an AE if it required treatment, modification or interruption of dose, judged to be of significant clinical importance (for example, a new disease process/organ toxicity, or an exacerbation of an existing condition), or led to subject discontinuation from the study.

8.2.4. Safety Results

Trial PPSO-003

During the PC period (Weeks 0-16) of trial PPSO-003, TEAEs, Adverse Reactions (AR: TEAEs suspected as related to study drug), and AELDs were more frequently reported for subjects in the apremilast groups than the placebo group; whereas severe AEs and SAEs were reported with similar frequency between groups, as presented in Table 31.

Table 31. Overview of Treatment-Emergent Adverse Events in the Placebo-Controlled Period (Weeks 0 to 16), Safety Population, Trial PPSO-003

	Placebo (N=80, SY =23.4)		Apremilast 20 mg BID (N=80, SY =23.7)		Apremilast 30 mg BID (N=83, SY =24.3)		Apremilast Total (N=163, SY =47.9)	
Group	**n (%)**	**EAIR/100 SY**	**n (%)**	**EAIR/100 SY**	**n (%)**	**EAIR/100 SY**	**n (%)**	**EAIR/100 SY**
TEAE	33 (41.3)	201.3	58 (72.5)	576.4	51 (61.4)	417.7	109 (66.9)	489.4
AR	12 (15.0)	55.7	36 (45.0)	240.2	34 (41.0)	216.4	70 (42.9)	228.0
Severe AE	1 (1.3)	4.3	2 (2.5)	8.5	0	0	2 (1.2)	4.2
SAE	1 (1.3)	4.3	2 (2.5)	8.5	0	0	2 (1.2)	4.2
Serious AR	0	0	0	0	0	0	0	0
AE -> interruption	2 (2.5)	8.6	6 (7.5)	25.8	3 (3.6)	12.7	9 (5.5)	19.2
AELD	1 (1.3)	4.3	3 (3.8)	12.7	2 (2.4)	8.3	5 (3.1)	10.5
Fatal AE	0	0	0	0	0	0	0	0

Sources: M 2.7.4, Table 4; and CSR for Study PPS0-003, Table 14-6.1.1. Consistent with Clinical Reviewer's analysis by Analysis Studio. Subject incidence is 100 times the number (n) of subjects reporting the event divided by N. EAIR per 100 SY is defined as 100 times the number (n) of subjects reporting the specific event divided by subject-years within the phase (up to the first event start date for subjects reporting the event).
TEAEs are coded using MedDRA version 25.1.
Abbreviations: AE, adverse event; AELD, TEAEs leading to drug discontinuation; AR, adverse reaction; BID, twice daily; EAIR, exposure-adjusted incidence rate; SAE, serious adverse event; SY, subject-years; TEAE, treatment-emergent adverse event

During the PC period of trial PPSO-003, pediatric subjects treated with apremilast (combined 20 mg or 30 mg BID dose groups), compared to adult subjects treated with apremilast 30 mg BID in the psoriasis trials PSOR-008/-009 (which were submitted and reviewed during the initial NDA review in 2014), respectively, were reported with the following (similar or lower Exposure-adjusted incidence rates: EAIR/100 subject-years):

Any TEAEs (489.4 v. 536.4), ARs (228.0 v. 211.4), severe AE (4.2 v. 13.7), SAE (4.2 v. 7.2), AELD (10.5 v. 19.2), and death (0 v. 0.4). A similar trend was reported for EAIRs for the apremilast-exposure periods (weeks 0-52).

Study PPSO-004

A total of 160 subjects from the parent study (PPSO-003) were enrolled in the long-term extension study (PPSO-004). As of the database cutoff date of March 27, 2023, and a snapshot date of May 10, 2023, the reported incidence rates of AEs (EAIR/100 subject-years) in Study PPSO-004 were lower than the corresponding incidence rates for trial PPSO-003:

Any TEAEs (51.7), ARs (9.4), severe AE (2.0), SAE (2.7), AELD (2.7), and death (0).

Study PPSO-001

Similar incidence rates of AEs were reported for adolescent subjects (12-17 years of age) treated with apremilast 20 mg or 30 mg QD, compared to pediatric subjects (6-11 years of age) treated with apremilast 20 mg QD:
Any TEAEs (95.2% v. 95.2%), ARs (81.0% v. 81.0%), severe AE (4.8% v. 4.8%), SAE (0 v. 4.8%), AELD (0 v. 9.5%), and death (0 v. 0).

Deaths

No deaths were reported during any of the studies PPSO-001/-003/-004.

Serious Adverse Events

Trial PPSO-003

During the PC period, the proportion of subjects with SAEs were low and similar between the apremilast (1.2%, EAIR: 4.2/100 SY) and the placebo group (1.3%, EAIR: 4.3/100 SY). SAEs were reported for 1 subject in the placebo group (testicular appendage torsion) and the following 2 subjects in the apremilast group:

- Subject: (b) (6) (apremilast 20 mg BID)- SAE of psoriasis (exacerbation) on D 44.
  A 12-year-old white female subject was hospitalized for psoriasis exacerbation and treated with multiple other medications. Apremilast dose was not changed, causality was reported as not suspected, and outcome as resolved.

- Subject: (b) (6) (apremilast 20 mg BID/apremilast 20 mg BID)- SAEs on D 100. A 13-year-old white female subject hospitalized for multiple SAEs including PTs of sinus tachycardia (severe), wandering pacemaker (severe), autonomic nervous system imbalance (severe), and iron deficiency anemia (mild). The causality/action taken/outcome for these SAEs were reported as not suspected/dose not changed/resolved.

Table 32. Summary of SAEs (Weeks 0-16), Safety Population, Trial PPSO-003

	Apremilast 20 mg BID		Apremilast 30 mg BID		Apremilast Total		Placebo	
	N=80		N=83		N=163		N=80	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any SAE	2	(2.5)	0	(0.0)	2	(1.2)	1	(1.3)
Autonomic nervous system imbalance	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Iron deficiency anaemia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Psoriasis	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Sinus tachycardia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Testicular appendage torsion	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Wandering pacemaker	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "20 mg BID" and SAFFL = "Y" (Apremilast 20 mg BID); TRT01A = "30 mg BID" and SAFFL = "Y" (Apremilast 30 mg BID); TRT01A = "30 mg BID" or "20 mg BID" and SAFFL = "Y" (Apremilast total); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and APERIOD =1 to 1 and AESER = "Y" (Adverse Events).). SAE: Serious Adverse Event.
Abbreviations: BID, twice daily; SAE, serious adverse event

During the apremilast-extension period (weeks 16-52), the following 2 subjects were reported with SAEs:

- Subject (b) (6) - SAE of appendicitis (D 195, not suspected, study drug interrupted, resolved on D 201).
- A 12-year-old white male subject hospitalized and underwent laparoscopic appendectomy.
- Subject (b) (6) - SAE of status migrainosus (D 171, not suspected, dose not changed, resolved on D 173).
- A 17-year-old white female subject was hospitalized and treated for severe migraine.

No SAEs in the SOC of Gastrointestinal disorders were reported for trial PPSO-003.

Study PPSO-004

The following 4 SAEs were reported for 4/160 (2.5%) subjects (EAIR/100 SY =2.7):

- Subject (b) (6) - SAE of Acute kidney injury (D 774, not suspected, dose not changed, resolved on D 779).

  An 11-year-old white female subject treated with apremilast 20 mg BID was hospitalized for flu symptoms (vomiting and diarrhea), dehydration, and SAE of acute kidney injury.

- Subject (b) (6) - SAE of Phimosis (D 546, not suspected, dose not changed, resolved on D 549).

  A 17-year-old male subject hospitalized and underwent circumcision.

- Subject (b) (6) - SAE of Abdominal pain syndrome (D 908, not suspected, dose not changed, resolved on D 909).

  An 11-year-old male subject hospitalized for suspected appendicitis for abdominal pain, did not receive treatment, with pain reported as resolved at discharge. This SAE was the only one reported in the SOC of Gastrointestinal disorders.

- Subject (b) (6) - SAE of Headache (D 510, not suspected, dose not changed, resolved on D 532).

  A 14-year-old white female subject hospitalized for a short stay in the emergency department for a brain MRI (results reported as normal) following repeated visits to her pediatrician for headaches.

Study PPSO-001

The following SAE was reported:

- Subject (b) (6) - SAE of syncope in a 10-year-old female subject (D 322, not suspected, dose not changed, resolved on D 323).

Dropouts and/or Discontinuations Due to Adverse Effects

Trial PPSO-003

During the placebo-controlled period, TEAEs leading to drug interruption were reported in 2 (2.5%) subjects in the placebo group, compared to 9 (5.5%) subjects in the apremilast (combined 20 mg or 30 mg QD) group.

During the PC period, the proportion of subjects with TEAEs leading to drug discontinuations (AELDs) were low but slightly higher in the apremilast (3.1%, EAIR: 10.5/100 SY) group compared to the placebo group (1.3%, EAIR: 4.3/100 SY). The following AELDs were reported in 1 subject in the placebo group, compared to 5 subjects in the apremilast group:

Table 33. Summary of AELDs (Weeks 0-16), Safety Population, Trial PPSO-003

	Apremilast 20 mg BID		Apremilast 30 mg BID		Apremilast Total		Placebo	
	N=80		N=83		N=163		N=80	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any AE	3	(3.8)	2	(2.4)	5	(3.1)	1	(1.3)
Abdominal pain	2	(2.5)	1	(1.2)	3	(1.8)	0	(0.0)
Abdominal pain upper	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Nausea	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Suicidal ideation	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Tremor	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Vomiting	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "20 mg BID" and SAFFL = "Y" (Apremilast 20 mg BID); TRT01A = "30 mg BID" and SAFFL = "Y" (Apremilast 30 mg BID); TRT01A = "30 mg BID" or "20 mg BID" and SAFFL = "Y" (Apremilast total); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and APERIOD =1 to 1 and AEACN = "DRUG WITHDRAWN" (Adverse Events). AELDs: Adverse Events Leading to Discontinuation
Abbreviations: AE, adverse event; AELD, TEAEs leading to drug discontinuation; BID, twice daily; TEAE, treatment-emergent adverse event

Abdominal pain (3) was the only AELD reported in >1 subject.

During the apremilast-extension period (weeks 16-52), the following 4 AELDs were reported in 3 subjects.

Table 34. Summary of AELDs (Weeks 16-52), Safety Population, Trial PPSO-003

	All Subjects in Apremilast-Extension Period	
	N=243	
Preferred Term	**n**	**(%)**
Any AE	4	(1.6)
Blood creatinine increased	1	(0.4)
Guttate psoriasis	1	(0.4)
Vomiting	2	(0.8)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "30 mg BID" or "Placebo" or "20 mg BID" and SAFFL = "Y" (All subjects in apremilast-extension period); TRTEMFL = "Y" and APERIOD =2 to 2 and AEACN = "DRUG WITHDRAWN" (Adverse Events).
Abbreviations: AE, adverse event; AELD, TEAEs leading to drug discontinuation; TEAE, treatment-emergent adverse event

Study PPSO-004

AELDs were reported for 4 subjects (2.5%, EAIR of 2.7 /100 SY), for PTs of abdominal pain upper (1), vomiting (1), mental disorder (1), psoriasis (1). No PT was reported in more than 1 subject.

Study PPSO-001

AELDs were reported for 2 subjects: one subject with PT of eosinophilia (1), and one subject with PTs of sleep disorder, headache, and crying.

Significant Adverse Events

No Adverse Events of Special Interest (AESI) were prespecified for trial PPSO-003.

Severe AEs

Trial PPSO-003

During the PC period, the proportion of subjects with severe AEs were low and similar between the apremilast (1.2%, EAIR: 4.2/100 SY) and the placebo group (1.3%, EAIR: 4.3/100 SY). A similar trend was reported for the frequency of severe AEs in the apremilast-extension period.

Table 35. Summary of Severe TEAEs (Weeks 0-16), Safety Population, Trial PPSO-003

	Apremilast 20 mg BID		Apremilast 30 mg BID		Apremilast Total		Placebo	
	N=80		N=83		N=163		N=80	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any AE	2	(2.5)	0	(0.0)	2	(1.2)	1	(1.3)
Autonomic nervous system imbalance	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Influenza	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Sinus tachycardia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Testicular appendage torsion	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Wandering pacemaker	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "20 mg BID" and SAFFL = "Y" (Apremilast 20 mg BID); TRT01A = "30 mg BID" and SAFFL = "Y" (Apremilast 30 mg BID); TRT01A = "30 mg BID" or "20 mg BID" and SAFFL = "Y" (Apremilast total); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and APERIOD =1 to 1 and AESEV = "SEVERE" (Adverse Events).
Abbreviations: AE, adverse event; BID, twice daily; TEAE, treatment-emergent adverse event

Table 36. Summary of Severe TEAEs (Weeks 16-52), Safety Population, Trial PPSO-003

	All Subjects in Apremilast-Extension Period	
	N=243	
Preferred Term	**n**	**(%)**
Any AE	3	(1.2)
Abdominal pain	1	(0.4)
Gastroenteritis	1	(0.4)
Headache	1	(0.4)
Migraine	1	(0.4)
Status migrainosus	1	(0.4)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "30 mg BID" or "Placebo" or "20 mg BID" and SAFFL = "Y" (All subjects in apremilast-extension period); TRTEMFL = "Y" and APERIOD =2 to 2 and AESEV = "SEVERE" (Adverse Events).
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event

Study PPSO-004

Severe AEs were reported for 3 (1.9%, EAIR 2.0/100SY) subjects for hyperthermia (1), COVID-19 (1), acute kidney injury (1).

Study PPSO-001

Severe AEs were reported for 2 (4.8%) subjects: 1 subject with PTs of headache and abdominal pain, and 1 subject with eosinophilia.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs

Trial PPSO-003

During the placebo-controlled period, TEAEs were reported at a higher frequency in subjects in the apremilast group 109/163 (66.9%) compared to the placebo group 33/80 (41.3%).

TEAEs reported in ≥5% of subjects in the apremilast group (and > placebo) compared to placebo group, respectively, included abdominal pain (19.6% v. 10.0%), diarrhea (19.6% v. 10.0%), nausea (19.6% v. 2.5%), vomiting (17.8% v. 2.5%), headache (10.4% v. 5.0%), dyspepsia (6.1% v. 0), nasopharyngitis (6.1% v. 3.8%), pyrexia (6.1% v. 1.3%), and abdominal pain upper (5.5% v. 5.0%).

Table 37. Summary of TEAEs by PT (in ≥1% of Subjects in Any Group) (Weeks 0-16), Safety Population, Trial PPSO-003

	20 mg BID		30 mg BID		Apremilast Total		Placebo	
	N=80		N=83		N=163		N=80	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any AE	58	(72.5)	51	(61.4)	109	(66.9)	33	(41.3)
Abdominal pain	23	(28.7)	9	(10.8)	32	(19.6)	8	(10.0)
Diarrhoea	15	(18.8)	17	(20.5)	32	(19.6)	8	(10.0)
Nausea	15	(18.8)	17	(20.5)	32	(19.6)	2	(2.5)
Vomiting	16	(20.0)	13	(15.7)	29	(17.8)	2	(2.5)
Headache	12	(15.0)	5	(6.0)	17	(10.4)	4	(5.0)
Dyspepsia	3	(3.8)	7	(8.4)	10	(6.1)	0	(0.0)
Nasopharyngitis	5	(6.3)	5	(6.0)	10	(6.1)	3	(3.8)
Pyrexia	7	(8.8)	3	(3.6)	10	(6.1)	1	(1.3)
Abdominal pain upper	5	(6.3)	4	(4.8)	9	(5.5)	4	(5.0)
Abdominal distension	3	(3.8)	4	(4.8)	7	(4.3)	2	(2.5)
Influenza	5	(6.3)	2	(2.4)	7	(4.3)	1	(1.3)
Respiratory tract infection viral	3	(3.8)	3	(3.6)	6	(3.7)	0	(0.0)
Covid-19	2	(2.5)	3	(3.6)	5	(3.1)	5	(6.3)
Decreased appetite	3	(3.8)	2	(2.4)	5	(3.1)	0	(0.0)
Cough	2	(2.5)	2	(2.4)	4	(2.5)	2	(2.5)
Fatigue	3	(3.8)	1	(1.2)	4	(2.5)	0	(0.0)
Frequent bowel movements	2	(2.5)	2	(2.4)	4	(2.5)	1	(1.3)
Pruritus	3	(3.8)	1	(1.2)	4	(2.5)	1	(1.3)
Abdominal discomfort	1	(1.3)	2	(2.4)	3	(1.8)	0	(0.0)
Dizziness	2	(2.5)	1	(1.2)	3	(1.8)	0	(0.0)
Epistaxis	0	(0.0)	3	(3.6)	3	(1.8)	0	(0.0)
Psoriasis	1	(1.3)	2	(2.4)	3	(1.8)	3	(3.8)
Sars-cov-2 test positive	2	(2.5)	1	(1.2)	3	(1.8)	0	(0.0)
Arthralgia	2	(2.5)	0	(0.0)	2	(1.2)	2	(2.5)
Back pain	1	(1.3)	1	(1.2)	2	(1.2)	0	(0.0)
Constipation	2	(2.5)	0	(0.0)	2	(1.2)	1	(1.3)
Crystal urine present	2	(2.5)	0	(0.0)	2	(1.2)	0	(0.0)
Erythema	1	(1.3)	1	(1.2)	2	(1.2)	0	(0.0)
Gastroenteritis	1	(1.3)	1	(1.2)	2	(1.2)	1	(1.3)
Limb injury	1	(1.3)	1	(1.2)	2	(1.2)	0	(0.0)

	20 mg BID		30 mg BID		Apremilast Total		Placebo	
	N=80		N=83		N=163		N=80	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Oropharyngeal pain	1	(1.3)	1	(1.2)	2	(1.2)	0	(0.0)
Upper respiratory tract infection	1	(1.3)	1	(1.2)	2	(1.2)	0	(0.0)
Acarodermatitis	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Acne	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Alanine aminotransferase increased	0	(0.0)	1	(1.2)	1	(0.6)	1	(1.3)
Alopecia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Anaemia	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Anxiety	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Arthropod bite	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Asthenia	1	(1.3)	0	(0.0)	1	(0.6)	1	(1.3)
Autonomic nervous system imbalance	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Bronchitis	1	(1.3)	0	(0.0)	1	(0.6)	1	(1.3)
Cerumen impaction	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Chalazion	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Conjunctivitis	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Crystalluria	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Dermatitis allergic	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Dry skin	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Eczema	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Eosinophilia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Faeces soft	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Fall	1	(1.3)	0	(0.0)	1	(0.6)	1	(1.3)
Gastroenteritis viral	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Gastrointestinal viral infection	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Hyperhidrosis	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Hyperkalaemia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Hypoglycaemia	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Impetigo	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Insomnia	0	(0.0)	1	(1.2)	1	(0.6)	1	(1.3)
Iron deficiency anaemia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Labyrinthitis	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Lice infestation	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Menstruation delayed	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Otitis media	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Pain in extremity	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Pharyngitis	1	(1.3)	0	(0.0)	1	(0.6)	2	(2.5)
Pityriasis rosea	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Radius fracture	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Rash	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Rash erythematous	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Rhinitis allergic	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Rhinorrhoea	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Seborrhoeic keratosis	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Sinus tachycardia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Skin exfoliation	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Skin papilloma	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Sleep apnoea syndrome	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Sleep disorder	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Sunburn	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Thrombocytosis	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Toothache	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Tremor	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)

	20 mg BID		30 mg BID		Apremilast Total		Placebo	
	N=80		N=83		N=163		N=80	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Urinary tract infection	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Urticaria	0	(0.0)	1	(1.2)	1	(0.6)	1	(1.3)
Varicella	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Viral infection	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Viral upper respiratory tract infection	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Wandering pacemaker	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Weight decreased	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Wrist fracture	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "20 mg BID" and SAFFL = "Y" (20 mg BID); TRT01A = "30 mg BID" and SAFFL = "Y" (30 mg BID); TRT01A = "30 mg BID" or "20 mg BID" and SAFFL = "Y" (Apremilast total); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and APERIOD =1 to 1 (Adverse Events).
Percent Threshold: any group ≥1%.
Abbreviations: AE, adverse event; BID, twice a day; PT, preferred term; TEAE, treatment-emergent adverse event

During the apremilast-extension period, TEAEs reported at a frequency of ≥5% included diarrhea (13.6%), nausea (11.5%), vomiting (8.6%), abdominal pain (7.8%), and psoriasis (5.8%); consistent with the TEAE profile reported during the PC period.

Table 38. Summary of TEAEs (in ≥1% of Subjects) (Weeks 16-52), Safety Population, Trial PPSO-003

	All Subjects in Apremilast-Extension Period	
	N=243	
Preferred Term	**n**	**(%)**
Any AE	123	(50.6)
Diarrhoea	33	(13.6)
Nausea	28	(11.5)
Vomiting	21	(8.6)
Abdominal pain	19	(7.8)
Psoriasis	14	(5.8)
Headache	12	(4.9)
Nasopharyngitis	11	(4.5)
Covid-19	7	(2.9)
Abdominal distension	6	(2.5)
Influenza	6	(2.5)
Respiratory tract infection viral	6	(2.5)
Abdominal pain upper	5	(2.1)
Arthralgia	5	(2.1)
Cough	5	(2.1)
Dyspepsia	4	(1.6)
Pyrexia	4	(1.6)
Tonsillitis	4	(1.6)
Ligament sprain	3	(1.2)
Pain in extremity	3	(1.2)
Respiratory tract infection	3	(1.2)
Sunburn	3	(1.2)
Upper respiratory tract infection	3	(1.2)

	All Subjects in Apremilast-Extension Period N=243	
Preferred Term	**n**	**(%)**
Urinary tract infection	3	(1.2)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "30 mg BID" or "Placebo" or "20 mg BID" and SAFFL = "Y" (All subjects in apremilast-extension period); TRTEMFL = "Y" and APERIOD =2 to 2 (Adverse Events).
Percent Threshold: All subjects in apremilast-extension period ≥1%.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event

Study PPSO-004

As of the data cutoff date, 55 subjects (34.4%) reported a TEAE in study PPSO-004. No TEAEs were reported for ≥5% of subjects. TEAEs reported in ≥3% of subjects included COVID-19 (4.4%), vomiting (4.4%), abdominal pain (3.1%), headache (3.1%), nausea (3.1%), psoriasis (3.1%), and respiratory tract infection viral (3.1%).

Study PPSO-001

TEAEs reported in 40/42 (95.2%) of subjects (combined 20 mg BID and 30 mg BID groups). TEAEs reported at a frequency of ≥10% included nausea (52.4%), headache (45.2%), abdominal pain (42.9%), nasopharyngitis (38.1%), diarrhoea (35.7%), vomiting (31.0%), gastroenteritis (19.0%), abdominal pain upper (16.7%), cough (14.3%), abdominal distension (11.9%), and oropharyngeal pain (11.9%).

Adverse Reactions (Related to Study Drug)

Trial PPSO-003

During the placebo-controlled period, Adverse Reactions were reported at a higher frequency for 70/163 (42.9%) subjects in the apremilast group compared to 12/80 (15.0%) subjects in the placebo group.

ARs reported in ≥5% of subjects in the apremilast group (and > placebo) compared to placebo group, respectively, included diarrhea (17.2% v. 6.3%), abdominal pain (16.0% v. 2.5%), nausea (16.0% v. 1.3%), and vomiting (12.3% v. 0).

Table 39. Summary of Adverse Reactions (in ≥1% of Subjects in Any Group) by (Weeks 0-16), Safety Population, Trial PPSO-003

	20 mg BID		30 mg BID		Apremilast Total		Placebo	
	N=80		N=83		N=163		N=80	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any AE	36	(45.0)	34	(41.0)	70	(42.9)	12	(15.0)
Diarrhoea	12	(15.0)	16	(19.3)	28	(17.2)	5	(6.3)
Abdominal pain	17	(21.3)	9	(10.8)	26	(16.0)	2	(2.5)
Nausea	11	(13.8)	15	(18.1)	26	(16.0)	1	(1.3)
Vomiting	10	(12.5)	10	(12.0)	20	(12.3)	0	(0.0)
Dyspepsia	3	(3.8)	5	(6.0)	8	(4.9)	0	(0.0)
Headache	5	(6.3)	3	(3.6)	8	(4.9)	1	(1.3)
Abdominal distension	3	(3.8)	4	(4.8)	7	(4.3)	1	(1.3)
Abdominal pain upper	3	(3.8)	4	(4.8)	7	(4.3)	3	(3.8)
Decreased appetite	2	(2.5)	2	(2.4)	4	(2.5)	0	(0.0)
Frequent bowel movements	2	(2.5)	2	(2.4)	4	(2.5)	1	(1.3)
Nasopharyngitis	2	(2.5)	2	(2.4)	4	(2.5)	0	(0.0)
Abdominal discomfort	0	(0.0)	2	(2.4)	2	(1.2)	0	(0.0)
Constipation	2	(2.5)	0	(0.0)	2	(1.2)	1	(1.3)
Fatigue	2	(2.5)	0	(0.0)	2	(1.2)	0	(0.0)
Asthenia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Dizziness	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Epistaxis	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Faeces soft	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Hyperhidrosis	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Influenza	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Pyrexia	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Thrombocytosis	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Tremor	1	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)
Weight decreased	0	(0.0)	1	(1.2)	1	(0.6)	0	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Blood creatinine increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Blood urea increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Faeces discoloured	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Insomnia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Psoriasis	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Suicidal ideation	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "20 mg BID" and SAFFL = "Y" (20 mg BID); TRT01A = "30 mg BID" and SAFFL = "Y" (30 mg BID); TRT01A = "30 mg BID" or "20 mg BID" and SAFFL = "Y" (Apremilast total); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and APERIOD =1 to 1 and AEREL = "SUSPECTED" (Adverse Events).
Abbreviations: AE, adverse event; BID, twice daily

Study PPSO-004

ARs were reported at a frequency of 13/160 (8.1%, EAIR: 9.4/100SY). ARs reported in ≥2 subjects included nausea (3.1%), vomiting (2.5%), abdominal pain (1.3%), and diarrhea (1.3%).

Study PPSO-001

ARs were reported for 33/42 (78.60%, AEIR: 217.8/100 SY) subjects, including the following ARs reported in ≥4 (9.5%) subjects: nausea (45.2%), abdominal pain (35.7%), diarrhea (31.0%),

headache (26.2%), vomiting (19.0%), abdominal pain upper (14.3%), abdominal distension (11.9%). Decreased appetite (9.5%).

90-Day Safety Update (for Priority Review)

Per 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 90-Day Safety Update Report (SDN 2104, dated January 19, 2024) for safety data reported in the ongoing LTS study PPSO-004 from the IA (data cutoff March 27, 2023) to the data cutoff date of August 22, 2023.

One subject (0.6%) was reported with severe depression (D 682) and was treated with ecitalopram. Suicidal ideation was reported as SAE (D 695) and led to discontinuation from the study. No treatment was reported after the onset of the event. The investigator considered the causality as suspected. The outcome of SAE was reported as recovered/ resolved on the same day.

The review team identified no new safety signals in the safety update report.

Laboratory Findings

Trial PPSO-003

During the placebo-controlled period, evaluation of systemic safety included assessments of clinical laboratory data (hematology, serum chemistry, and urinalysis). Abnormal laboratory measurements were mild, transient, and not reported as SAE or AELD. No clinically significant mean changes from baseline, or clinically significant shifts in laboratory values were reported. The only laboratory abnormality reported for ≥10% of subjects was hemoglobin >15.0 g/dL which was reported with similar frequency for subjects in the apremilast group (18.5%) and placebo group (22.8%). No abnormal liver enzyme measurements met Hy's law criteria.

During the apremilast-extension period, assessments of the results of clinical laboratory measurements were consistent with the results reported during the PC period.

Study PPSO-004

Laboratory safety results were consistent with those reported for trial PPSO-003.

Study PPSO-001

Laboratory safety results were consistent with those reported for trial PPSO-003. One subject was reported with an AELD of eosinophilia considered as not related to study drug.

Vital Signs

Trial PPSO-003

During the PC period, no clinically significant abnormalities in vital signs were reported in any treatment group. For subjects in the (combined 20 mg and 30 mg BID dose) apremilast group compared to subjects in the placebo group, respectively, changes from baseline to week 16 in the mean values for the following parameters were reported: body temperature (-0.03 v. -0.01) degrees Centigrade, systolic blood pressure (-0.14 v. +0.78) mm Hg, diastolic blood pressure (+0.16 v. +2.11) mm Hg, and a mean increase in pulse rate (-0.8 v. -0.73) beats per minute.

During the apremilast-extension period, vital signs assessment results were consistent with the results from the PC period.

Study PPSO-004

Vital signs measurement results were consistent with those reported for trial PPSO-003.

Study PPSO-001

Vital signs measurement results were consistent with those reported for trial PPSO-003.

Electrocardiograms

Electrocardiogram measurements were conducted only for Study PPSO-001, and no clinically significant finding was reported.

QT

Not applicable.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Current OTEZLA label (Sec. 5, WARNINGS AND PRECAUTIONS) includes hypersensitivity AEs and AEs potentially associated with the PDE-4 inhibitor class of drug products (Weight decrease, Gastrointestinal AEs and Psychiatric AEs) which were monitored (in addition to AEs related to Growth and Tanner stage (relevant to the pediatric patient population), and psoriasis rebound and flare during clinical studies of apremilast in pediatric subjects. The following subsection includes a summary of the results reported by the Applicant.

Weight Decrease

Trial PPSO-003

No clinically significant changes from baseline (CFB) were reported for body weight, height, or body mass index (BMI) in any group, for both the PC and the apremilast-extension periods.

During the PC period, for subjects in the (combined 20 mg and 30 mg BID dose) apremilast group compared to subjects in the placebo group, respectively, changes from baseline to week 16 in the mean values for the following parameters were reported: Weight (-0.09 v. +1.82) kg, %CFB in Weight (+0.01 v. +4.11), Height (+1.07 v. 1.25) Cm, %CFB in Height (+0.74% v. +0.88%), BMI (-0.35 v. +0.46) kg/m^2 and %CFB in BMI (-1.45% v.+2.27%).

A Weight decrease between 0 to -5 kg was reported in 67 (41.1%) subjects in the apremilast group, compared to 15 (18.8%) subjects in the placebo group. A Weight increase between 0 to +5 kg was reported in 73 (44.8%) subjects in the apremilast group, compared to 57 (71.3%) subjects in the placebo group. A Weight decrease between -5 to -10 kg was reported in 2 (1.2%) subjects in the apremilast group, compared to 0 subjects in the placebo group.

At the end of the trial (week 52), the mean change from baseline in Weight was +1.03 kg, with a mean %CFB in Weight (+3.1%). A Weight decrease between 0 to -5 kg reported in 71 (30.2%) subjects, between -5 to -10 kg was reported in 9 (3.8%) subjects, and between 10 to 20 kg in 2 (0.9%) subjects.

Study PPSO-004

No clinically significant changes from baseline in Weight were reported for the mean CFB (3.37 kg) and %CFB (8.3%) at the end of phase visit.

Study PPSO-001

At the Week 52 follow-up visit, the mean CFB and %CFB, respectively, in Weight were +9.6 kg, +15.1 for adolescent subjects (12 to 17 years of age) in 20 mg QD dose group, -0.8 kg, -0.4% for adolescents in 30 mg QD dose, and +7.4 kg, +23.2% for subjects (6 to 11 years of age) in the 20 mg QD dose group. Three subjects (12-17 years of age) had (intentional) Weight decrease of between -10% to -20% during this study.

Gastrointestinal AEs

Gastrointestinal AEs Include AEs in the SOC of Gastrointestinal disorders.

Trial PPSO-003

During the PC period, no SAEs or severe AEs were reported. AEs in the SOC of Gastrointestinal disorders were more frequently reported for 78 (47.9%) subjects in the apremilast group compared to 16 (20%) in the placebo group. For apremilast v. placebo group, respectively, the

following AEs were reported (at a rate of ≥5%): diarrhea (19.6% v. 10.0%), abdominal pain (19.6% v. 10.0%), nausea (19.6% v. 2.5%), vomiting (17.8% v. 2.5%), abdominal pain upper (5.5% v. 5.0%), and dyspepsia (6.1% v. 0). The following AELDs were reported for 5 (3.1%) subjects in the apremilast group: abdominal pain (3), abdominal pain upper (1), nausea (1), and vomiting (1).

The frequency of diarrhea (defined as ≥3 liquid or watery stools in a day measured by stool diaries) and other Gastrointestinal AEs in the apremilast group decreased over time for the duration of trial.

Study PPSO-004

Gastrointestinal AEs were reported for 16 (10%, EAIR: 11.8/100 SY) subjects, including vomiting (7), abdominal pain (5), nausea (5), diarrhea (3), abdominal pain upper (2), constipation (2), dyspepsia (1), and food poisoning (1). AEs included 1 SAE (abdominal pain, not related), 0 severe AEs, and 2 AELDs of abdominal pain upper (1) and vomiting (1).

Study PPSO-001

AEs in the SOC of Gastrointestinal disorders (reported at a frequency of ≥5%) included nausea (52.4%), abdominal pain (42.9%), diarrhea (35.7%), vomiting (31.0%), abdominal pain upper (16.7%), abdominal distension (11.9%), and dyspepsia (9.5%) [Decreased appetite (9.5%) was reported in the SOC of Metabolism and nutrition disorders]. The frequency of diarrhea reported by stool diary was consistent with its reported frequency as an AE (most occurred during the first 4 weeks of treatment and resolved within 3 days). Of note, dose titration was not done in this open-label study.

Psychiatric AEs: Depression and Suicidal Ideation and Behavior (SIB)

Trial PPSO-003

During the PC period, no AE of depression or suicidal ideation (on C-SSRS) was reported in the apremilast group. An AELD of Suicidal ideation was reported in a subject in the placebo group. AEs reported in the SOC of Psychiatric disorders for the apremilast group compared to the placebo group, respectively, included insomnia (0.6% v. 1.3%), anxiety (0.6% v. 0), and sleep disorder (0.6% v. 0). Similar results were reported in the apremilast-extension period.

Study PPSO-004

No AEs of depression was reported; and no suicidal ideation or suicidal behavior was reported on C-SSRS.

Study PPSO-001

One adolescent subject was reported with AELD of suicidal ideation (answered “yes” to “Wish to be dead” and “yes” to “Engaged in non-suicidal self-injurious behavior” at Week 32 on C-

SSRS) and was discontinued from study. Follow-up psychiatric evaluations were negative, and this subject was deemed not to be at risk of suicide.

Hypersensitivity AEs

Trial PPSO-003

No AE was reported with a PT of hypersensitivity during this study. No SAEs were identified by the Applicant from the hypersensitivity standardized Medical Dictionary for Regulatory Activities query (SMQ).

An FDA medical Query for the broad term "hypersensitivity" identified 14 AEs in 8 subjects during the placebo-controlled period of trial PPSO-003, as listed in Table 40.

Table 40. Summary of AEs Reported With FMQ of Hypersensitivity, Safety Population, Trial PPSO-003

	Subject Identifier for the Study	Actual Treatment for Period 01	Dictionary-Derived Term	Serious Event	Severity/ Intensity	Causality	Action Taken with Study Treatment	Outcome of Adverse Event
1	(b) (6)	20 mg BID	Pruritus	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
2		30 mg BID	Pruritus	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
3		30 mg BID	Erythema	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
4		20 mg BID	Eosinophilia	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	NOT RECOVERED/NO...
5		30 mg BID	Dermatitis allergic	N	MODERATE	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
6		20 mg BID	Pruritus	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
7		20 mg BID	Rash	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
8		20 mg BID	Pruritus	N	MILD	NOT SUSPECTED	DRUG INTERRUPTED	RECOVERED/RESOLVED
9		30 mg BID	Rash erythematous	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
10		30 mg BID	Urticaria	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
11		20 mg BID	Pruritus	N	MODERATE	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
12		20 mg BID	Pruritus	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
13		20 mg BID	Erythema	N	MODERATE	NOT SUSPECTED	DOSE NOT CHANGED	RECOVERED/RESOLVED
14		20 mg BID	Skin exfoliation	N	MILD	NOT SUSPECTED	DOSE NOT CHANGED	NOT RECOVERED/NO...

Source: Clinical Reviewers analysis, FDA Medical Query Explorer, JMP Clinical 8.1
Abbreviations: AE, adverse event; BID, twice daily

Study PPSO-004

No AE was reported with a PT of hypersensitivity during this study. Five (5) nonserious, mild AEs were identified from the hypersensitivity SMQ: seasonal allergies (1), eosinophilia (1), allergic rhinitis(1), stridor(1), left elbow skin peeling (1).

Study PPSO-001

No AE was reported with a PT of hypersensitivity during this study.

Tanner Stage

Tanner staging of sexual maturity was conducted at baseline and at 52-week interval visits during studies PPSO-001/-003/-004 and were consistent with the expected development for male and female subjects between ages 6 to 17 years.

Psoriasis Rebound and Flare

Trial PPSO-003

During the PC period, psoriasis flare was reported for 2 (1.2%) subjects in the apremilast group and 3 subjects (3.8%) in the placebo group. During the apremilast-exposure period, psoriasis flare was reported for 18 (7.7%, EAIR: 9.8/100SY) subjects.

Psoriasis rebound (an AE of psoriasis after the last dose of apremilast) was reported for 4 (9.1%) subjects.

Study PPSO-004

Psoriasis flare was reported for 5 (3.1%, EAIR: 3.5/100 SY) subjects. No psoriasis rebound was reported.

Study PPSO-001

Psoriasis flares during apremilast treatment, or psoriasis rebound during follow-up period were not collected as AEs (unless reported as an SAE). Subjects with psoriasis flare requiring prohibited concomitant therapies were discontinued from study.

Growth and Development

The DDD clinical review team requested the assistance of the DPMH-pediatrics in reviewing growth and development adverse reaction data (specifically, changes in body mass index (BMI) and weight) potentially associated with apremilast use in the pediatric age group of 6 to 17 years of age.

A DPMH consult review memorandum dated April 18, 2024, included the following conclusions: "In clinical studies of pediatric subjects with PP [plaque psoriasis], Otezla (apremilast) was associated with slowed weight gain and weight loss compared to placebo (Week 16). The most common weight loss bracket in APR-treated subjects during the controlled phase was 0 to <5% (68/163, 42%). After switching from placebo to apremilast, slowed weight gain and weight loss were also seen in PBO/APR group at Week 52. At Week 52, 2% (5/235) APR-treated subjects experienced at least 10% weight loss.

BMI is a function of both weight and height. Since there was no apparent adverse effect on height, the effect on BMI (Figures 3 and 5) appears greater than the effect on weight (Figures 2 and 4)."

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

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

In view of the small sample size, the utility of analyzing TEAEs by demographic subgroups is limited. The review of safety data revealed no substantial differences in the risk of adverse reactions in demographic subgroups. However, because the trial was not powered for these analyses, the data must be interpreted with caution.

The Applicant submitted safety analyses for trial PPSO-003 by subgroups of age, sex, and race under sNDA submission (SDN 2063). The Applicant submitted safety analysis by ethnicity subgroups in response to an FDA request conveyed in the filing communication letter (December 11, 2023).

In general, the frequency of reported TEAEs for apremilast-treated subjects during the PC period by age, sex, race, and ethnicity were balanced between demographic subgroups.

Analysis of TEAEs (observed in ≥5% of subjects in any treatment group during the PC period of trial PPSO-003) by subgroup category for apremilast-treated subjects are presented below.

Age Category

Subgroup analysis for subjects between 6 to 11 years of age, compared to subjects between 12 to 17 years of age respectively, reported more frequent abdominal pain (31.3%% vs. 11.5%), abdominal pain upper (10.4%% vs. 2.1%), headache (14.9% vs. 7.3%), nasopharyngitis (9.0% vs. 4.2%), pyrexia (10.4% v. 3.1%), and vomiting (20.9% v. 15.6%) as summarized in Table 41.

Table 41. Analysis by Age of TEAEs ≥5%) in Any Group During the PC Period (Weeks 0-16), Safety Population

	Apremilast Total, 6-11 Years		Apremilast Total, 12-17 Years		Placebo, 6-11 Years		Placebo, 12-17 Years	
	N=67		N=96		N=32		N=48	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any AE	49	(73.1)	60	(62.5)	15	(46.9)	18	(37.5)
Abdominal distension	2	(3.0)	5	(5.2)	2	(6.3)	0	(0.0)
Abdominal pain	21	(31.3)	11	(11.5)	5	(15.6)	3	(6.3)
Abdominal pain upper	7	(10.4)	2	(2.1)	2	(6.3)	2	(4.2)
Arthralgia	2	(3.0)	0	(0.0)	2	(6.3)	0	(0.0)
Covid-19	1	(1.5)	4	(4.2)	2	(6.3)	3	(6.3)
Diarrhoea	13	(19.4)	19	(19.8)	5	(15.6)	3	(6.3)
Dyspepsia	4	(6.0)	6	(6.3)	0	(0.0)	0	(0.0)
Headache	10	(14.9)	7	(7.3)	2	(6.3)	2	(4.2)
Influenza	5	(7.5)	2	(2.1)	1	(3.1)	0	(0.0)
Nasopharyngitis	6	(9.0)	4	(4.2)	0	(0.0)	3	(6.3)
Nausea	12	(17.9)	20	(20.8)	1	(3.1)	1	(2.1)
Pharyngitis	1	(1.5)	0	(0.0)	2	(6.3)	0	(0.0)
Pharyngitis streptococcal	0	(0.0)	0	(0.0)	2	(6.3)	0	(0.0)
Psoriasis	0	(0.0)	3	(3.1)	0	(0.0)	3	(6.3)
Pyrexia	7	(10.4)	3	(3.1)	1	(3.1)	0	(0.0)
Respiratory tract infection viral	1	(1.5)	5	(5.2)	0	(0.0)	0	(0.0)

	Apremilast Total, 6-11 Years		Apremilast Total, 12-17 Years		Placebo, 6-11 Years		Placebo, 12-17 Years	
	N=67		N=96		N=32		N=48	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Vomiting	14	(20.9)	15	(15.6)	1	(3.1)	1	(2.1)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer. Consistent with PPSO-003 CSR, Table 14-6.6.1.
Filters: TRT01A = "20 mg BID" or "30 mg BID" and AGEGR1 = "6-11" and SAFFL = "Y" (Apremilast total, 6-11 years); TRT01A = "30 mg BID" or "20 mg BID" and AGEGR1 = "12-17" and SAFFL = "Y" (Apremilast total, 12-17 years); TRT01A = "Placebo" and AGEGR1 = "6-11" and SAFFL = "Y" (Placebo, 6-11 years); TRT01A = "Placebo" and AGEGR1 = "12-17" and SAFFL = "Y" (Placebo, 12-17 years); TRTEMFL = "Y" and APERIOD =1 to 1 (Adverse Events).
Percent Threshold: Any Column ≥5%.
Abbreviations: AE, adverse event; PC, placebo-controlled; TEAE, treatment-emergent adverse event

Sex Category

Subgroup analysis for male subjects, compared to female subjects respectively, reported with less frequent abdominal pain (14.9%% vs. 23.6%) and more frequent nasopharyngitis (10.8 vs. 2.2%) as summarized in Table 42.

Table 42. Analysis by Sex of TEAEs ≥5%) in Any Group During the PC Period (Weeks 0-16), Safety Population

	Apremilast Total, Male N=74		Apremilast Total, Female N=89		Placebo, Male N=43		Placebo, Female N=37	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any AE	47	(63.5)	62	(69.7)	17	(39.5)	16	(43.2)
Abdominal distension	1	(1.4)	6	(6.7)	2	(4.7)	0	(0.0)
Abdominal pain	11	(14.9)	21	(23.6)	4	(9.3)	4	(10.8)
Abdominal pain upper	3	(4.1)	6	(6.7)	3	(7.0)	1	(2.7)
Arthralgia	1	(1.4)	1	(1.1)	0	(0.0)	2	(5.4)
Cough	1	(1.4)	3	(3.4)	0	(0.0)	2	(5.4)
Covid-19	3	(4.1)	2	(2.2)	2	(4.7)	3	(8.1)
Decreased appetite	4	(5.4)	1	(1.1)	0	(0.0)	0	(0.0)
Diarrhoea	14	(18.9)	18	(20.2)	4	(9.3)	4	(10.8)
Dyspepsia	4	(5.4)	6	(6.7)	0	(0.0)	0	(0.0)
Headache	7	(9.5)	10	(11.2)	1	(2.3)	3	(8.1)
Nasopharyngitis	8	(10.8)	2	(2.2)	2	(4.7)	1	(2.7)
Nausea	15	(20.3)	17	(19.1)	1	(2.3)	1	(2.7)
Pharyngitis	1	(1.4)	0	(0.0)	0	(0.0)	2	(5.4)
Pharyngitis streptococcal	0	(0.0)	0	(0.0)	0	(0.0)	2	(5.4)
Psoriasis	0	(0.0)	3	(3.4)	3	(7.0)	0	(0.0)
Pyrexia	5	(6.8)	5	(5.6)	0	(0.0)	1	(2.7)
Respiratory tract infection viral	1	(1.4)	5	(5.6)	0	(0.0)	0	(0.0)
Vomiting	13	(17.6)	16	(18.0)	1	(2.3)	1	(2.7)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer. Consistent with PPSO-003 CSR, Table 14-6.6.3.
Filters: TRT01A = "20 mg BID" or "30 mg BID" and SEX = "M" and SAFFL = "Y" (Apremilast total, Male); TRT01A = "30 mg BID" or "20 mg BID" and SEX = "F" and SAFFL = "Y" (Apremilast total, Female); TRT01A = "Placebo" and SEX = "M" and SAFFL = "Y" (Placebo, Male); TRT01A = "Placebo" and SEX = "F" and SAFFL = "Y" (Placebo, Female); TRTEMFL = "Y" and APERIOD =1 to 1 (Adverse Events).
Percent Threshold: Any Column ≥5%.
Abbreviations: AE, adverse event; BID, twice daily; PC, placebo-controlled; TEAE, treatment-emergent adverse event

Race Category

Subgroup analysis for white subjects, compared to subjects of other races respectively, reported less frequent overall AEs (62.1% v. 95.7%), abdominal pain (17.9% v. 30.4%), nausea (17.9% v. 30.4%), vomiting (15.0% v. 34.8%), pruritus (1.4% v. 8.7%), and pyrexia (5.0% v. 13.0%); but more frequent, headache (10.7% vs. 8.7%) as summarized in Table 43.

Table 43. Analysis by Race of TEAEs ≥5%) in Any Group During the PC Period (Weeks 0-16), Safety Population

	Apremilast Total, White		Apremilast Total, Subjects of Other Races		Placebo, White		Placebo, Subjects of Other Races	
	N=140		N=23		N=71		N=9	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any AE	87	(62.1)	22	(95.7)	27	(38.0)	6	(66.7)
Abdominal distension	6	(4.3)	1	(4.3)	1	(1.4)	1	(11.1)
Abdominal pain	25	(17.9)	7	(30.4)	8	(11.3)	0	(0.0)
Abdominal pain upper	9	(6.4)	0	(0.0)	2	(2.8)	2	(22.2)
Alanine aminotransferase increased	1	(0.7)	0	(0.0)	0	(0.0)	1	(11.1)
Asthma	0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	1	(1.4)	1	(11.1)
Constipation	0	(0.0)	2	(8.7)	0	(0.0)	1	(11.1)
Cough	2	(1.4)	2	(8.7)	2	(2.8)	0	(0.0)
Covid-19	4	(2.9)	1	(4.3)	4	(5.6)	1	(11.1)
Diarrhoea	30	(21.4)	2	(8.7)	7	(9.9)	1	(11.1)
Dyspepsia	10	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Epistaxis	1	(0.7)	2	(8.7)	0	(0.0)	0	(0.0)
Faeces discoloured	0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)
Frequent bowel movements	2	(1.4)	2	(8.7)	1	(1.4)	0	(0.0)
Headache	15	(10.7)	2	(8.7)	3	(4.2)	1	(11.1)
Insomnia	0	(0.0)	1	(4.3)	0	(0.0)	1	(11.1)
Nasopharyngitis	8	(5.7)	2	(8.7)	2	(2.8)	1	(11.1)
Nausea	25	(17.9)	7	(30.4)	1	(1.4)	1	(11.1)
Pruritus	2	(1.4)	2	(8.7)	1	(1.4)	0	(0.0)
Psoriasis	3	(2.1)	0	(0.0)	2	(2.8)	1	(11.1)
Pyrexia	7	(5.0)	3	(13.0)	1	(1.4)	0	(0.0)
Skin odour abnormal	0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)
Vomiting	21	(15.0)	8	(34.8)	2	(2.8)	0	(0.0)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer. Consistent with PPSO-003 CSR, Table 14-6.6.5.
Filters: TRT01A = "20 mg BID" or "30 mg BID" and RACEGR1 = "White" and SAFFL = "Y" (Apremilast total, White); TRT01A = "30 mg BID" or "20 mg BID" and RACEGR1 = "Non-White" and SAFFL = "Y" (Apremilast total, Non-white); TRT01A = "Placebo" and RACEGR1 = "White" and SAFFL = "Y" (Placebo, White); TRT01A = "Placebo" and RACEGR1 = "Non-White" and SAFFL = "Y" (Placebo, Non-white); TRTEMFL = "Y" and APERIOD =1 to 1 (Adverse Events).
Percent Threshold: Any Column ≥5%.
Abbreviations: AE, adverse event; BID, twice daily; PC, placebo-controlled; TEAE, treatment-emergent adverse event

Ethnicity Category

Subgroup analysis for Hispanic/Latino subjects, compared to Non-Hispanic/Non-Latino subjects respectively, reported less frequent abdominal pain (12.5% v. 21.7); but more frequent diarrhea (25.0% v. 18.6%), nausea (29.2% v. 18.6%), pruritus (8.3% v. 1.6%), headache (12.5% vs. 10.9%) as summarized in Table 44.

Table 44. Analysis by Ethnicity of TEAEs (≥5%) in Any Group During the PC Period (Weeks 0-16), Safety Population

	Apremilast Total, Hispanic or Latino		Apremilast Total, Not Hispanic or Latino		Placebo, Hispanic or Latino		Placebo, Not Hispanic or Latino	
	N=24		N=129		N=8		N=69	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any AE	17	(70.8)	85	(65.9)	4	(50.0)	26	(37.7)
Abdominal discomfort	2	(8.3)	1	(0.8)	0	(0.0)	0	(0.0)
Abdominal pain	3	(12.5)	28	(21.7)	1	(12.5)	7	(10.1)
Abdominal pain upper	1	(4.2)	8	(6.2)	0	(0.0)	2	(2.9)
Arthralgia	1	(4.2)	1	(0.8)	1	(12.5)	1	(1.4)
Asthenia	0	(0.0)	1	(0.8)	1	(12.5)	0	(0.0)
Bronchitis	0	(0.0)	1	(0.8)	1	(12.5)	0	(0.0)
Covid-19	0	(0.0)	5	(3.9)	1	(12.5)	3	(4.3)
Diarrhoea	6	(25.0)	24	(18.6)	1	(12.5)	6	(8.7)
Dyspepsia	0	(0.0)	10	(7.8)	0	(0.0)	0	(0.0)
Eosinophilic oesophagitis	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Fall	0	(0.0)	1	(0.8)	1	(12.5)	0	(0.0)
Headache	3	(12.5)	14	(10.9)	1	(12.5)	2	(2.9)
Hypercholesterolaemia	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Hypertransaminasaemia	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Nasopharyngitis	0	(0.0)	9	(7.0)	0	(0.0)	2	(2.9)
Nausea	7	(29.2)	24	(18.6)	0	(0.0)	1	(1.4)
Osteochondrosis	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Overweight	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Pharyngitis	0	(0.0)	1	(0.8)	2	(25.0)	0	(0.0)
Pharyngitis streptococcal	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.4)
Pruritus	2	(8.3)	2	(1.6)	0	(0.0)	1	(1.4)
Psoriasis	0	(0.0)	3	(2.3)	1	(12.5)	2	(2.9)
Pyrexia	1	(4.2)	8	(6.2)	0	(0.0)	1	(1.4)
Vomiting	5	(20.8)	24	(18.6)	0	(0.0)	2	(2.9)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer. Consistent with PPSO-003 CSR, Table 14-6.6.5.1.
Filters: TRT01A = "20 mg BID" or "30 mg BID" and ETHNIC = "HISPANIC OR LATINO" and SAFFL = "Y" (Apremilast total, Hispanic or Latino); TRT01A = "30 mg BID" or "20 mg BID" and ETHNIC = "NOT HISPANIC OR LATINO" and SAFFL = "Y" (Apremilast total, Not Hispanic or Latino); TRT01A = "Placebo" and ETHNIC = "HISPANIC OR LATINO" and SAFFL = "Y" (Placebo, Hispanic or Latino); TRT01A = "Placebo" and ETHNIC = "NOT HISPANIC OR LATINO" and SAFFL = "Y" (Placebo, Not Hispanic or Latino); TRTEMFL = "Y" and APERIOD =1 to 1 (Adverse Events).
Percent Threshold: Any Column ≥5%.
Abbreviations: AE, adverse event; BID, twice daily; PC, placebo-controlled; TEAE, treatment-emergent adverse event

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

According to the Applicant, as of March 20, 2023, apremilast has been approved for adult patients in 53 countries with the overall cumulative exposure to apremilast estimated as 858,164 patients from all geographic areas. Apremilast has not yet been approved for children in any country. The safety profile of apremilast in the postmarketing setting is similar to that reported in the registrational trials for the psoriasis and psoriatic arthritis clinical programs.

The Applicant reported a total of 2,481 adverse events in 1,389 pediatric patients who received apremilast (off-label) in the postmarketing setting. The Applicant did not identify any new

safety concerns in the pediatric population, reported generally similar types of adverse events in the pediatric and adult patient populations, and concluded that the (off-label) postmarketing safety profile of apremilast in children and adolescents was consistent with the safety profile reported for the clinical studies in children and adolescents and the overall safety profile of apremilast.

Expectations on Safety in the Postmarket Setting

The reported safety profile of apremilast for moderate to severe psoriasis in pediatric patients between 6 to 17 years of age is similar to the reported safety profile of apremilast in adult patients with psoriatic arthritis, psoriasis, and oral ulcers associated with Behcet's disease.

8.2.9. Integrated Assessment of Safety

Not applicable. Because of different study designs, the Applicant submitted safety data for each study (PPSO-003, PPSO-001, and PPSO-004 interim safety analysis) separately and did not pool or integrate safety data (e.g., as an ISS).

8.3. Statistical Issues

There were no major statistical issues affecting the overall conclusions. The treatment effects were consistent across the endpoints. There was minimal impact of remote visits on the efficacy results. For handling of missing data, the results were similar irrespective of the methods used to impute the missing data. In addition, there were no substantial differences in efficacy among subgroups except in the subgroup of subjects that identified as Hispanic or Latino; however, the number of subjects in this subgroup was relatively small (i.e., 24 in the apremilast group and 8 in the placebo group).

8.4. Conclusions and Recommendations

Trial PPSO-003 achieved statistical significance for both the primary and key secondary efficacy endpoints, and the key secondary efficacy endpoint was supportive of the primary efficacy endpoint. The safety data in trial PPSO-003 identified no new safety signals and was consistent with the known safety profile of apremilast.

In the opinion of the Clinical and Statistical review teams, there is sufficient evidence to conclude that the benefits of apremilast outweighs its potential risks for the treatment of moderate to severe plaque psoriasis in pediatric patients between 6 to 17 years of age, inclusive. We recommend inclusion of the results of the primary and secondary efficacy endpoints in Subsection 14.3; and inclusion of the pertinent safety results in Subsections 5.1 (Depression), 5.4 (Weight Decrease), and 6.1 (Clinical Trial Experience) of the OTEZLA label.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee was deemed necessary for this supplemental NDA.

10 Pediatrics

The Applicant submitted the results of study PPSO-001 (PREA PMR 2791-1), trial PPSO-003 (PREA PMR 2791-2), and interim results of the long-term extension study PPSO-004 under Supplement-013 to support broadening the patient population (for the indication of treatment of moderate to severe psoriasis) from adults to patients ≥6 years of age.

Additionally, the Agency had issued a Written Request (WR) in May 2015 in response to the Applicant's PPSR in December 2014. WR Amendment-2 was issued in April 2021.

The review team presented and discussed the Applicant's request for pediatric exclusivity determination at the pediatric exclusivity board meeting on April 10, 2024. The review team agreed with the Applicant that the terms of the WR were met and recommended granting pediatric exclusivity.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The Applicant submitted proposed Prescribing Information (PI), Container labels, and Carton labeling with Efficacy Supplement-13 on 25 October 2023. The Division of Medication Error Prevention and Analysis (DMEPA) consult review dated March 13, 2024, of the proposed prescribing information (PI), Container labels, and Carton labeling made recommendations for their improvement to promote the safe use of this product from a medication error perspective. DMEPA consult review dated April 17, 2024, made additional recommendations for improvements to the Container Labels and Carton Labeling. DMEPA consult review dated April 24, 2024, included the following conclusion: "Amgen Inc. implemented all of our recommendations and we have no additional recommendations at this time."

The Office of Prescription Drug Promotion (OPDP) memorandum dated April 5, 2024, for the review of the proposed PI, Carton, and Container labeling did not include any comments to be conveyed to the Applicant.

Other Prescription Drug Labeling

Labeling negotiations are currently ongoing as of the date of this review. The final agreed-upon label will be appended to this review.

12 Risk Evaluation and Mitigation Strategies (REMS)

No additional safety concerns were identified, and no REMS were deemed necessary by the review team for this supplemental NDA.

13 Appendices

13.1. References

References to sources cited were provided as footnotes.

13.2. Financial Disclosure

The Applicant submitted financial certifications and financial disclosure information (FDA Forms 3454, 3455) in Section 1.3.4 of this sNDA submission.

Covered Clinical Study (CC-10004-PPSO-003):

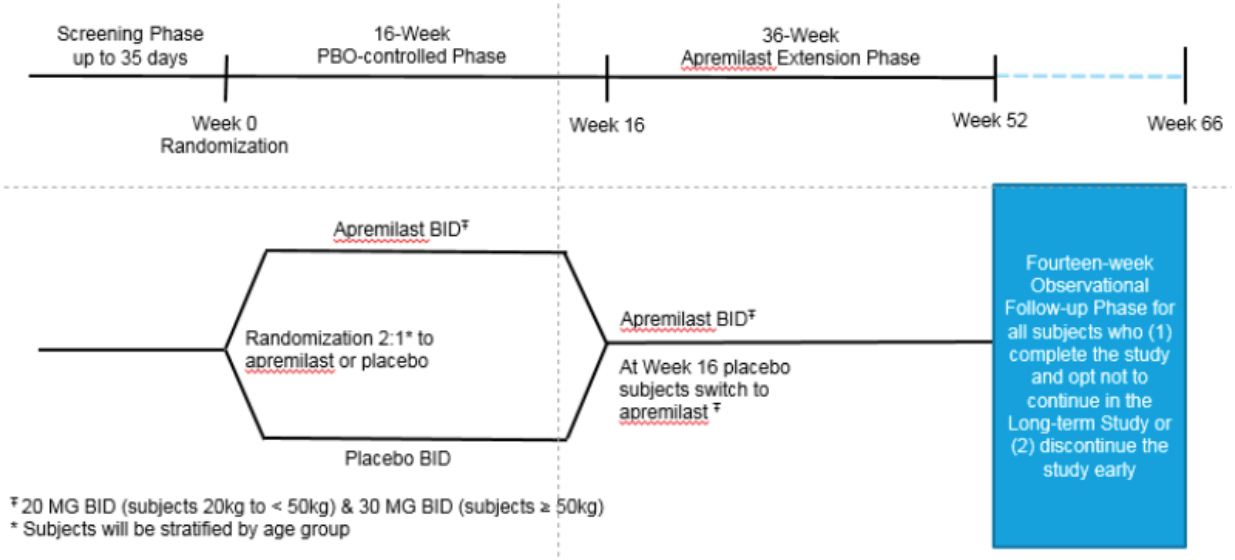
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 346		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator Significant equity interest held by investigator in 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) 340		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Study Designs for Trials PPSO-003/-004

Figure 14. Overall Study Design, Trial PPSO-003

Apremilast
Protocol CC-10004-PPSO-003 Amgen Inc.

Figure 1: Overall Study Design

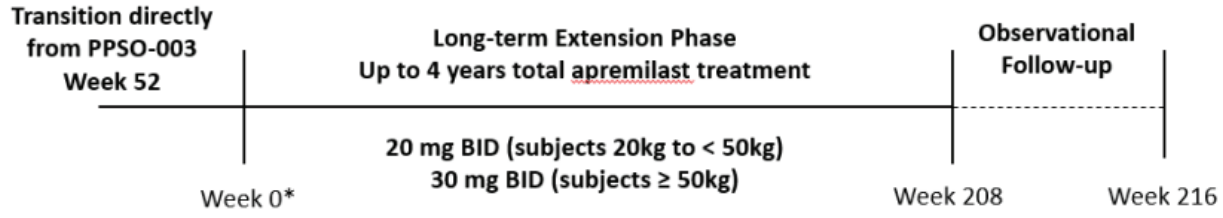


Source: sNDA 205437-013, M. 5, CSR for trial PPSO-003.
Abbreviations: BID, twice daily

Figure 15. Overall Study Design, Trial PPSO-004

Apremilast
Protocol CC-10004-PPSO-004 Amgen Inc.

Figure 1: Overall Study Design



* Data and study assessments scheduled to be collected for Visit 1 (Week 0) will be populated with information collected at Visit 16 (Week 52) of study PPSO-003 with the exception of consent/assent forms and eligibility criteria.

Source: sNDA 205437-013, M. 5, CSR for trial PPSO-004.
Abbreviation: BID, twice daily

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/

DAVID L KETTL
04/25/2024 04:05:47 PM

TATIANA OUSSOVA
04/25/2024 04:59:38 PM