19 September 2024
EMA/484631/2024 Corr [1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Otezla

International non-proprietary name: Apremilast

Procedure No. EMEA/H/C/003746/II/0044/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] 14.10.2024

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List of abbreviations

ANCOVA	analysis of covariance
AUC	area under the curve
BID	twice daily
BSA	body surface area
cAMP	cyclic adenosine monophosphate
CDLQI	Children's Dermatology Life Quality Index
C_{max}	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
EU	European Union
FDA	Food and Drug Administration
IL	interleukin
ICH	International Conference on Harmonisation
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NDA	New Drug Application
NRI	non-responder imputation
NRS	numeric rating scale
PASI	Psoriasis Area Severity Index
PASI-50	at least 50% reduction in PASI
PASI-75	at least 75% reduction in PASI
PBRER	Periodic Benefit-Risk Evaluation Report
PDE4	phosphodiesterase type 4
PIP	Pediatric Investigational Plan
PK	pharmacokinetic(s)
PSUR	Periodic Safety Update Report
QD	once daily
ScPGA	Scalp Physician Global Assessment
sPGA	static Physician Global Assessment
tmax	time to maximum observed plasma concentration
TNF $_{-\alpha}$	tumour necrosis factor alpha
US	United States
WR	Written Request

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 29 November 2023 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	A, I, IIIA and IIIB
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	A, I, IIIA and IIIB

- Type II (C.I.6.a): Extension of indication to include the treatment of moderate to severe chronic plaque psoriasis in children and adolescents from the age of 6 years who have a contraindication, have an inadequate response, or are intolerant to at least one other systemic therapy or phototherapy for OTEZLA, based on final results from study CC-10004-PPSO-003 as well as results from studies CC-10004-PPSO-001 and CC-10004-PPSO-004. CC-10004-PPSO-003 is a phase 3, multi-center, randomised, double-blind, placebo-controlled study to assess the efficacy and safety of apremilast in paediatric subjects from 6 through 17 years of age with moderate to severe plaque psoriasis. As a consequence, sections 4.1, 4.2, 4.4 ,4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 15.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial and formatting changes to the PI and to update the list of local representatives in the Package Leaflet.
- 2 Type IA (B.II.e.5.a.1): Update of sections 6.5 and 8 of the SmPC to introduce two new pack sizes within approved range as a result of the indication update (27 film-coated tablets (4 x 10 mg, 23 x 20 mg) and 14 film-coated tablets (14 x 20mg), in a pack size of 56 tablets).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) EMEA-C-000715-PIP03-11-M06 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-C-000715-PIP03-11-M06 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Finbarr Leacy Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	29 November 2023
Start of procedure:	23 December 2023
CHMP Rapporteur Assessment Report	16 February 2024
PRAC Rapporteur Assessment Report	21 February 2024
PRAC members comments	28 February 2024
PRAC Outcome	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 March 2024
Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	25 June 2024
PRAC Rapporteur Assessment Report	27 June 2024
PRAC members comments	03 July 2024
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	11 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur Assessment Report	18 July 2024
Request for supplementary information (RSI)	25 July 2024
MAH's responses submitted to the CHMP on:	19 August 2024
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	04 September 2024
CHMP members comments	09 September 2024
PRAC members comments	09 September 2024
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	n/a
CHMP opinion:	19 September 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Psoriasis is a chronic, inflammatory skin disorder that is estimated to affect up to 2.5% of the world's population (Christophers, 2001[2]). In Europe, the prevalence of paediatric psoriasis ranges between 0.17% and 1.5% (Peris et al, 2022[3]). European populations have a higher prevalence than African and Asian populations (Michalek et al, 2017[4]). Plaque psoriasis is the most common form of the disease in both adults and children, characterised by erythematous plaques with silvery white scales (Lebwohl, 2003[5]; Weinstein and Menter, 2003[6]). The symptoms of psoriasis, including, but not limited to, scaling, flaking, itching, soreness, and pain of the skin, can have considerable detrimental effects on a patient's quality of life, ability to function in daily activities, and overall social and societal engagement (Armstrong et al, 2012[7]). In addition, psoriasis in both adults and children is associated with a variety of comorbid conditions such as psoriatic arthritis, obesity, dyslipidemia, metabolic syndrome, and cardiovascular disease (Menter et al, 2020[8]; Elmets et al, 2019[9]).

The claimed therapeutic indication was

Paediatric psoriasis

Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis in children and adolescents from the age of 6 years, who have a contraindication, have an inadequate response, or are intolerant to at least one other systemic therapy or phototherapy.

Management

The treatment options for paediatric patients with plaque psoriasis remain limited. Current therapeutic options include topical agents for mild, localised psoriasis, phototherapy for older children and adolescents with extensive areas of involvement or refractory plaque disease, and systemic medications for more extensive or refractory disease (Marqueling and Cordoro, 2013[10]; Shah, 2013[11]; Vogel et al,

[2] Christophers E. Psoriasis - epidemiology and clinical spectrum. Clin Exp Dermatol. 2001 Jun;26(4):314-20.
[3] Peris, Ketty, et al. "Update on the management of pediatric psoriasis: an Italian consensus." Dermatology and Therapy 12.8 (2022): 1753-1775.
[4] Michalek IM, Loring B, John SM A systemic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017 Feb;31(2):205-212.
[5] Lebwohl M. Psoriasis. Lancet. 2003;361:1197-1204.
[6] Weinstein GD, Menter MA. An overview of psoriasis. In: eds. Weinstein GD, Gottlieb AB. Therapy of moderate to severe psoriasis. New York, NY. National Psoriasis Foundation. 2003; 1-28.
[7] Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation survey data 2003-2011. PLoS One. 2012;7(12):e52935.
[8] Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology- National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. J Am Acad Dermatol. 2020 Jan;82(1):161-201.
[9] Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol. 2019 Apr;80(4):1073-1113.
[10] Marqueling AL, Cordoro KM. Systemic treatments for severe pediatric psoriasis: a practical approach. Dermatol Clin. 2013 Apr;31(2):267-88.
[11] Shah KN. Diagnosis and treatment of pediatric psoriasis: Current and future. Am J Clin Dermatol. 2013 Jun;14(3):195-213.

2012[12]). Systemic medications utilised in children with moderate to severe plaque psoriasis include conventional therapies, such as methotrexate, retinoids, and cyclosporine, or biologics. However, fewer therapies, including antibody therapies across mechanisms of action, are approved for paediatric patients with moderate to severe plaque psoriasis compared with adults. Systemic therapies approved for paediatric patients with moderate to severe plaque psoriasis include biologic medications. However, injection site reactions, infections, reactivation of tuberculosis, congestive heart failure, and new onset or exacerbation of demyelinating diseases may be safety concerns of these agents. Baseline and regular monitoring are advised for these biological therapies. In addition, fear of needles is common in children and can contribute to negative experiences with the use of biologics (McMurtry et al, 2016[13]). As a result of the limitations of the treatment landscape, many children are treated off-label with the same agents approved for adults (Stahle et al, 2010[14]), despite limited safety and efficacy information to support the use of these agents in a paediatric population. Thus, there remains an unmet need for effective systemic therapies that offer convenient oral dosing and a favourable benefit-risk profile for the treatment of paediatric patients with moderate to severe plaque psoriasis.

2.1.2. About the product

Apremilast is an orally active compound that modulates multiple inflammatory pathways through targeted phosphodiesterase type 4 (PDE4) enzyme inhibition. Specifically, apremilast blocks the degradation of cyclic adenosine monophosphate (cAMP) through potent inhibition of the PDE4 enzyme, resulting in an increase of cAMP in PDE4 expressing cells including monocytes, T cells, and neutrophils. As a result, this downregulates the inflammatory response by reducing the expression of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-a), interleukin (IL)-23, IL-17, and other inflammatory cytokines, and increasing the production of anti-inflammatory mediators. In completed pivotal studies in adult patients with plaque psoriasis, adult patients with active psoriatic arthritis, and adult patients with oral ulcers associated with Behçet's disease, treatment with apremilast was associated with statistically significant and clinically meaningful improvements in multiple efficacy measures and was demonstrated to be safe and well-tolerated. On the basis of these studies, apremilast was approved for the treatment of these conditions in adults across multiple regions, including the US, European Union (EU), and other countries. The recommended dosage of apremilast for the approved indications is 30 mg twice daily (BID) after an initial 5-day titration period using 10, 20, and 30 mg tablets. Given its oral route of administration and favourable benefit-risk profile, apremilast can address the unmet need for an effective, systemic therapy that offers convenient dosing and is well tolerated compared to the currently available treatment options in paediatric patients with moderate to severe plaque psoriasis.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

In the EU, Studies PPSO-003 and PPSO-004 are included in the Investigation Plan (PIP) for psoriasis (EMEA 00715 PIP03-11-M06). In addition, Study PPSO-004 is being conducted to continue follow-up in subjects who have completed Study PPSO-003, as described in the EU psoriasis PIP.

[12] Vogel SA, Yentzer B, Davis SA, Feldman SR, Cordoro KM. Trends in pediatric psoriasis outpatient health care delivery in the United States. Arch Dermatol. 2012;148(1):66-71.
[13] McMurtry CM, Taddio A, Noel M, et al. Exposure-based interventions for the management of individuals with high levels of needle fear across the lifespan: a clinical practice guideline and call for further research. Cogn Behav Ther. 2016 Apr;45(3):217- 35.
[14] Ståhle M, Atakan N, Boehncke WH, et al. Juvenile psoriasis and its clinical management: a European expert group consensus. J Dtsch Dermatol Ges. 2010 Oct;8(10):812-818.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

An updated environmental risk assessment (ERA) was performed to include the proposed new indication, paediatric plaque psoriasis, in addition to the approved indications psoriatic arthritis (PsA), plaque psoriasis and Behcet's disease (BD).

The partition coefficient (n-octanol/water) for apremilast was experimentally determined by the shake flask method. The logKow was determined to be 1.8 (below the trigger of 4.5). Thus, on the basis of this evaluation, apremilast is not considered to be persistent, bioaccumulative and toxic (PBT). The estimation of the predicted environmental concentration (PEC) has been calculated based on a refined market penetration factor (F_{pen} = 0.045), and a maximum daily dose of 60 mg. The phase I $PEC_{surfacewater}$ of aprelimast was 1.35 µg/L and exceeds the action limit of 0.01 µg/L, triggering a Phase II environmental fate and effects assessment. A phase II Tier A and Tier B assessment was previously triggered in the initial application.

The MAH calculated the temperature adjusted degradation rates for apremilast and metabolites (M1 and M2). For apremilast, the DT_{50} values in water (dissipation) were similar for both systems (3.2 days and 1.3 days). The degradation rates in sediment could not be determined. In the total system, similar DT50 values were found for the two systems (4.0 days and 1.5 days). No degradation rates could be determined for M1 (DT_{50} in two systems > 2123 days). The DT_{50} values in the total system for M2 were similar (73.5 days and 78.3 days). In both systems, the temperature adjusted DT_{50} values in the total system for the metabolite M1 were > 180 days. Therefore, based on the simultaneous fitting of apremilast and metabolite M1 degradation data, apremilast is considered as being very persistent (vP).

An investigation into the structure of these two metabolites in a single natural aquatic sediment system under aerobic conditions in the laboratory has been performed. In water, apremilast was degraded to Component 2 (M1), (up to 38.9% applied radioactivity after 7 days) and Component 3 (M2) (up to 38.4% applied radioactivity after 4 days). In addition, apremilast was degraded to two low-level and unidentified transformation products (≤0.6% applied radioactivity). The two components (Components 2 and 3) were tentatively identified as phase I metabolites indicating hydrolysis of the isoindoline-1,3-dione ring and gave identical MS data. The specific structure has not been assigned and were considered to be the metabolites 'M1 and M2', respectively, as previously described.

Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- $log_{10}P_{ow}$	'Shake flask method' (OECD107)	$Log_{10}P_{ow}$ = 1.8	Not Potential PBT ($log_{10}P_{ow}$ < 4.5)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF		Not B
Persistence	DT_{50}	M1 metabolite: >2123 days (fresh-water sediment)	vP
Toxicity	NOEC	µg/L	Not T

PBT-statement:	The compound is not considered as PBT nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$ refined Fpen = 0.045	1.35	µg/L			> 0.01 threshold (Y) Phase II Tier A required
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Adsorption (L/kg): K_{Foc} sludge = 70 K_{Foc} sludge = 91 K_{Foc} loamy sand = 295 K_{Foc} sandy loam = 263 K_{Foc} clay = 457 Desorption (L/kg): K_{Foc} sludge = 101 K_{Foc} sludge = 110 K_{Foc} loamy sand = 471 K_{Foc} sandy loam = 542 K_{Foc} clay = 528			The Koc in sewage sludge <1000 L/kg The Phase II Tier A exposure assessment and effect assessment for soil are not triggered
Ready Biodegradability Test	OECD 301B	Not readily biodegradable after 28 days			Not readily biodegradable Proceed with an aquatic sediment study
Aerobic Transformation in Aquatic Sediment systems Swiss Lake System (SL) Schoonrewoerdsewiel System (SW)	OECD 308	Apremilast: $DT_{50, water}$ = 3.2 days (SL) and 1.3 days (SW) $DT_{50, sediment}$ = Not determined $DT_{50, whole\ system}$ = 4.0 days (SSL) and 1.5 days (SW) Metabolites: No degradation rates determined for M1. M1 $DT_{50, whole\ system}$ > 2123 (SL and SW) M2 $DT_{50, whole\ system}$ = 73.5 days (SL) and 78.3 days (SW) Mean % shifting to sediment (total radioactivity): 17.8% (SL) and 32.6% (SW); (Apremilast); 0.6% (SL) and 0.4% (SW) Volatiles: 3.7% (SL); 10.6% (SW)			Data at 62 days post application. DT_{50} at 12°C for metabolite M1 OECD 218 study to be conducted
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	3.5 x 10^3	µg/L	the unicellular green alga, *Pseudokirchneriell*

					a subcapitata (now known as *Raphidocelis subcapitata*)
Daphnia sp. Reproduction Test	OECD 211	NOEC	6.3 x 10^3	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	7.2 x 10^3	µg/L	the fathead minnow (*Pimephales promelas*)
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC (EC_{50}>1000 mg/L)	1x 10^6	µg/L	
Phase IIb Studies					
Bioaccumulation					Not B
Aerobic and anaerobic transformation in soil					Not triggered
Soil Micro organisms: Nitrogen Transformation Test					Not triggered
Terrestrial Plants, Growth Test/*Species*					Not triggered
Earthworm, Acute Toxicity Tests					Not triggered
Collembola, Reproduction Test					Not triggered
Sediment dwelling organism	OECD 218	NOEC	3684	mg/kg dw sediment	the non-biting midge *Chironomus riparius* Corrected for 10% organic carbon

The outcome of the Phase II Tier A and Tier B assessment confirmed that apremilast is unlikely to pose a risk to surfacewater, groundwater or to microorganisms and is unlikely to pose a risk to sediment dwelling organisms.

Phase IIa and IIb risk evaluation summary:

Environmental compartment	PEC (µg/L)	PNEC	PEC/PNEC	Trigger value	Conclusion
Phase II Tier A					
Surfacewater	1.35 µg/L	350 µg/L	0.0039	1	No risk
Microorganism	13.5 µg/L	1 x 10^5 µg/L	1.35 x 10^{-4}	0.1	No risk
Groundwater	0.3375 µg/L	35 µg/L	0.0096	1	No risk
Phase II Tier B					
Sediment	0.0666 mg/kg dw	36.84 mg/kg dw	0.0018	1	No risk

In conclusion, based on the updated ERA, apremilast is very persistent (vP) in fresh-water sediment. It is unlikely to pose a risk to the aquatic or soil environments and is not expected to have the potential for secondary poisoning nor be bioaccumulative in fish.

2.2.2. Discussion on non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Based on the updated ERA submitted in this application, apremilast has the potential to be very persistent (vP) to the environment. No potential for bioaccumulation nor toxicity has been identified. Apremilast is thus not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of apremilast.

- Considering the above data, apremilast is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has confirmed that no GCP inspections were performed for studies PPSO-001, PPSO-003, or PPSO-004.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study title	Study number	Date of completion	Date of submission of final Report	Countries
A Phase 2, Multicentre, Open-Label Study to Assess the Safety, Tolerability and Pharmacokinetics of Apremilast (CC-10004) in Paediatric Subjects with Moderate to Severe Plaque Psoriasis	CC-10004-PPSO-001	29 Jul 2019	13 Feb 2020	Canada, Germany, United Kingdom, United States
A Phase 3, Multi-Center, Randomized, Double- Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Apremilast (CC-10004) in Paediatric Subjects from 6 through 17 Years of Age with Moderate to Severe Plaque Psoriasis	CC-10004-PPSO-003	27 Mar 2023	29 Aug 2023	Belgium Canada Czech Republic France Germany Israel Italy Russia Spain United States
A Phase 3B, Multi-Center, Open-Label Long Term Extension Study of Apremilast (CC-10004) in Paediatric Subjects from 6 through 17 Years of Age with Moderate to Severe Plaque Psoriasis	CC-10004-PPSO-004	17 Feb 2027 (Projected)	Within 6months of Date of completion	Belgium Canada Czech Republic France Germany Israel Italy Netherlands Russia Spain United States

2.3.2. Pharmacokinetics

The clinical pharmacology package for the present application includes the pharmacokinetic (PK) data from 2 clinical studies in paediatric subjects 6 to 17 years of age with moderate to severe plaque psoriasis, study PPSO-001 and study PPSO-003, as well as associated population PK and exposure-response analyses conducted to support selection and establishment of the dosages for this paediatric population.

Study PPSO-001 was a phase 2, open-label study that evaluated the safety, tolerability, and PK of apremilast in subjects 6 to 17 years of age with moderate to severe plaque psoriasis. The results from this study determined the dosages to be evaluated in the pivotal phase 3 Study PPSO-003.

Study PPSO-003 was a phase 3, randomised, placebo-controlled, study that evaluated the efficacy and safety of apremilast compared to placebo in subjects 6 to 17 years with moderate to severe plaque psoriasis.

Studies PPSO-001 and PPSO-003 are part of the Paediatric Investigation Plan for psoriasis in the European Union.

Bioanalytical methods

The validated bioanalytical assays for determination of apremilast in lithium heparinised human plasma by LC/MS/MS (CC-10004-DMPK-024) and for the determination of apremilast in human dry blood spot (DBS) by LC-MS/MS (CC-10004-DMPK-1232) are the same as previously described in the initial MAA. The MAH states these were fit for purpose for determination of apremilast in these studies.

CC-10004-PPSO-001-BA-1 (heparinized human plasma)

A statement on GLP compliance was provided for this study. Certificates of analysis for reference standards were provided. A total of 268 human plasma samples were analysed for apremilast. All samples were assayed within the demonstrated stability periods of 520 days at -20°C. Samples were reanalysed if there were clear analytical grounds for rejection. Incurred sample reanalysis was performed for 31 plasma samples (>10% of total samples) and the % difference between measurements was within 20% for ≥2/3 of the duplicate pairs. A set of chromatograms was provided that include a blank, a blank with internal standard (IS), QCs, and at least five percent (5%) of subject samples.

Table 1. Validation summary of CC-10004 in Plasma

Report Title	Validation of a Method for the Determination of CC-10004 in Lithium Heparinized Human Plasma by LC-MS/MS
Report Number	QPS 155-0701G, Celgene No. CC-10004-DMPK-024
Analyte Name	CC-10004
Internal Standard	CC-16305
Analytical Method Type	LC-MS/MS
Extraction Method	Liquid-liquid
QC Concentrations	1.00, 3.00, 50.00, and 750.00 ng/mL
Standard Curve Concentrations	1.00, 3.00, 10.00, 30.00, 100.00, 300.00, 600.00, 1000.00 ng/mL
LLOQ	1.00 ng/mL
Upper Limit Of Quantification (ULOQ)	1000.00 ng/mL
Average Recovery of Drug (%)	100.6
Average Recovery of Internal Standard (%)	101.1
QC Intra-Day Precision Range (%CV)	1.4 to 2.8
QC Inter-Day Precision Range (%CV)	0.0 to 2.6
QC Inter-Day Accuracy Range (%RE)	-0.2 to 3.7
Stability	520 Days at -20°C/ -70°C

% CV = coefficient of variation expressed as a percentage; IS = internal standard; LC MS/MS = liquid chromatography tandem mass spectrometry; LLOQ = lower limit of quantification; No. = number; QC = quality control; % RE = relative error expressed as a percentage.

CC-10004-PPSO-001-BA-2 (DBS)

A statement on GLP compliance was provided for this study. Certificates of analysis for reference standards were provided. A total of 175 DBS were analysed for apremilast. All samples were assayed within the demonstrated stability periods of 167 days at room temperature. Samples were reanalysed if there were clear analytical grounds for rejection. Incurred sample reanalysis was performed for 22 DBS (>10% of total samples) and the % difference between measurements was within 20% for ≥2/3 of the duplicate pairs. A set of chromatograms was provided that include a blank, a blank with internal standard (IS), QCs, and at least five percent (5%) of subject samples.

Table 2. Validation summary of CC-10004 in Dry Blood Spot

Report Title	Validation of a Method for the Determination of CC-10004 in Human Dry Blood Spot (DBS) by LC-MS/MS
Report Number	QPS 155-1108, Celgene No. CC-10004-DMPK-1232
Analyte Name	CC-10004
Internal Standard (IS)	CC-16305
Analytical Method Type	LC-MS/MS
Extraction Method	Protein Precipitation
QC Concentrations	1.00, 3.00, 15.00, 450.00, and 900.00 ng/mL
Standard Curve Concentrations	1.00, 3.00, 10.00, 30.00, 100.00, 300.00, and 1000.00 ng/mL
LLOQ	1.00 ng/mL
Upper Limit Of Quantitation (ULOQ)	1000.00 ng/mL
Average Recovery of Drug (%)[a]	74.3
Average Recovery of IS (%)[a]	98.7
Average Recovery of Drug (%)[b]	64.4
Average Recovery of IS (%)[b]	106.1
QC Intra-Day Precision Range (% CV)[a]	2.1 to 10.6
QC Intra-Day Accuracy Range (% RE)[a]	-17.0 to 4.3
QC Inter-Day Precision Range (% CV)[a]	2.3 to 9.1
QC Inter-Day Accuracy Range (% RE)[a]	-12.0 to 0.0
QC Intra-Day Precision Range (% CV)[b]	1.2 to 11.3
QC Intra-Day Accuracy Range (% RE)[b]	-7.3 to 15.0
QC Inter-Day Precision Range (% CV)[b]	0.8 to 8.5
QC Inter-Day Accuracy Range (% RE)[b]	-4.0 to 5.0
Stability	29 Days at 35°C 167 Days at Room Temperature

DBS = dry blood spot; IS = internal standard; LC-MS/MS = liquid chromatography-tandem mass spectrometry; LLOQ = Lower Limit of Quantitation; QC = Quality Control; ULOQ = Upper Limit of Quantitation; % CV = coefficient of variation, expressed as a percent; % RE = relative error, expressed as a percent.
[a] Analysis perform using a 6 mm size puncher Uni-Core Punch
[b] Analysis perform using a 3 mm size puncher Uni-Core Punch

Study PPSO-003

A statement on GLP compliance was provided for this study. Certificates of analysis for reference standards were provided. A total of 819 human plasma samples were analysed for apremilast. With the exception of 12 samples, all study samples were assayed within the established long-term stability of 520 days at -70°C. Samples were reanalysed if there were clear analytical grounds for rejection. Incurred sample reanalysis was performed for 85 plasma samples (>10% of total samples) and 96.5% met the acceptance criteria for CC-10004. A set of chromatograms was provided that include a blank, a blank with internal standard (IS), QCs, and at least five percent (5%) of subject samples.

Study PPSO-001

The dosing regimen in this study was weight-based with a staggered, stepwise study design (starting enrolment with older and heavier adolescents) that guided dosing of subsequently enrolled subjects (younger and lighter weight children). The clinical study report presented the 2-week PK data.

A total of 42 subjects were enrolled into this study to provide an adequate PK profile in subjects of different ages and body weight ranges. Subjects were divided into 2 age groups: Group 1 (n=21) consisted of adolescents (ages 12 to 17 years, inclusive), and Group 2 (n=21) consisted of children (ages 6 to 11 years, inclusive). In Group 1, subjects ≥ 35 kg to <70 kg were administered apremilast 20 mg BID, and subjects ≥ 70 kg were administered apremilast 30 mg BID. In Group 2 all subjects were administered apremilast 20 mg BID. A total of 31 subjects completed the treatment period and 11 discontinued. A total of 38 subjects had evaluable PK data for inclusion in the 2-week PK analysis.

PK parameters for apremilast were estimated using non-compartmental methods. PK endpoints Cmax, Tmax, AUC0-12, AUC0-t, CL/F, Vss/F, and the t½ were estimated. Blood collection for PK parameters were taken on Day 1 (2 hours post morning dose), and on Day 14. Blood collection on Day 14 varied by group. For Group 1 blood was collected on Day 14 predose (prior to morning dose) and 1, 2, 3, 5, 8, and 12 hours post morning dose. For Group 2 blood was collected on Day 14 predose (prior to morning dose) and 2, 5, and 12 hours after the morning dose.

Pharmacokinetic Results

Mean (± SD) apremilast plasma concentrations versus time profiles on Day 14 by group and dose are presented on linear scale in Figure 1. Mean (± SD) apremilast plasma concentrations versus time profiles on Day 14 by baseline body weight and dose are presented on linear scale in Figure 2. These figures consistently show apremilast concentrations tend to be lower in adolescents treated with apremilast 20 mg BID.

Figure 1. Mean (+/- SD) Apremilast Plasma Concentration-time Profiles on Day 14, by Group and Dose (Linear Scale) (PK Population)

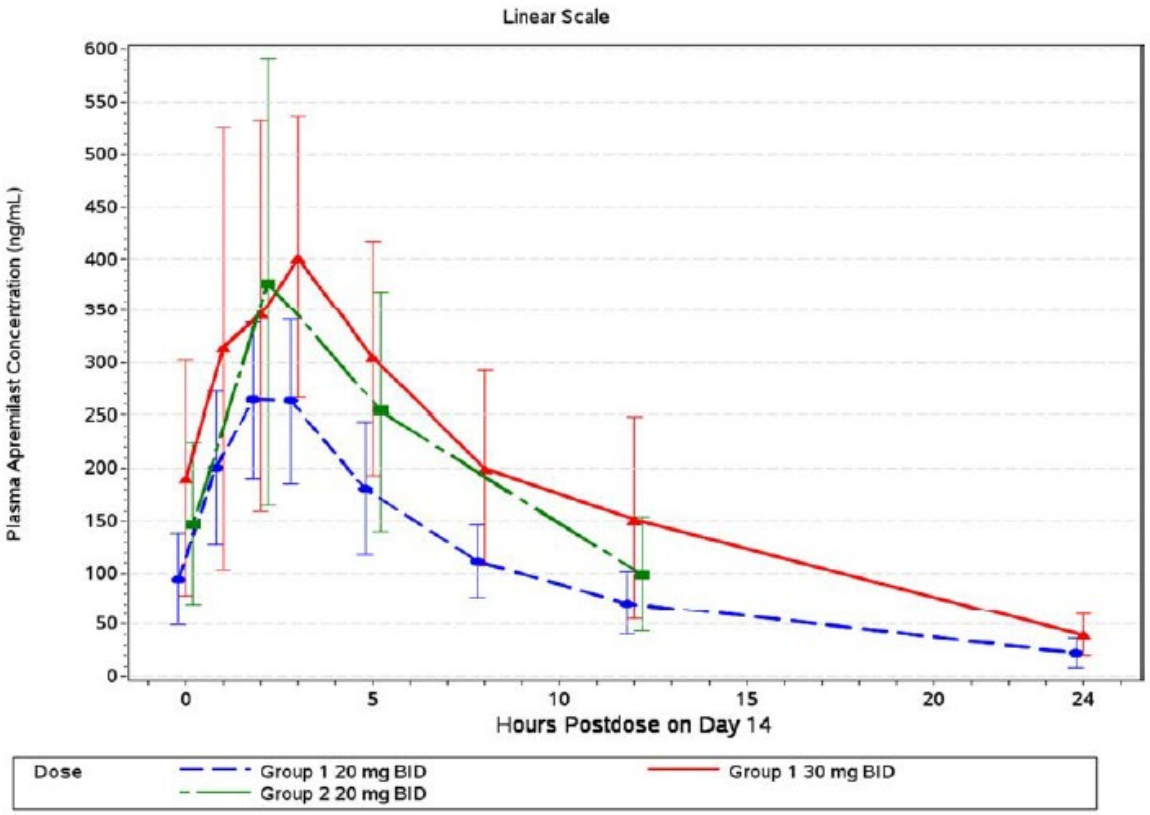
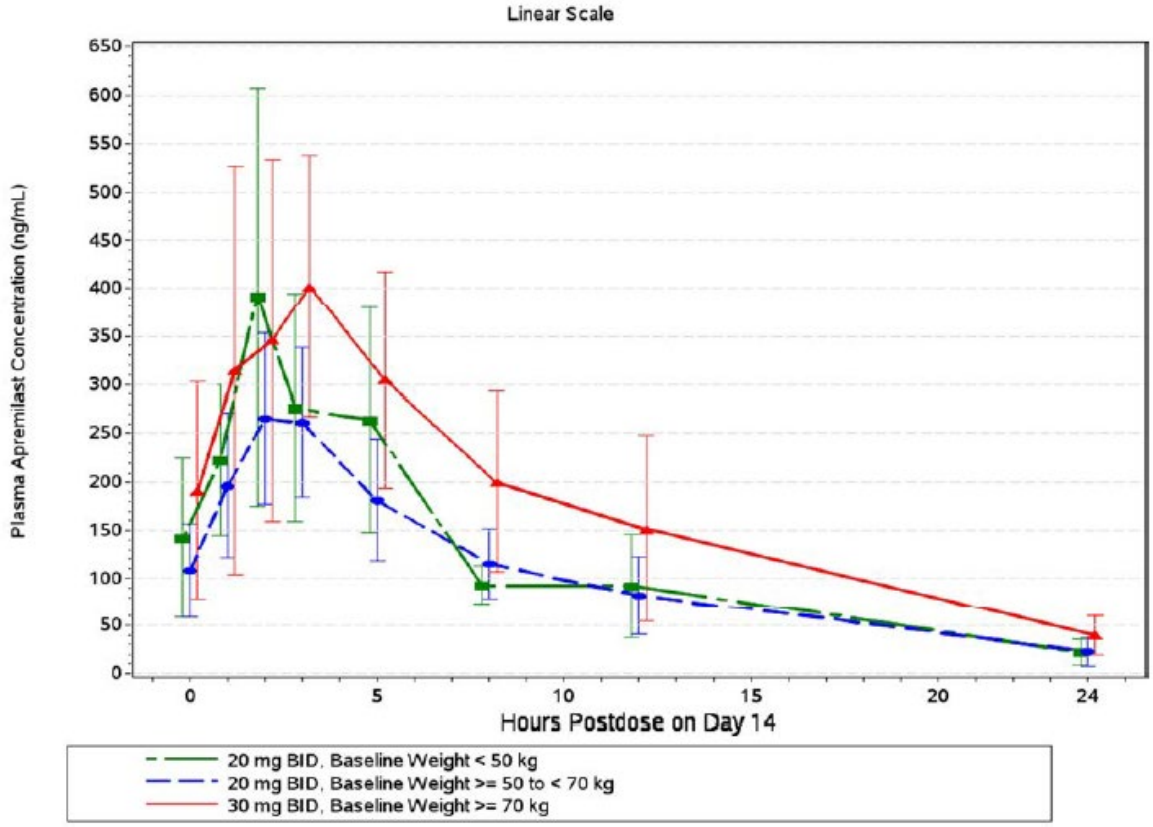


Figure 2. Mean (+/- SD) Apremilast Plasma Concentration-time Profiles on Day 14, by Baseline Body Weight and Dose (Linear Scale) (PK Population)



Plasma PK parameters on Day 14 by group and dose, and dose and baseline weight group are summarised in Table 3 and Table 4 respectively.

Table 3. Geometric Mean (Geometric CV%) Estimates of Apremilast Pharmacokinetics Parameters on Day 14, by Group and Dose (PK Population)

Pharmacokinetic Parameter (unit)	Group 1 (Adolescents[a]) N = 20		Group 2 (Children[b]) N = 18
	APR 20 BID n = 12	APR 30 BID n = 8	APR 20 BID n = 18
AUC_{0-t} (ng•h/mL)	1795 (35.9)	2900 (41.4)	2368 (50.2)
AUC_{0-12} (ng•h/mL)	1800 (36.0)	2902 (41.2)	2545 (40.8)
C_{max} (ng/mL)	274 (34.3)	411 (39.7)	348 (47.4)
t_{max} (h)[c]	2.50 (1.00, 3.00)	3.00 (1.00, 5.00)	2.00 (1.90, 5.00)
$t_{½}$ (h)	5.42 (43.1)	6.78 (50.3)	4.86 (30.2)
CL/F (L/h)	11.1 (36.0)	10.3 (41.2)	7.9 (40.8)
V_{ss}/F (L)	87 (56.1)	101 (31.6)	55 (51.2)

APR 20 BID = apremilast 20 mg twice daily; APR 30 BID = apremilast 30 mg twice daily; AUC_{0-12} = area under the plasma concentration-time curve from time zero to 12 hours postdose; AUC_{0-t} = area under the plasma concentration-time curve from time zero to last quantifiable time point; CL/F = apparent clearance of drug from plasma after extravascular administration; C_{max} = maximum observed plasma concentration, $t_{1/2}$ = terminal phase elimination half-life; t_{max} = time to maximum observed plasma concentration; V_{ss}/F = apparent total volume of distribution when dosed orally, based on steady-state.

[a] Adolescents are 12 to 17 years of age.

[b] Children are 6 to 11 years of age.

[c] Median (range).

Table 4. Geometric Mean (Geometric CV%) Estimates of Apremilast Pharmacokinetics Parameters on Day 14, by Dose and Baseline Weight Group (PK Population)

Pharmacokinetic Parameter (unit)	APR 20 BID BWT < 50 kg n = 16	APR 20 BID BWT ≥ 50 to < 70 kg n = 14	APR 30 BID BWT ≥ 70 kg n = 8
AUC_{0-t} (ng•h/mL)	2501 (41.8)	1754 (44.5)	2900 (41.4)
AUC_{0-12} (ng•h/mL)	2519 (41.5)	1872 (38.3)	2902 (41.2)
C_{max} (ng/mL)	368 (44.6)	266 (35.9)	411 (39.7)
t_{max} (h)[a]	2.0 (1.9, 5.0)	2.0 (1.0, 3.0)	3.0 (1.0, 5.0)
$t_{1/2}$ (h)	4.5 (29.2)	5.9 (38.3)	6.8 (50.3)
CL/F (L/h)	7.94 (41.5)	10.7 (38.3)	10.3 (41.2)
V_{ss}/F (L)	51.9 (50.3)	90.4 (49.0)	101 (31.6)

APR 20 BID = apremilast 20 mg twice daily; APR 30 BID = apremilast 30 mg twice daily; AUC_{0-12} = area under the plasma concentration-time curve from time zero to 12 hours postdose; AUC_{0-t} = area under the plasma concentration-time curve from time zero to last quantifiable time point; BWT = body weight; CL/F = apparent clearance of drug from plasma after extravascular administration; C_{max} = maximum observed plasma concentration, $t_{1/2}$ = terminal phase elimination half-life; t_{max} = time to maximum observed plasma concentration; V_{ss}/F = apparent total volume of distribution when dosed orally, based on steady-state.

[a] Median (range)

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Subjects (n=245 enrolled) were stratified by age group and randomised (2:1) to receive apremilast (n=163) or placebo (n=82) for 16 weeks, followed by apremilast treatment to 52 weeks. Treatment was assigned by weight with subjects 20 to < 50 kg receiving apremilast 20 mg BID or placebo BID and subjects ≥ 50

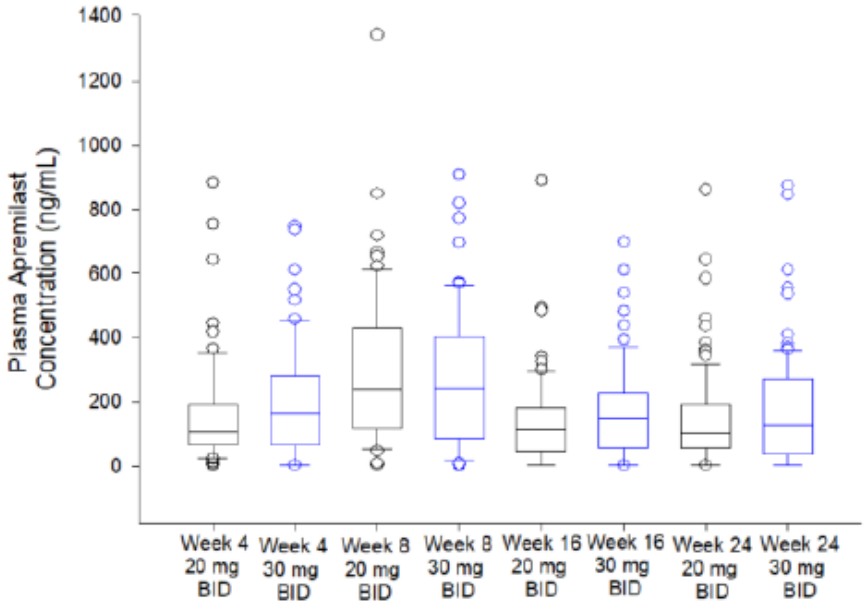
kg receiving apremilast 30 mg BID or placebo BID, following an initial titration. At week 16, placebo subjects were switched to receive apremilast 20 or 30 mg BID (following titration), according to baseline weight.

Sparse PK sampling was performed during the placebo-controlled phase at Weeks 4, 8, 16, and during the apremilast extension phase at Week 24. Trough concentrations (predose) were measured at Weeks 4, 16, and 24. 30-minute post-dose concentrations were measured at Week 8.

Pharmacokinetic Results

Plasma apremilast concentrations by treatment and week are presented in Figure 3, and the descriptive summary statistics for plasma trough concentrations are tabulated in Table 5.

Figure 3. premilast concentrations after 20 or 30 mg apremilast BID oral administration in paediatric subjects from 6 through 17 years of age with moderate to severe plaque psoriasis



BID – twice daily
Nominal times (weeks postdose) were used for presenting data. Weeks 4, 16, and 24 are predose concentrations. Week 8 is 30 minutes postdose concentration.
Solid lines within the boxes represent the median, whiskers (error bars) above and below the box indicate the 90th and 10th percentiles.
Data for Week 24 shown here is pooled data for all subjects, including subjects who switched from placebo to active treatment at Week 16

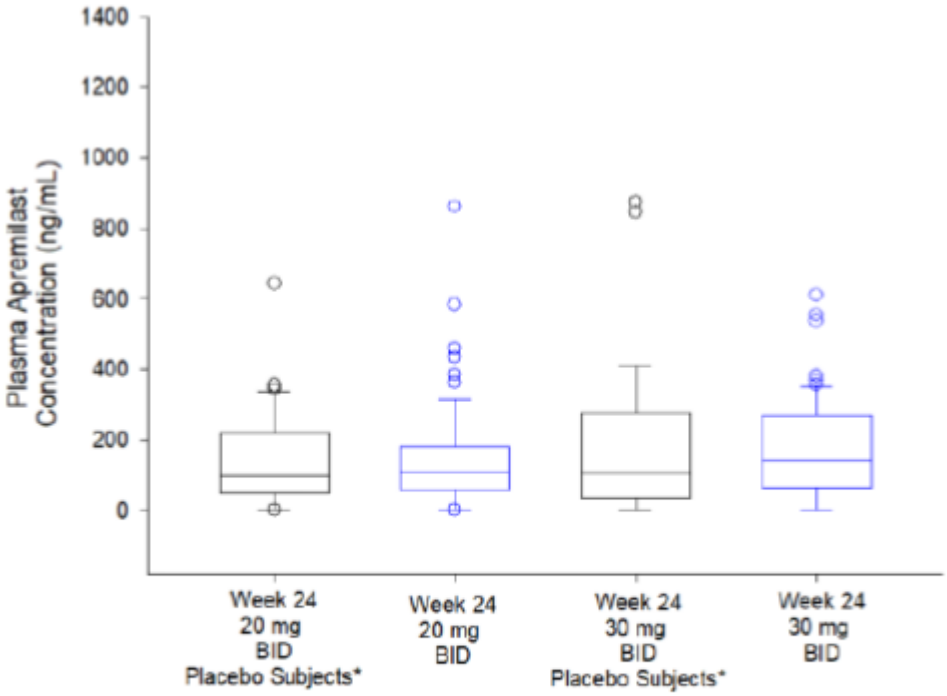
Table 5. Descriptive statistics of apremilast concentration (ng/mL) estimates after BID oral administration in paediatric subjects from 6 through 17 years of age with moderate to severe plaque psoriasis

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% – percent coefficient of variation; GeoMean – geometric mean
Weeks 4, 16, and 24 are predose concentrations. Week 8 is 30 minutes postdose concentration.
Descriptive statistics are presented to 3 significant figures except for CV%, which is presented to the nearest integer. Values below the limit of quantitation were set to 0.5 ng/mL, half the lower limit of quantitation (1.00 ng/mL), to calculate GeoMean.

Sixty-one subjects originally randomised to placebo and who switched to apremilast at week 16 were included in the PK dataset. Plasma apremilast concentrations by treatment are presented in Figure 4. A summary of the observed trough plasma concentrations in the placebo subjects who switched to apremilast at week 16 are presented in Table 6, suggesting that the subjects were at steady-state at week 24, when compared with the observed trough concentrations for the subjects who continued on apremilast.

Figure 4. Apremilast plasma concentrations at Week 24 after 20mg or 30 mg BID Oral Administration in paediatric subjects from 6 through 17 years of age with moderate to severe plaque psoriasis



BID – twice daily
Nominal times (weeks postdose) were used for presenting data.
Solid lines within the boxes represent the median, whiskers (error bars) above and below the box indicate the 90th and 10th percentiles.
* Placebo subjects switched to apremilast at week 16.

Table 6. Descriptive statistics of apremilast through concentration (ng/mL) at Week 24 in paediatric subjects from 6 through 17 years of age with moderate to severe plaque psoriasis

Dose	Statistic	Week 24	Week 24 Placebo Subjects[a]
20 mg BID	N	68	32
	Mean	145	144
	SD	149	139
	Min	0.5	0.5
	Median	109	99.1
	Max	860	643
	CV%	103	97
	GeoMean	65.2	67.4
30 mg BID	N	66	29
	Mean	168	181
	SD	142	223
	Min	0.5	0.5
	Median	145	105
	Max	610	874
	CV%	84	123
	GeoMean	64.5	47.5

BID – twice daily; CV% – percent coefficient of variation; GeoMean – geometric mean; LLOQ – lower limit of quantification
Descriptive statistics are presented to 3 significant figures except for CV%, which is presented to the nearest integer. Values below the limit of quantitation were set to 0.500 ng/mL, half the LLOQ (1.00 ng/mL), to calculate GeoMean.
[a] These subjects were switched from placebo to active treatment at week 16 per the protocol.

2.3.3. Pharmacodynamics

Mechanism of action

Apremilast is an orally administered drug that inhibits the enzyme phosphodiesterase (PDE)4, which is a cyclic adenosine monophosphate (cAMP)−specific PDE and the dominant PDE in inflammatory cells. By inhibiting PDE4, apremilast elevates intracellular cAMP levels, which in turn modulates a network of pro- and anti- inflammatory mediators and downregulates the inflammatory response.

2.3.4. PK/PD modelling

Population pharmacokinetics and exposure-response analyses in paediatric subjects (≥6 years of age) with moderate to severe plaque psoriasis (Report 157167)

These analyses were conducted to characterise the apremilast PK in paediatric subjects with moderate to severe plaque psoriasis, to characterise the exposure-response (sPGA and PASI-75) relationship of apremilast in moderate to severe plaque psoriasis in paediatric subjects relative to their adult counterparts, and to confirm the proposed dosing regimen for this population.

Population PK analysis

Data from 7 clinical studies (two phase 1 studies in adult healthy volunteers [20200164 and 20200167], 3 studies in adult subjects with moderate to severe plaque psoriasis [20200184, 20200185 and 20200188], and 2 studies in paediatric subjects with moderate to severe plaque psoriasis [20200171 and 20200056]) were included in the population PK analysis.

Methodology

The analysis was conducted via nonlinear mixed effects modelling with NONMEM software (version 7.4 or later). First-order conditional estimation with interaction (FOCEI) and stochastic approximation expectation maximization (SAEM) methods were used.

Plasma concentration-time profiles of apremilast in adult subjects with psoriasis were described in a previously submitted report with a one-compartment model with first order absorption and linear clearance (CC-10004-PSOR-011-PK). A similar PK model structure was used as a starting point for the present analysis. Once the base model was identified, the effect of covariates on the PK of apremilast were evaluated using a stepwise forward inclusion/backward elimination method. Covariates evaluated at baseline, including age, sex, body weight, race, creatinine clearance, and psoriasis disease status, were considered for their potential to reduce unexplained variability in population PK model parameters. Models were evaluated using a standard model discrimination process including statistical criteria (eg, objective function value), the precision of the parameter estimates and goodness-of-fit plots. Prediction corrected visual predictive check (VPC) was used as an internal model evaluation method.

The final population PK model was used to simulate apremilast exposure metrics ($AUC_{\tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$) for adult and paediatric subjects treated based on the proposed dosing regimens. Model-based simulations were also performed to further explore the effects of significant covariates on apremilast exposures.

Results

Apremilast concentration data were available from 611 subjects (74 healthy subjects, 537 psoriasis patients), including 200 paediatric patients. A total of 8694 apremilast concentration values were available of which 30 (0.3%) were below the lower limit of quantification (LLOQ) of 1 ng/mL. Since observations

below the LLOQ, constituted less than 5% of the observations they were retained in the dataset but excluded from the analysis. Summaries of continuous and categorical baseline covariates for subjects included in the population PK analysis stratified by study are shown in Table 7.

Table 7. Summary statistics of subjects 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%)

SD: Standard Deviation. Min: minimum. Max: maximum.

The PK of apremilast was characterised by a one-compartment model with first order absorption and linear elimination. The final covariate model parameters are presented in Table 8. Clearance (CL) and central volume (VC) were found to increase with increasing body weight and VC was larger for males as compared to females. The goodness of fit (GOF) plots for the final model show random normal scatter with minimal

deviation around the lines of identity over the range of predicted concentrations and over time (Figure 5). IIV shrinkage was 14.6%, 41.8% and 58.4% for CL, VC and absorption rate (KA), respectively.

Table 8. 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

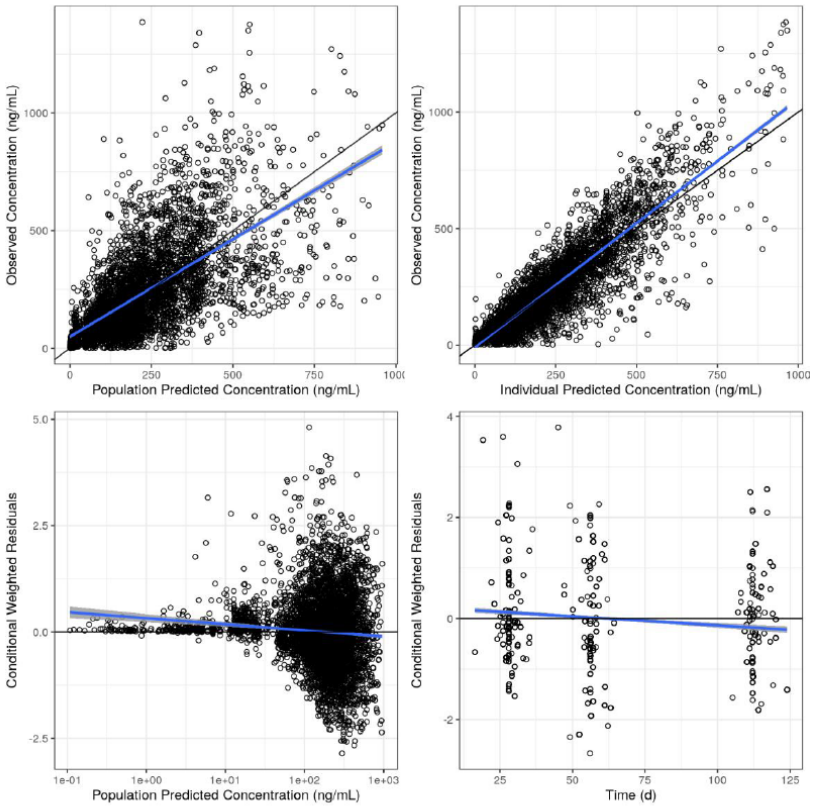
RSE: Relative Standard Error; RSE = (SE/ PE)*100.
CL: Clearance from central compartment.
VC: Volume of central compartment.
KA: 1st order rate absorption into the central compartment

Table 10-8. 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

RSE: Relative Standard Error; RSE = (SE/ PE)*100.
CL: Clearance from central compartment.
VC: Volume of central compartment.
KA: 1st order rate absorption into the central compartment

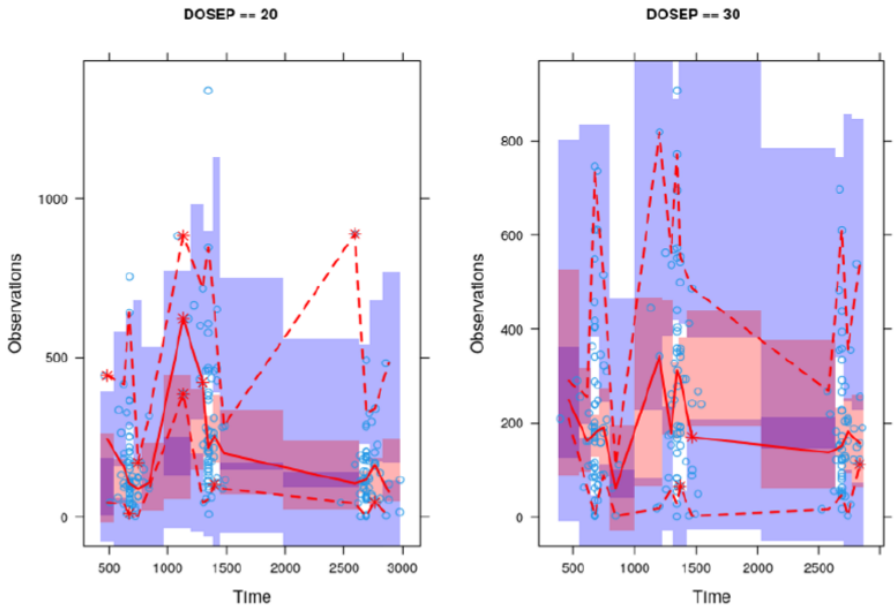
Figure 5. Goodness of fit plots for the final PK model



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

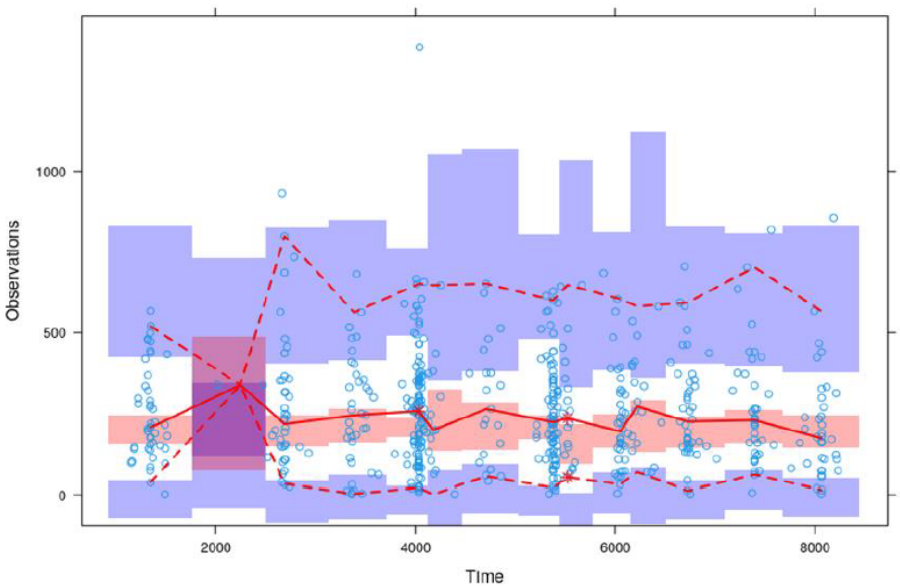
VPCs of the final PK model demonstrated adequate predictability of the model for each study. The observed median, 5th and 95th percentiles of apremilast concentrations (solid and dashed red lines) were within the 95% prediction interval (shaded areas) of the corresponding simulation-based percentiles at the majority of timepoints for each study (Figure 6 to Figure 12). The final PK model was deemed adequate to analyse the combined dataset and was appropriate for conducting simulations evaluating the appropriateness of the chosen paediatric apremilast dosing.

Figure 6. Prediction corrected visual predictive check for the final apremilast PK model stratified for Study 20200056 and dose level



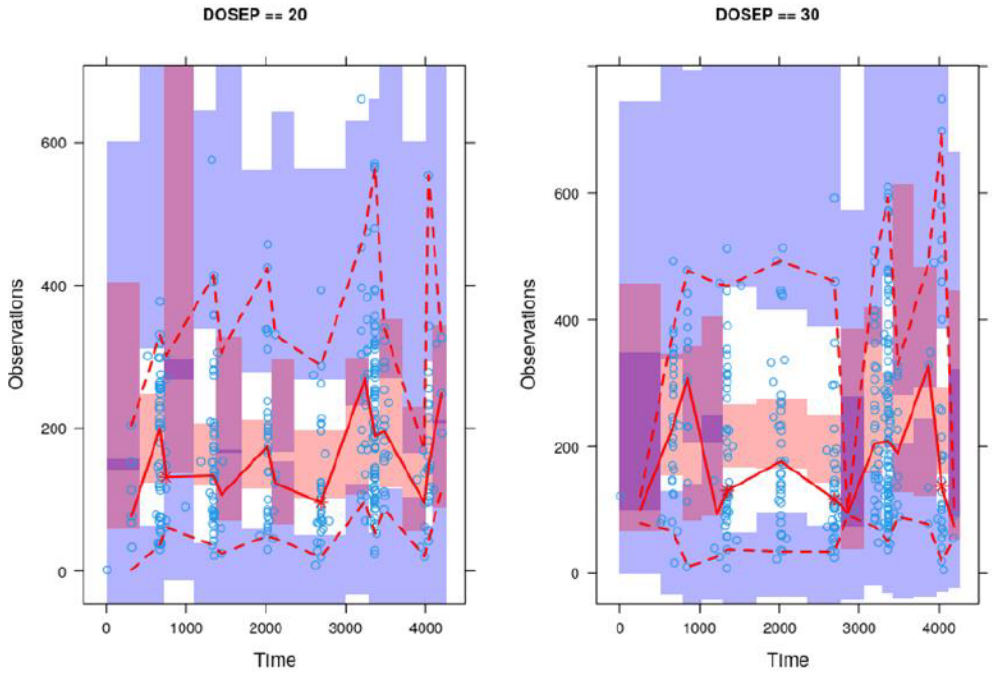
Lines represent prediction corrected observed data (solid red: median, dashed red: 5th and 95th percentiles, blue: observed proportion) and shaded areas (5th, 50th, 95th, or proportion) represent 90%PI of prediction corrected simulated metrics. Observed and predicted concentrations are plotted as prediction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

Figure 7. *Prediction corrected visual predictive check for the final apremilast PK model stratified for Study 20200185* and dose level



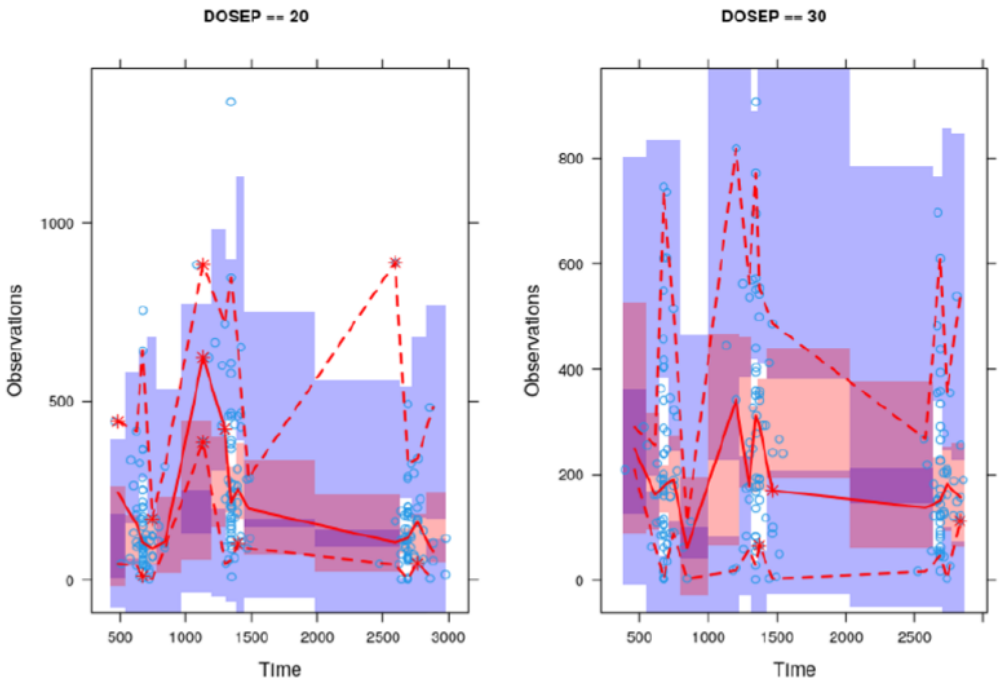
Lines represent prediction corrected observed data (solid red: median, dashed red: 5th and 95th percentiles, blue: observed proportion) and shaded areas (5th, 50th, 95th, or proportion) represent 90%PI of prediction corrected simulated metrics. Observed and predicted concentrations are plotted as prediction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

Figure 8. Prediction corrected visual predictive check for the final apremilast PK model stratified for Study 20200188 and dose level



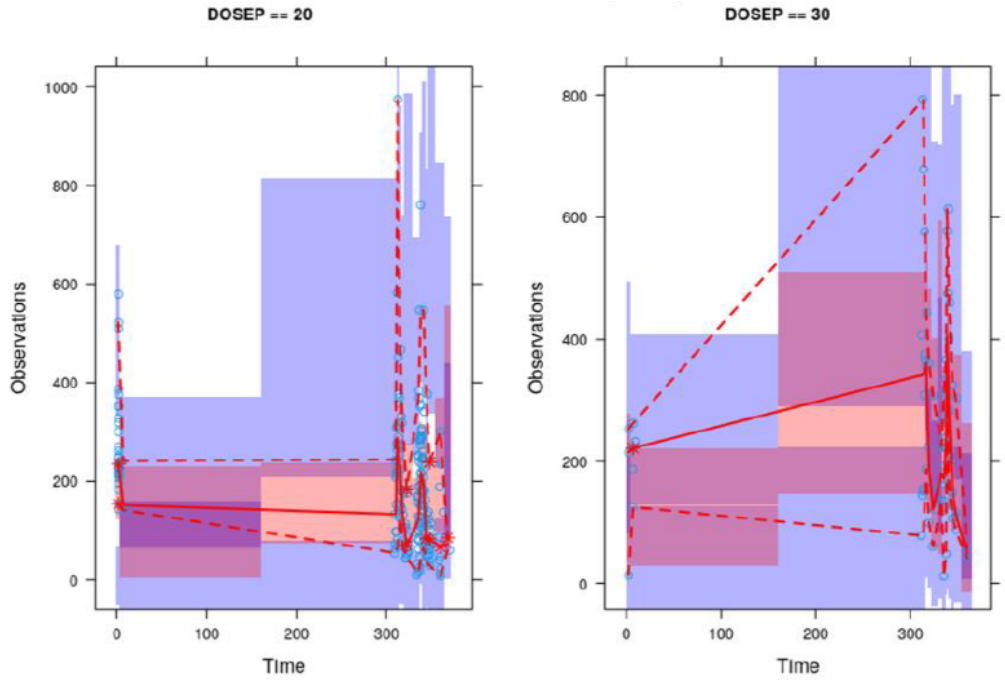
Lines represent prediction corrected observed data (solid red: median, dashed red: 5th and 95th percentiles, blue: observed proportion) and shaded areas (5th, 50th, 95th, or proportion) represent 90%PI of prediction corrected simulated metrics. Observed and predicted concentrations are plotted as prediction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

Figure 9. Prediction corrected visual predictive check for the final apremilast PK model stratified for Study 20200184 and dose level



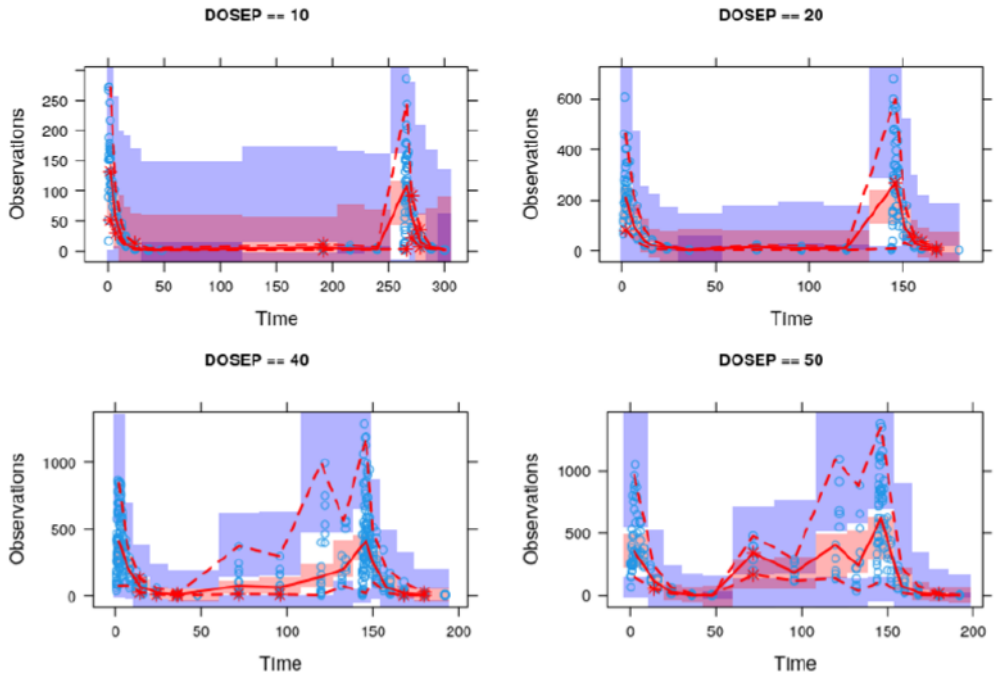
Lines represent prediction corrected observed data (solid red: median, dashed red: 5th and 95th percentiles, blue: observed proportion) and shaded areas (5th, 50th, 95th, or proportion) represent 90%PI of prediction corrected simulated metrics. Observed and predicted concentrations are plotted as prediction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

Figure 10. Prediction corrected visual predictive check for the final apremilast PK model stratified for Study 20200171 and dose level



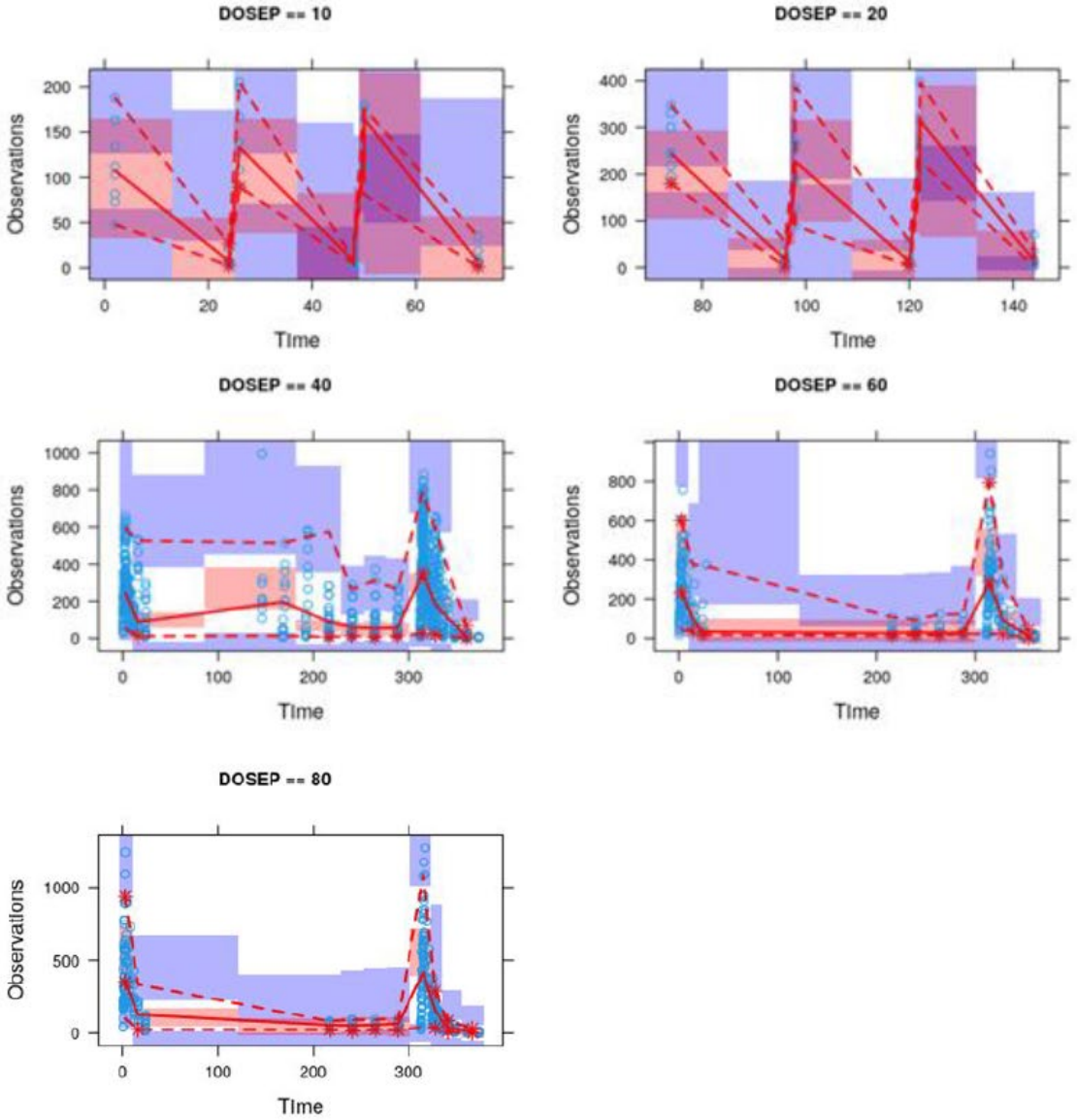
Lines represent prediction corrected observed data (solid red: median, dashed red: 5th and 95th percentiles, blue: observed proportion) and shaded areas (5th, 50th, 95th, or proportion) represent 90%PI of prediction corrected simulated metrics. Observed and predicted concentrations are plotted as prediction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

Figure 11. Prediction corrected visual predictive check for the final apremilast PK model stratified for Study 20200164 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.

Figure 12. Prediction corrected visual predictive check for the final apremilast PK model stratified for Study 20200167 and dose level

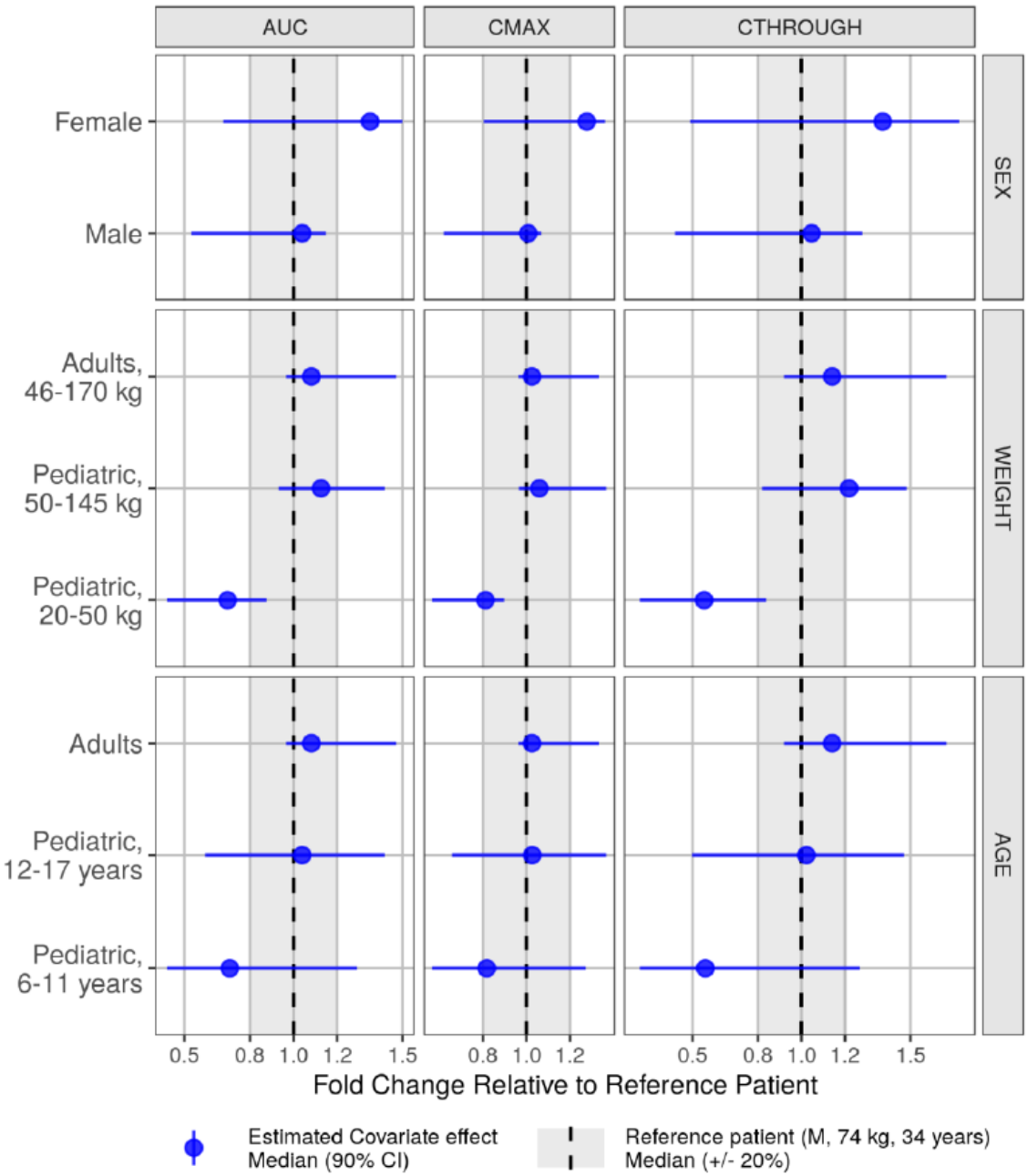


Lines represent prediction corrected observed data (solid red: median, dashed red: 5th and 95th percentiles, blue: observed proportion) and shaded areas (5th, 50th, 95th, or proportion) represent 90%PI of prediction corrected simulated metrics. Observed and predicted concentrations are plotted as prediction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

Simulations

The impact of covariates on apremilast PK are presented in Figure 13.

Figure 13. Predicted exposure fold change by final PK model covariates (Body weight, sex, age) per dosing group



Simulations exploring the effect of covariates demonstrated no clinically meaningful impact of each of the covariates on paediatric apremilast exposures relative to adults. To confirm this, paediatric subjects were stratified by body weight quartiles or age sextiles and apremilast exposure metrics were calculated for each group and compared to predicted adult exposures. Paediatric apremilast exposures across the entire body weight and age range were comparable to those predicted for adults. Furthermore, no clear trends were observed between apremilast exposure and body weight or age (Table 9 and Table 10). These outcomes confirmed that there is no need for further adjusting the proposed paediatric dosing regimen based on the covariates identified in the final model.

Table 9. Summary of model predicted paediatric steady state apremilast exposures by body weight quartiles

	1st quartile N = 50	2nd quartile N = 50	3rd quartile N = 50	4th quartile N = 50	Overall N = 200
Weight (kg)					
Mean (SD)	28 (5)	44 (4)	56 (3)	80 (20)	52 (22)
Median (Min-Max)	29 (20-38)	44 (38-50)	55 (50-62)	70 (63-145)	50 (20-145)
Cmax,ss (ng/mL)					
Mean (SD)	407 (161)	322 (112)	373 (155)	340 (142)	360 (146)
Median (Min-Max)	359 (247-949)	294 (184-685)	354 (177-878)	307 (127-860)	331 (127-949)
Ctrough,ss (ng/mL)					
Mean (SD)	159 (111)	149 (81)	199 (122)	190 (106)	174 (107)
Median (Min-Max)	130 (60-649)	122 (70-506)	170 (64-588)	166 (53-648)	140 (53-649)
AUCt,ss (ng/mL)					
Mean (SD)	3166 (1466)	2652 (1042)	3242 (1554)	3002 (1371)	3016 (1381)
Median (Min-Max)	2735 (1817-8644)	2305 (1501-6794)	2962 (1473-7903)	2744 (1031-8517)	2692 (1031-8644)

SD: Standard Deviation. Min: minimum. Max: maximum. Cmax,ss: maximum concentration at steady state. Ctrough,ss: trough exposure at steady state. AUCt,ss: Area under the curve 12 hours post dose (dosing Interval) at steady state

Table 10. Summary of model predicted paediatric steady state apremilast exposures by age sextiles

Characteristic	1st quantile, N = 27	2nd quantile, N = 27	3rd quantile, N = 26	4th quantile, N = 26	5th quantile, N = 26	6th quantile, N = 26	Overall, N = 158
Age (years)							
Mean (SD)	7 (1)	9 (1)	12 (1)	14 (1)	15 (0)	16 (0)	12 (3)
Median (Min-Max)	7 (6-8)	10 (8-10)	12 (10-13)	14 (13-15)	15 (15-16)	16 (16-17)	13 (6-17)
$C_{max,ss}$ (ng/mL)							
Mean (SD)	457 (194)	349 (95)	382 (177)	357 (151)	312 (98)	381 (135)	373 (151)
Median (Min-Max)	397 (288-949)	334 (221-574)	349 (181-878)	326 (177-685)	304 (177-563)	373 (185-697)	346 (177-949)
$C_{trough,ss}$ (ng/mL)							
Mean (SD)	208 (150)	155 (69)	200 (142)	197 (115)	156 (49)	208 (110)	187 (113)
Median (Min-Max)	156 (60-649)	138 (70-314)	142 (75-648)	165 (70-506)	151 (81-254)	193 (75-474)	156 (60-649)
$AUC_{0-12h,ss}$ (ng/mL)							
Mean (SD)	3758 (1874)	2,842 (873)	3,274 (1,758)	3,146 (1,480)	2,638 (754)	3,351 (1,380)	3,170 (1,440)
Median (Min-Max)	3188 (1957-8644)	2779 (1768-4662)	2815 (1495-8517)	2835 (1473-6794)	2674 (1494-4467)	3323 (1501-6561)	2860 (1473-8644)

SD: Standard Deviation. Min: minimum. Max: maximum
Cmax,ss: maximum concentration within a dosing cycle at steady state
Ctrough,ss: exposure archived immediately before a dose after achieving steady state
AUC0-12,ss: Area under the exposure curve 12 hours post dose at steady state

Exposure response analysis

Data collected from four Phase 2/3 studies of apremilast in subjects with moderate-to-severe plaque psoriasis (20200184, 20200185, 20200188, 20200056) were used in the exposure-efficacy analysis.

Methodology

Exposure-response models were developed to assess changes in PASI-75 and sPGA responses over time. Individual steady state exposure estimates were generated based on the population PK model. For subjects without any available PK measurements, exposure was calculated from simulations including their own subject level covariate effects and random effects sampled from the model distributions.

Aprimelast exposures were linked to response variables using logistic regression. The models included a logit function to characterise the probability of sPGA and PASI-75 responses, a saturating Emax-type drug effect and placebo effect with an exponential delay component, and time-fixed as well as time-varying

effects. Differentiation and selection of exposure-response models and covariate analysis were performed in a similar manner as the population PK analysis.

Results

The analysis dataset included a total of 10242 sPGA evaluations from 1670 subjects (1137 apremilast and 533 placebo), including 236 paediatric subjects (155 apremilast and 81 placebo). Similarly, a total of 10 255 PASI-75 evaluations from 1661 subjects (1132 apremilast and 529 placebo), including 234 paediatric subjects (155 apremilast and 79 placebo) were included in the analysis dataset. Summaries of continuous and categorical baseline covariates for subjects included in the sPGA and PASI exposure-response analyses stratified by study are shown in Table 11 and Table 12.

Table 11. Summary statistics of subject level covariates included in the sPGA exposure-response analysis 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%)

SD: Standard Deviation. Min: minimum. Max: maximum.

Table 12. Summary statistics of subject level covariates included in the PASI-75 exposure-response analysis 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%)

SD: Standard Deviation. Min: minimum. Max: maximum.

Age, body weight, and sex were included as covariates in both sPGA and PASI-75 exposure-response models. The final covariate model parameters are presented in Table 13 for sPGA and Table 14 for PASI-75.

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

RSE: Relative Standard Error; RSE = (SE/ PE)*100. S0: final placebo effect. kpbl: 1st order rate on the placebo effect. Emax: maximal drug effect attainable in logit space. Intercept: a value in logit space chosen to represent 0% incidence. EC50: parameter denotes the apremilast concentration corresponding to the 50% maximal drug effect. BW: body weight (kg)

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

RSE: Relative Standard Error; RSE = (SE/ PE)*100. S0: final placebo effect. kpbl: 1st order rate on the placebo effect. Emax: maximal drug effect attainable in logit space. Intercept: a value in logit space chosen to represent 0% incidence. EC50: parameter denotes the apremilast concentration corresponding to the 50% maximal drug effect. BW: body weight (kg)

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. 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.

Internal validation of the final exposure response models for sPGA and PASI-75 demonstrated successful prediction of the response rates over time of adults treated at the approved apremilast dose (30 mg BID) or with placebo as well as both paediatric dose groups and their corresponding placebo group. The observed mean and 99% confidence interval of the probability of response for both endpoints (solid colour circles and solid vertical lines) were within the 99% prediction interval (shaded areas) of the corresponding population simulation-based response projections at the majority of timepoints for all evaluated treatment groups of interest (Figure 14). Similarly, placebo corrected plots of sPGA and PASI-75 response at steady state (16 weeks of treatment) showed good agreement with observed mean response values observed for both the adult and paediatric subjects stratified by study and dose level (Figure 15 and Figure 16). These results confirmed the suitability of the model to describe apremilast exposure-response profiles for both clinical endpoints in the adult and paediatric populations.

Figure 14. Internal validation of PASI-75 and sPGA exposure-response model performance against corresponding observed data in adult and paediatric subjects treated with placebo or the approved/proposed apremilast dose

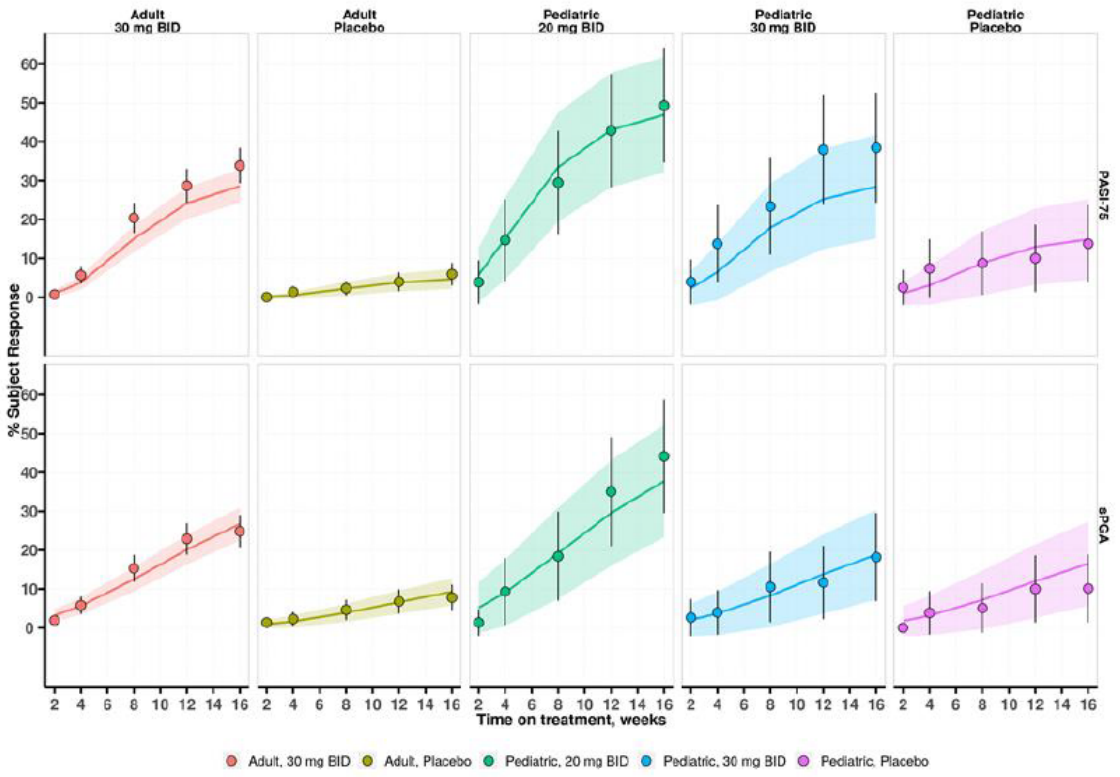


Figure 15. Placebo-corrected exposure-sPGA response after 16 weeks of apremilast treatment by study and dosing regimen

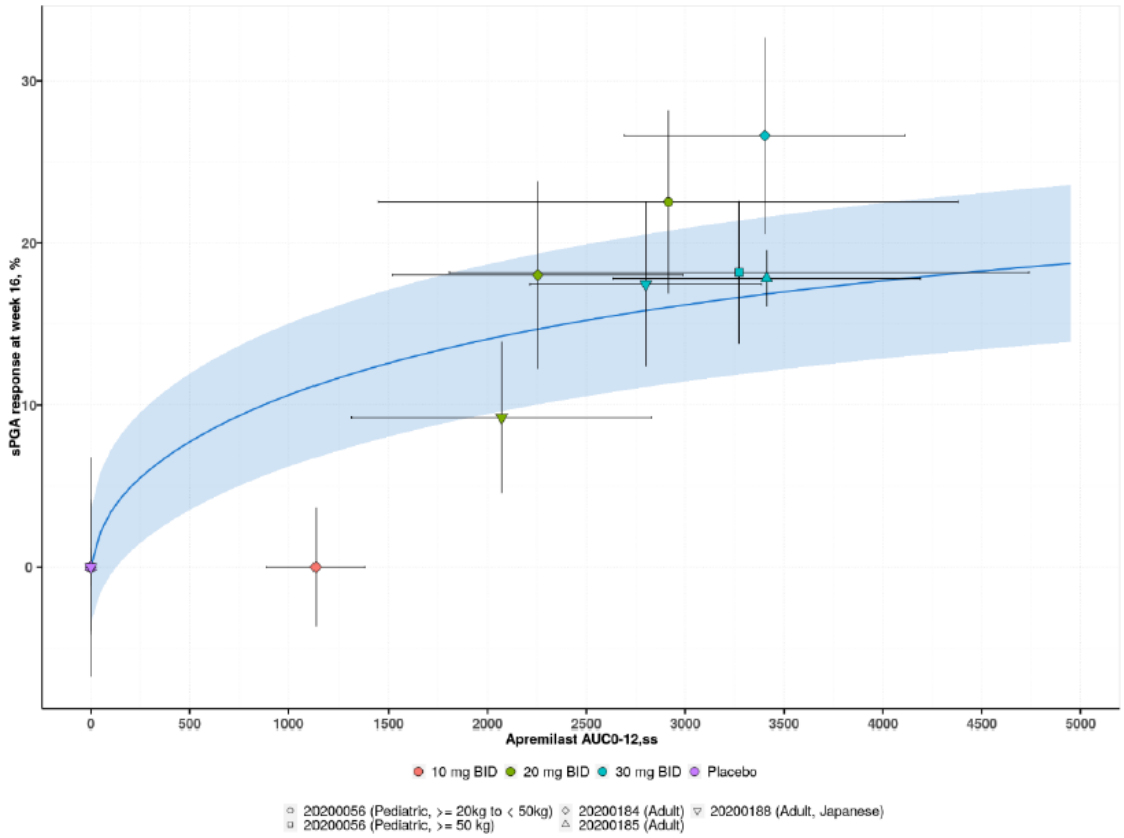
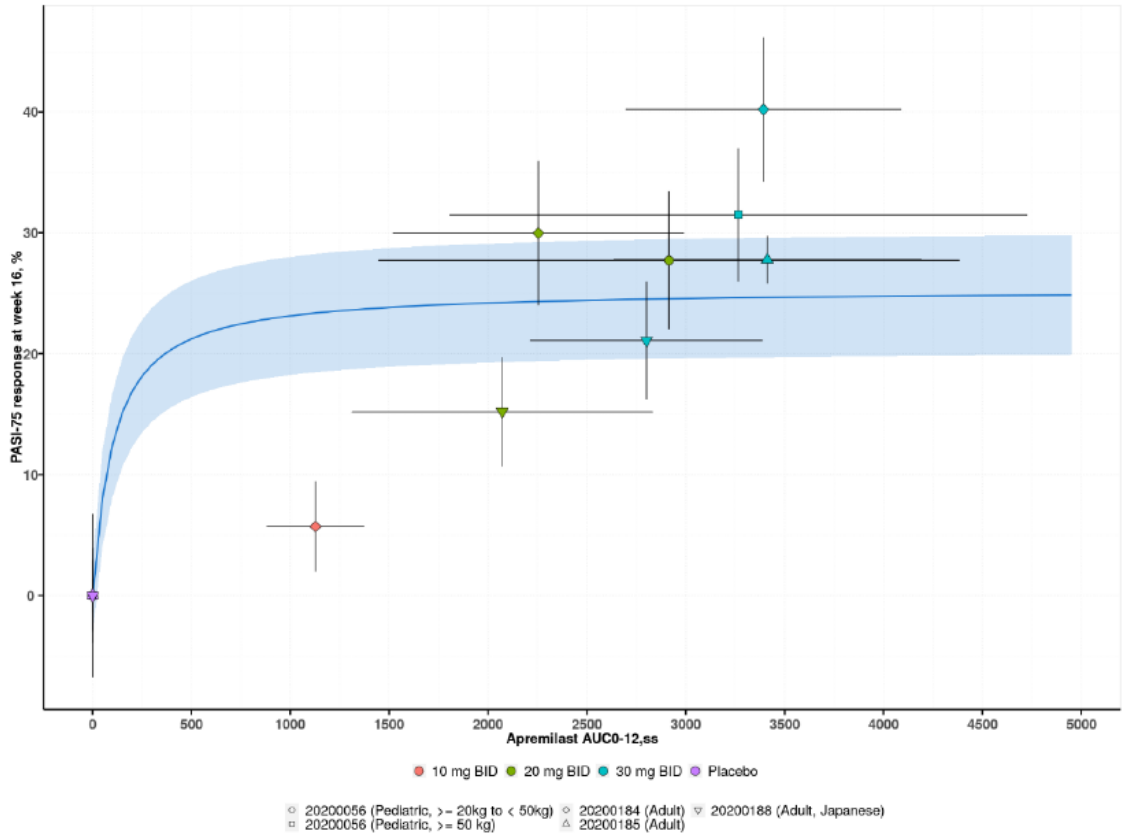


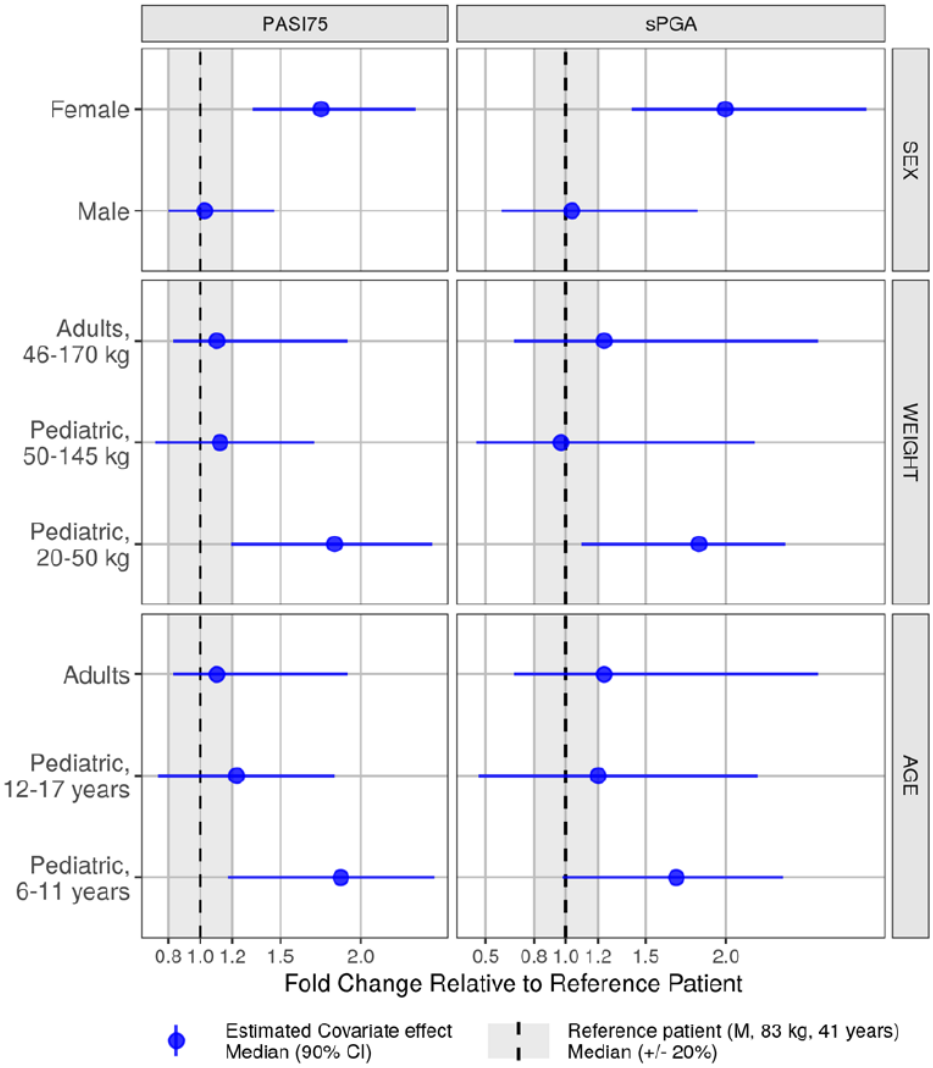
Figure 16. Placebo-corrected exposure-PASI-75 response after 16 weeks of apremilast treatment by study and dosing regimen



Simulations

Simulations evaluating the impact of covariates on sPGA and PASI-75 response rates of treatment are presented in Figure 17. The analysis revealed that age, body weight and sex have an impact the exposure-response rate of apremilast for both sPGA and PASI-75, but their effects were not deemed clinically significant.

Figure 17. Predicted sPGA and PASI-75 response fold change by covariates of final exposure-response models (body weight, sex, age) per dosing group



2.3.5. Discussion on clinical pharmacology

The clinical pharmacology package for this application includes the PK data from 2 clinical studies in paediatric subjects 6 to 17 years of age with moderate to severe plaque psoriasis, as well as the associated population PK and exposure-response analyses conducted to support selection of the dosages for this paediatric population. No specific pharmacodynamic studies were conducted which was considered acceptable by the CHMP.

Pharmacokinetics

Bioanalytical methods

The methods used for apremilast determination are acceptable to the CHMP and have been previously assessed as part of the initial MAA. The ICH guideline M10 on bioanalytical method validation and study sample analysis superseded the previous EMA guideline for bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr.2**) since the initial MAA and analysis of the samples from studies PPSO-001 and PPSO-003. The MAH has confirmed that the validated plasma LC-MS/MS method is aligned with the requirements of the ICH M10 guideline. The matrix effect experiment was not performed

as described in ICH M10. However, the used method still provided an appropriate assessment of the matrix effect.

The analytical methods for studies PPSO-001 and PPSO-003 are acceptable to the CHMP. Sample handling and storage are acceptable. The bioanalytical assessment reports exhibit acceptable calibration curve and QC sample performance. Accuracy and precision are acceptable. Incurred sample reanalysis was carried out sufficiently and showed reproducibility. The MAH provided representative chromatograms as part of the reports.

Study PPSO-001

The overall design and methodology of Study PSO-001 is acceptable to the CHMP for the PK objectives. Standard non-compartmental models were used to derive the PK parameters of interest which is acceptable to the CHMP.

This study investigated the PK parameters of apremilast in paediatric patients aged 6 to 17 years with moderate to severe plaque psoriasis. The subjects were split into two groups, where the results from Group 1, subjects aged 12 to 17 years inclusive informed the dosing for subsequently enrolled Group 2 subjects, aged 6 to 11 inclusive. A total of 21 subjects were enrolled in each group, with 20 subjects from Group 1 and 18 Subjects from Group 2 being included in the non-compartmental analysis. The PK parameters investigated are acceptable to the CHMP.

The time-points in this study are overall acceptable to the CHMP. It is noted that the Cmax was observed in the first time-point in some subjects for both Group 1 and Group 2. The measured Cmax/Tmax may not have been adequately characterised in these subjects, however, as the objective of the study was to identify a dose based on safety, efficacy and PK, as opposed to fully characterising the PK, this was found acceptable to the CHMP.

Similar concentration-time profiles were shown between Group 1 (30 mg BID) and Group 2 (20 mg BID). Group 1 (30 mg BID, AUC0-12: 2902 ng.h/mL) also showed similar exposure to Group 2 (20 mg BID, AUC0-12: 2545 ng.h/mL). Group 1 (20 mg BID) showed an overall lower concentration-time profile than the other groups, and notably reduced exposure (AUC0-12: 1800 ng.h/mL).

The MAH also provided further summarisation of the data using 50 kg as a cut-off. Similar concentration-time profiles and exposure were seen in the <50 kg 20 mg BID and ≥70 kg 30 mg BID groupings. The ≥50 kg to <70 kg 20 mg BID grouping showed overall lower exposure and lower concentration-time profile than the other groupings. From this data, the MAH concluded that subjects ≥50 kg were to be recommended to take the full 30 mg BID dosing which is acceptable to the CHMP.

Absorption rates were shown to be overall faster in the younger and lighter groups, with Group 2 20 mg BID (6-11 years) showing median Tmax of 2 h compared to Group 1 30 mg BID showing a median Tmax of 3 h. The t½, CL/F and Vss/F overall acceptable to the CHMP.

Study PPSO-003

This study took sparse PK samples for apremilast in paediatric patients aged 6 to 17 years with moderate to severe plaque psoriasis. The subjects were split into two groups in a 2:1 ratio of apremilast treatment and placebo (up to Week 16). The dosing regimen of apremilast 20 mg BID for subjects <50 kg or apremilast 30 mg BID for subjects ⩾ 50 kg was informed by study PSO-001. This is acceptable to the CHMP.

Sparse PK sampling for the trough concentration (predose) were taken at Weeks 4, 16, and 24. The observed geometric mean plasma trough concentrations were slightly higher at each time-point in the 30 mg BID dose when compared with the 20 mg BID dose but are considered comparable overall. PK sampling

30-minutes postdose was taken at Week 8, and the geometric mean plasma concentration was similar between both the 20 mg BID and 30 mg BID groups.

Week 24 shows the first apremilast concentration measurement for subjects who had received placebo up to Week 16. The trough concentrations were similar between the subjects who had previously received placebo and the subjects who had continued to receive apremilast at Week 24. This indicates that steady state had been reached in the placebo group within 8 weeks, which is expected given the low half-life of apremilast when given orally BID.

Overall, the sparse PK sampling demonstrates that the dosing regimens of 20 mg BID in <50 kg subjects and 30 mg BID in ⩾ 50 kg subjects are overall similar, and that steady state levels are reached rapidly.

PK/PD modelling

Population PK analysis

The population PK analysis was performed using data from 5 adult studies and two paediatric studies (20200171, 20200056). The methods used for model development and evaluation are acceptable to the CHMP. Data exclusions were detailed and acceptable.

A one-compartment model with first-order absorption and linear elimination was used to describe the time course of apremilast concentrations. Comparable models have been previously developed based on the adult data from studies in both healthy volunteers and psoriasis patients. The final model included psoriasis disease status, sex, and weight effects on CL and body weight and psoriasis disease status effects on VC. Allometric exponents for the effect of body weight on CL and VC were estimated at 0.246 and 0.901, respectively. This approach is justified since fixing allometric exponents at 0.75 and 1.00 for CL and VC, respectively, produced a worse overall fit compared to the fit using estimated exponents (ΔOFV=+63.9). The parameters of the final population PK model were estimated with adequate precision (all %RSE <45%). IIV shrinkage was low for CL (14.6%) and moderate for VC (43.5%).

The goodness-of-fit plots for the final model indicated that the model adequately described the data. The performance of the final model for predicting apremilast exposures in the paediatric and adult studies is fair. Peak concentrations are not well captured, and variability is generally overpredicted. As such, the model is only considered acceptable for supportive purposes.

Notwithstanding reservations about the predictive performance of the PK model, the predicted paediatric steady-state exposures of apremilast across the bodyweight and age range at the proposed doses appear comparable to adult steady-state exposures. This provided support for the proposed paediatric dose regimens. The CHMP agreed that no further adjustments are necessary in terms of covariates.

Exposure-response analyses

The exposure-response (ER) analyses of apremilast were conducted for patients with moderate to severe plaque psoriasis based on data pooled from three adult studies and one study in paediatric patients. The analysis characterised the relationship of steady-state apremilast exposure and the probability of subjects achieving sPGA and PASI-75 scores of clear or almost clear, with apremilast exposures linked to response variables using logistic regression. The probability of subjects achieving these efficacy endpoints increased with time and apremilast exposure and tended to reach a plateau around week 16 in both the adult and paediatric patients, suggesting comparable exposure-response relationships between these groups.

Internal validation of the final ER models indicated reasonable prediction of response rates over time in adults treated at the approved apremilast dose or with placebo, as well as both paediatric dose groups and the corresponding placebo group. Placebo-corrected plots of sPGA and PASI-75 response at steady-state generally showed agreement with observed mean response values in adult and paediatric patients although observed means were not included in the prediction intervals for all doses in all studies. Overall, the

exposure-response analyses support the proposed apremilast dosing regimens in paediatric subjects with moderate-to-severe plaque psoriasis.

Based on the final ER models, the EC50 was estimated to be 1800 and 60.5 ng*h/mL for sPGA and PASI-75, respectively. Therefore, based on the proposed dosing regimen, paediatric subjects in both dosing groups are predicted to achieve steady-state apremilast exposures higher than the EC50 values for each endpoint and comparable to those achieved by adults treated at the approved dose. Although the EC50 was estimated with poor precision (RSE 193%) in the PASI-75 model, the anticipated steady-state AUC_{0-12} of both paediatric weight cohorts at their proposed dosing regimens is greater than 5-fold above the upper bound of the 95% confidence interval for the estimated EC50 (290 ng/mL*h). Therefore, while the uncertainty in the estimate of EC50 is high, it is not expected to impact predictions of clinical efficacy in paediatric subjects ages 6 to 17 years of age.

Simulations evaluating the impact of covariates on PASI-75 and sPGA response indicated that age, body weight, and sex had an impact on the exposure-response rate. However, their effects are considered clinically insignificant**.**

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology data are sufficient to support the following posology (SmPC Section 4.2) of apremilast in the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years and weighing at least 20 kg who are candidates for systemic therapy:

- The recommended dosage is based on body weight. The recommended dosage of apremilast is 20 mg taken orally twice daily for paediatric patients who weigh from 20 to less than 50 kg, and 30 mg taken orally twice daily for paediatric patients who weigh at least 50 kg following the initial titration schedule.

2.4. Clinical efficacy

2.4.1. Main study

Study CC-10004-PPSO-003 (PPSO-003): A Phase 3, Multi-Centre, Randomized, Double- Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Apremilast (CC-10004) in Paediatric Subjects from 6 to less than 18 years of Age with Moderate to Severe Plaque Psoriasis.

Methods

This was a phase 3, multicentre, randomized, placebo-controlled, double-blind study designed to evaluate the efficacy and safety of apremilast in paediatric subjects with moderate to severe plaque psoriasis. The study included a placebo-controlled treatment phase (weeks 0 to 16), an apremilast extension phase (weeks 16 to 52), and a 14-week observational follow-up phase.

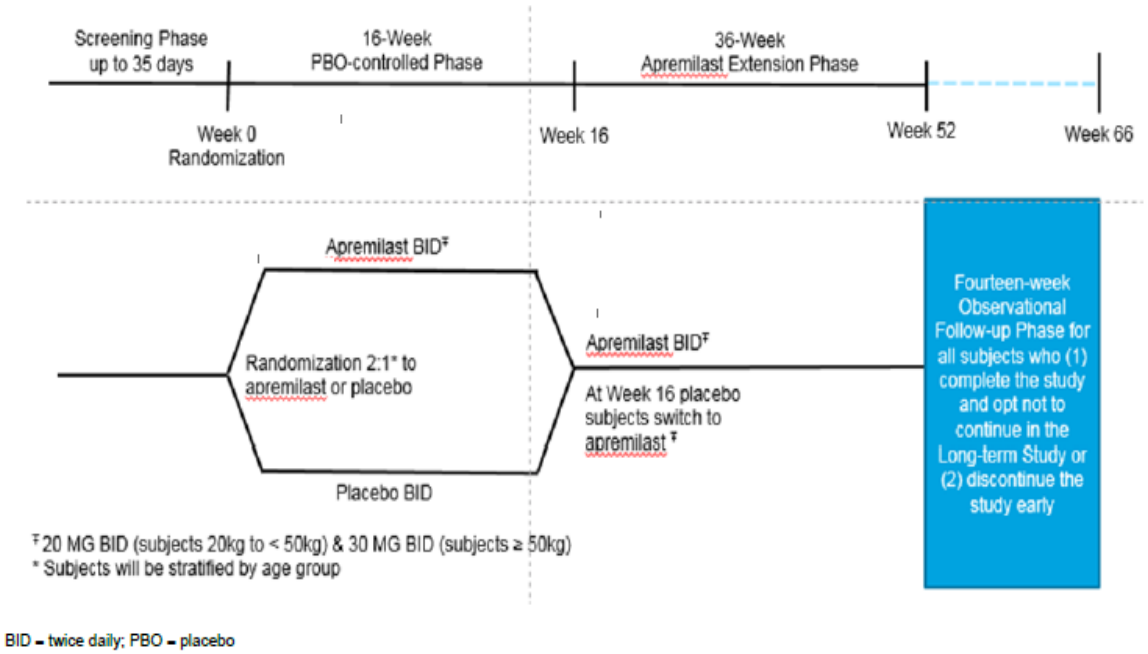
Study Initiation Date: 26 November 2018

Study Completion Date: 27 March 2023

The study had 4 phases:

- a screening phase (up to 35 days),
- a placebo-controlled treatment phase (weeks 0 to 16),
- an apremilast extension phase (weeks 16 to 52), 45

- an observational follow-up phase (14 weeks).



BID = twice daily; PBO = placebo

The double-blind, placebo-controlled phase of the study evaluated subjects randomised in a 2 (apremilast):1 (placebo) ratio for the first 16 weeks. Subjects 20 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. Treatment assignment was stratified by baseline age group (6 to 11 years or 12 to 17 years).

At week 16, subjects in the placebo group were switched to apremilast based on baseline weight and subjects in the apremilast group continued to receive their original dosing assignment through week 52.

Early escape

From weeks 8 through 16, any subject with PASI total score increase ≥ 50% from baseline was eligible for early escape, was allowed to commence treatment with moderate-to-high potency topical steroid preparations, and could continue with randomised investigational product.

Long-term extension study

All eligible subjects who completed the apremilast extension phase had the option of enrolling in a separate long-term extension study (Study CC-10004-PPSO-004 [20200057]). Subjects who chose not to participate in the long-term extension study or discontinued Study CC-10004-PPSO-003 early entered the observational follow-up phase with visits 4, 8, and 14 weeks after the last dose of investigational product.

Study participants

Subject must satisfy the following criteria to be enrolled in the study:

1. Males or female subjects 6 to 17 years of age, inclusive, at the time the informed consent form is signed by the legal guardian
2. Subjects must have a weight of ≥ 20 kg

3. Subjects must have an age and sex specific BMI value no lower in range than the 5th percentile on the Centers for Disease Control (CDC) growth chart for children and adolescents (CDC, 2000).
4. Subject is able to swallow the study medication tablet
5. Able to sign an age-appropriate assent with a legal guardian(s) who understand(s) and voluntarily sign(s) an informed consent prior to any study-related assessments/procedures being conducted.
6. Be willing and able to adhere to the study visit schedule and other protocol requirements.
7. Diagnosis of chronic plaque psoriasis for at least 6 months prior to Screening.
8. Has moderate to severe plaque psoriasis at Screening and Baseline as defined by:
    - PASI score ≥ 12; and
    - Body surface area (BSA) ≥ 10%; and
    - sPGA ≥ 3 (moderate to severe)
9. Disease inadequately controlled by or inappropriate for topical therapy for psoriasis
10. Candidate for systemic therapy or phototherapy
11. At Screening, laboratory values must be within the following ranges:

- White blood cell (WBC) count

Age (years)	Males (x 10^3 /µL)	Females (x 10^3 /µL)
6-11	3.5 – 13.5	3.5 – 13.5
12-18	3.5 – 13.5	3.5 – 13.5

- Platelet count

Age (years)	Males (x 10^3 /µL)	Females (x 10^3 /µL)
6-11	125 – 500	125 – 500
12-18	125 – 500	125 – 500

    - Serum creatinine ≤ 1.2 x upper-limit of normal (ULN) for age and gender.
    - Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase[SGOT]) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) ≤ 1.5 x ULN for age and gender. If initial test of ALT orAST is > 1.5 x ULN, one repeat test was allowed during Screening.
    - Total bilirubin ≤ 2 mg/dL (≤ 34 µmol/L). If initial test result is > 2 mg/dL, one repeat test is allowed during the Screening period
    - Hemoglobin (Hb)

Age (years)	Males (g/dL)	Females (g/dL)
6-11	10.0 – 15.0	10.0 – 15.0
12-18	11.0 – 16.5	10.5 – 15.5

12. All females of childbearing potential (FCBP) must either practice abstinence* from heterosexual contact or use one of the approved contraceptive options as described in the protocol.

Exclusion Criteria

1. Other than psoriasis, history of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease

2. Any condition, including the presence of laboratory abnormalities, or psychiatric illness, that would place the subject at unacceptable risk if he/she were to participate in the study
3. Any condition that confounds the ability to interpret data from the study
4. Evidence of skin conditions, other than psoriasis, that would interfere with clinical assessments
5. Pregnant or breastfeeding
6. Guttate, erythrodermic, or pustular psoriasis at Screening and Baseline
7. Psoriasis flare or rebound within 4 weeks prior to Screening
8. Positive Hepatitis B surface antigen, or anti-hepatitis C antibody, at Screening
9. History of positive human immunodeficiency virus infection (HIV), congenital and acquired immunodeficiencies (eg, common variable immunodeficiency, immunoglobulin A deficiency)
10. Active tuberculosis (TB) or a history of incompletely treated TB
11. History of recurrent significant infections
12. Active infection or infection treated with antibiotic treatment within 2 weeks of first dose
13. Any history of or active malignancy
14. History of allergy/intolerance to any component of the investigational product
15. Deficiencies in lactose metabolism
16. Prior history of suicide attempt at any time in the subject's lifetime prior to Screening or randomization in the study, or major psychiatric illness requiring hospitalization within 3 years prior to signing the assent and informed consent
17. Answer "Yes" to any question on the Columbia-Suicide Severity Rating Scale during Screening or at Baseline
18. Current or planned concurrent use of the following therapies that may have a possible effect on psoriasis Topical therapy, including but not limited to topical corticosteroids (exceptions: low potency or weak corticosteroids for treatment of the face, axillae, and groin; unmedicated skin moisturizers for body lesions); conventional systemic therapy for psoriasis within 4 weeks prior to randomization (, including but not limited to corticosteroids; Phototherapy treatment; within 4 weeks prior to randomization Biologic therapy;
    i. Etanercept (or biosimilar) treatment four weeks prior to randomization
    ii. Adalimumab (or biosimilar) treatment ten weeks prior to randomization
    iii. Other TNF or IL-17 blockers (such as infliximab, certolizumab pegol,secukinumab, ixekizumab, brodalumab, or their biosimilars) within 12 weeks prior to randomization
    iv. Anti-IL-12 or anti-IL-23 treatment (such as ustekinumab, guselkumab, or tildrakizumab) within 24 weeks prior to randomization and/or any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
19. Prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources
20. Children in Care
21. Prior treatment with apremilast

Treatments

Subjects were dispensed blister cards with 10, 20, and 30 mg apremilast tablets, depending on baseline weight, or identically appearing placebo tablets, for the 7-day dose titration at the baseline visit (week 0). The blister cards contained all investigational product required for 4 weeks of treatment and were used throughout the placebo-controlled treatment phase (week 16). Titration supplies or matching placebo were dispensed over the first 3 days for the 20 mg BID treatment group (20 to < 50 kg), and over the first 5 days for the 30 mg BID treatment group (≥ 50 kg). Starting at week 16, all subjects were switched to, or continued with, apremilast (either 20 or 30 mg BID, depending on baseline weight). Subjects randomized to apremilast at week 0 remained on their assigned apremilast dose level. To maintain the blind, all subjects received dose titration cards at the week 16 visit, although only subjects initially randomized to placebo were dose titrated.

Subjects were treated with investigational product for up to 52 weeks.

The dosing selected was based on the outcomes of a paediatric phase 2 study (Study CC-10004-PPSO-001) that evaluated the PK profiles of 2 effective adult dosages, 20 and 30 mg BID. The PK results from this study show that the apremilast exposure (area under the plasma concentration-time curve over the dosing interval [AUCtau] and peak observed plasma concentration of drug [Cmax]) on day 14 in adolescents (12 to 17 years) treated with 30 mg BID and children (6 to 11 years) treated with 20 mg BID appear to be comparable to the exposure observed in adult patients treated with 30 mg BID (Study CC-10004-PSOR-011). A population PK model was subsequently developed based on the data pooled from the paediatric Study CC-10004-PPSO-001, and the adult Studies CC-10004-PSOR-005 and CC-10004-PSOR-011. Based on modeling and simulation, the exposure of apremilast 20 mg BID in paediatric subjects weighing between ≥ 20 and <50 kg was predicted to be similar to the exposure of apremilast 30 mg BID in adults (median of ratio within 0.8 and 1.25). Paediatric subjects weighing ≥ 50 kg were recommended to take the adult dosage of 30 mg BID.

Objectives

Primary Objective

- To evaluate the clinical efficacy of apremilast compared with placebo in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis

Secondary Objectives

- To evaluate the safety and tolerability of apremilast compared with placebo in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis
- To evaluate the effect of apremilast compared with placebo on health-related quality of life

Outcomes/endpoints

Endpoint	Assessment	Description	Timeframe
Primary Efficacy	Static Physician Global Assessment (sPGA) 0/1	Proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline	Week 16
Major Secondary Efficacy	At least 75% reduction in Psoriasis Area Severity Index (PASI-75)	Proportion of subjects who achieved PASI-75 from baseline	Week 16

Other Secondary Efficacy	At least 50% reduction in Psoriasis Area Severity Index (PASI-50)	Proportion of subjects who achieved PASI-50 from baseline	Week 16
	Psoriasis Area Severity	Percent change from baseline in total PASI score	Week 16
	Body surface area (BSA)	Percent change from baseline in affected BSA	Week 16
	Children's Dermatology Life Quality Index (CDLQI [0/1])	Proportion of subjects who achieved CDLQI (0/1)	Week 16
	CDLQI	Change from baseline in CDLQI	Week 16
Safety			
Adverse events	Type, frequency, severity, and relationship of adverse events to investigational product	Day 0 through end of observational follow-up	Study duration (up through
Diarrhea	Stool diary (frequency, duration, and associated symptoms)	Completed daily by subject/parent(s)/guardian(s) and reviewed at each visit by study investigator	Study duration (up through
Depression, suicidal thoughts and behavior	Columbia-Suicide Severity Rating Scale (C-SSRS)	Questionnaire completed at screening, baseline, and visits thereafter as indicated in	Study duration (up through week 52)

Growth and development	Tanner Staging of sexual development	Assessment of sexual maturity	Performed at beginning and end of study (week 52 or early termination)
	Body weight, height, and body mass index	Height and body weight measured and recorded at each visit	Study duration
Psoriasis Flare	Psoriasis disease flare	Proportion of subjects with sudden intensification of psoriasis (new generalized erythrodermic, inflammatory or pustular psoriasis) requiring medical intervention beyond allowable medications	Study duration (while taking study medication)
Psoriasis Rebound	Rebound	Severe and sudden worsening of disease (PASI ≥ 125% of baseline or new generalized, pustular, erythrodermic psoriasis) after treatment has been discontinued	14-week follow-up period

Sample size

Number of Subjects Planned:

At least 230 subjects were planned to be randomized with a minimum of 75 subjects in each age group (6 to 11 years of age and 12 to 17 years of age).

The sample size estimation is based on the results of the adult Phase 3 and 3b studies with apremilast (CC-10004-PSOR-008, PSOR-009 and PSOR-010) which demonstrated positive treatment effects between apremilast and placebo in the proportion of subjects achieving sPGA response and PASI-75 response at Week 16.

With a total of 230 patients and a randomization ratio of 2:1, the study will have 90% power to detect a 15% difference (20% versus 5%) between the apremilast arm and the placebo arm for the proportion of subjects achieving sPGA response at Week 16, based on a Chi-square test at a two-sided significance level of 0.05. The study will also have more than 95% power to detect a 20% difference (30% versus 10%) between apremilast and placebo for the proportion of subjects achieving PASI-75 response at Week 16.

Randomisation

Subjects who met all eligibility requirements were randomized, using centralised interactive response technology (IRT), in a 2:1 ratio to receive either apremilast or placebo in a double-blind manner.

Blinding (masking)

This was a double-blind, placebo-controlled study. The identity of investigational product assigned to subject numbers was contained in the IRT. The investigator was provided with an emergency unblinding personal identification number to access the IRT to obtain unblinding information in the event of an emergency.

Statistical methods

For the placebo-controlled phase (weeks 0 to 16), the analyses for efficacy endpoints were based on the intent-to-treat (ITT) population, defined as all subjects who were randomized. The primary and secondary efficacy endpoints were hierarchically ranked for testing, to control the overall type I error rate in claiming statistical significance at the 2-sided 0.05 significance level, as follows:

- proportion of subjects who achieved sPGA response at week 16 (defined as sPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline at week 16)
- proportion of subjects who achieved PASI-75 response at week 16 (defined as atleast a 75% reduction in total PASI score from baseline at week 16)

Specifically, for the primary efficacy endpoint (sPGA response at week 16), if the 2-sided p-value from the comparison between the apremilast and placebo groups was below 0.05, the outcome was considered statistically significant and apremilast was declared effective. For the major secondary endpoint, statistical significance was claimed only if its 2-sided p-value was below 0.05 and tests for the primary endpoint were significant at the 2-sided 0.05 level.

The primary, major secondary, and other binary variable secondary efficacy endpoints were analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factor at randomization. The 2-sided p-values from the CMH test were provided, along with the adjusted treatment difference in proportion

using the weighted average of the treatment differences across the strata with the CMH weights and the associated 2-sided 95% CIs using a normal approximation to the weighted average.

Missing values for the primary endpoint were imputed using the multiple imputation (MI) method. Sensitivity analyses of the primary and major secondary endpoints were conducted.

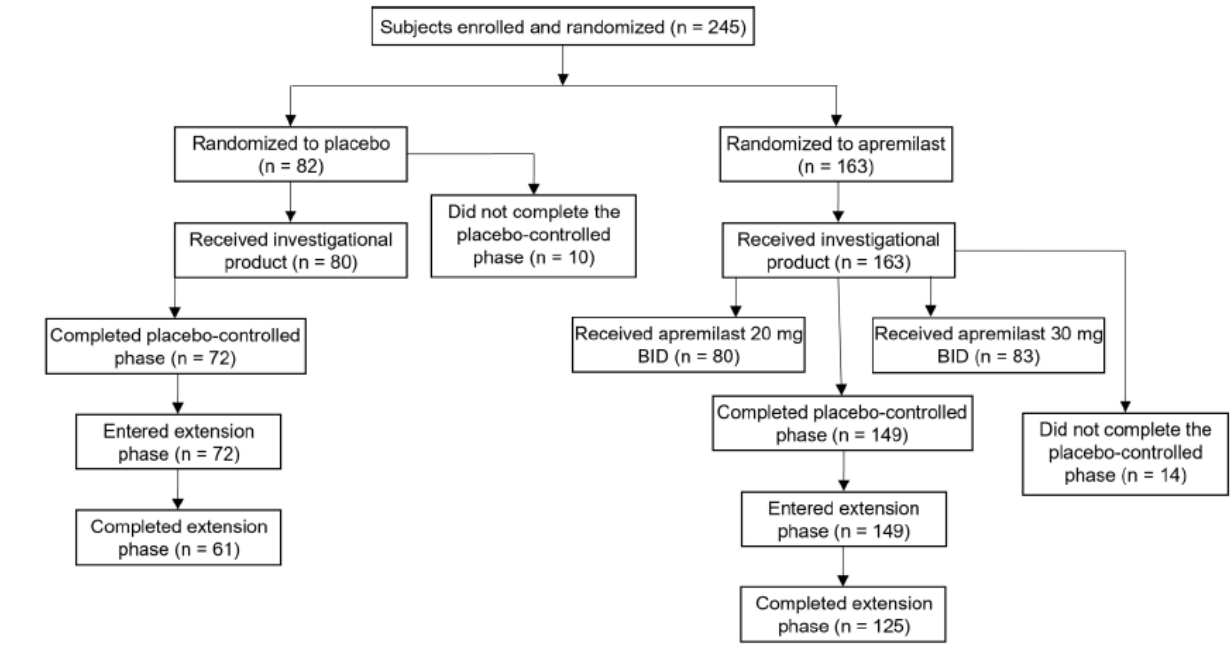
For continuous secondary endpoints, an analysis of covariance (ANCOVA) model was used with the change or percent change from baseline as the dependent variable, treatment group and stratification factor as independent variables, and the baseline value as a covariate variable. Within-group and treatment differences in least squares (LS) mean changes from baseline at week 16 and the associated 2-sided 95% CIs, SEs, and p-values, as applicable, were derived from the ANCOVA model. Missing values at week 16 were imputed using the MI method.

Efficacy endpoints for time points in the apremilast extension phase (weeks 16 to 52) were summarized for subjects who continued apremilast treatment or who switched to apremilast from placebo according to the treatment groups assigned at randomization.

For all subjects, changes in measurements were calculated relative to measurements obtained at baseline (week 0). Descriptive summary statistics or proportion of subjects achieving specified criteria were summarized by treatment group. For continuous variables, descriptive statistics for baseline and changes or percent changes from baseline were provided. Categorical variables were summarized with frequency tabulations. Two-sided 95% CIs were provided for changes or percent changes and response rates.

Results

Participant flow



BID = twice daily

Table 15. Subject Disposition in the Placebo-controlled Phase (Weeks 0 to 16) (All Randomized Subjects)

	Placebo (N = 82) n (%)	Apremilast (N = 163) n (%)	Total (N = 245) n (%)
Entered[a]	82 (100.0)	163 (100.0)	245 (100.0)
Took at least 1 dose of IP	80 (97.6)	163 (100.0)	243 (99.2)
Completed[b]	72 (87.8)	149 (91.4)	221 (90.2)
Discontinued	10 (12.2)	14 (8.6)	24 (9.8)
Primary reason for discontinuation			
Adverse event	1 (1.2)	5 (3.1)	6 (2.4)
Lack of efficacy	2 (2.4)	0 (0.0)	2 (0.8)
Withdrawal by subject	2 (2.4)	3 (1.8)	5 (2.0)
Lost to follow-up	0 (0.0)	1 (0.6)	1 (0.4)
Withdrawal by parent/guardian	3 (3.7)	5 (3.1)	8 (3.3)
Other	2 (2.4)	0 (0.0)	2 (0.8)

IP = investigational product; ITT = intent-to-treat
Percentages are based upon the number of subjects in the ITT population.
[a] Includes all subjects who were randomized/enrolled, regardless of whether they received treatment or not.
[b] Includes subjects who completed week 16 visit with study drug dispensed for the extension phase.

Table 16. Subject Disposition in the Apremilast Extension Phase (Weeks 16 to 52) (Subjects Who Entered the Apremilast Extension Phase)

Population	Placebo/APR[a] (N = 72) n (%)	APR/APR[b] (N = 149) n (%)	Total (N = 221) n (%)
Apremilast Extension Phase (Weeks 16 to 52)			
Entered[c]	72 (100.0)	149 (100.0)	221 (100.0)
Took at Least 1 Dose of IP[d]	72 (100.0)	149 (100.0)	221 (100.0)
Completed[e]	61 (84.7)	125 (83.9)	186 (84.2)
Discontinued	11 (15.3)	24 (16.1)	35 (15.8)
Primary Reason for Discontinuation			
Adverse Event	3 (4.2)	1 (0.7)	4 (1.8)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Lack of Efficacy	3 (4.2)	8 (5.4)	11 (5.0)
Withdrawal by Subject	1 (1.4)	3 (2.0)	4 (1.8)
Non-compliance with Study Drug	1 (1.4)	1 (0.7)	2 (0.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow Up	0 (0.0)	2 (1.3)	2 (0.9)
Protocol Deviation	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Parent/Guardian	1 (1.4)	8 (5.4)	9 (4.1)
Other	2 (2.8)	1 (0.7)	3 (1.4)
Entered the Long-term Study	54 (75.0)	106 (71.1)	160 (72.4)

APR = apremilast; BID = twice daily; IP = investigational product; ITT = intent-to-treat
Percentages are based upon the number of subjects who entered the apremilast extension phase.
[a] Includes subjects in the ITT population who were initially randomized to placebo and entered the apremilast extension phase.
[b] Includes subjects in the ITT population who were initially randomized to apremilast and entered the apremilast extension phase.
[c] Includes subjects who had IP dispensed for the apremilast extension phase (weeks 16 to 52).
[d] Includes subjects who took at least 1 dose of IP in the apremilast extension phase (weeks 16 to 52).
[e] Includes subjects who completed week 52 visit.

Recruitment

This study was conducted at 106 centres in Belgium, Canada, Czech Republic, France, Israel, Italy, Netherlands, Russia, Spain, and the United States. Sixty-one subjects were recruited in the EU, 74 subjects in North America, 103 subjects in Russia and 7 subjects in Israel.

Conduct of the study

There were 5 protocol amendments resulting in substantial changes in the conduct of the study are described in the table below. Of note the study began in November 2018, which included the period during which the coronavirus disease 2019 (COVID-19) pandemic was occurring globally. The study was at the stage of recruiting and enrolling subjects when the pandemic occurred. From the 19 March 2020, screening and enrollment were temporarily paused at all participating countries/sites to limit potential COVID-19 exposure. From June 2020, enrollment resumed over the following months in a staggered fashion across countries and study sites. Amgen did not amend the study protocol for COVID-19-related impacts; instead, any changes to study conduct were documented as protocol deviations in accordance with the recommendations provided in health authority guidance documents.

Amendment	Major Changes
Original Protocol 15 August 2018	
Amendment 1 12 April 2019	• Added an inclusion criterion for baseline minimum allowable body mass index • Added a specific body mass index parameter as a reason for mandatory subject withdrawal • Revised hemoglobin ranges for subject eligibility • Added a note to contraception options to clarify options considered "highly effective contraception" may differ per local guidelines/regulations
Amendment 2 23 September 2019	• Replaced depictions of investigational product blister card packaging to align with redesigned packaging • Added text informing of switch from blister card investigational product to bottles during the apremilast extension phase • Revised platelet ranges for subject eligibility • Removed requirement for reporting of pregnancies of partners of male subjects
Amendment 3 01 May 2020	• References to Celgene were replaced with Amgen • Updated to align with Amgen Global Drug Safety and Amgen Product Complaint Reporting processes • Updated to include instructions for paper reporting of serious adverse events • Added Sample Serious Adverse Event Form, Pregnancy Notification Form, and Lactation Notification Form to align with Amgen processes
Amendment 4 26 August 2021	• Reduced the study sample size from at least 230 randomized subjects to at least 180 randomized subjects • Updated the power calculations based on the change in sample size • Added language regarding reporting of serious adverse events
Amendment 5 17 December 2021	• Reverted the study sample size from at least 180 randomized subjects to the original protocol goal of at least 230 randomized subjects • Updated the power calculations based on the change in sample size

Protocol deviations

Parameter	Placebo (N = 82) n (%)	Apremilast (N = 163) n (%)	Total (N = 245) n (%)
Number of subjects with at least 1 important protocol deviation	14 (17.1)	15 (9.2)	29 (11.8)
Total number of important protocol deviations[a]	19	17	36
Important protocol deviations			
Inclusion exclusion criteria	3 (3.7)	4 (2.5)	7 (2.9)
Informed consent issues	1 (1.2)	3 (1.8)	4 (1.6)
Other[b]	4 (4.9)	1 (0.6)	5 (2.0)
Laboratory tests / procedures	1 (1.2)	1 (0.6)	2 (0.8)
Safety reporting	1 (1.2)	1 (0.6)	2 (0.8)
IP issues / IP compliance	6 (7.3)	4 (2.5)	10 (4.1)
IP withdrawal / study discontinuation criteria	1 (1.2)	0 (0.0)	1 (0.4)

C-SSRS = Columbia-Suicide Severity Rating Scale; IP = investigational product; ITT = intent-to-treat; PI = principal investigator
This table summarized important protocol deviations for the entire study based on the initial randomized treatment groups.
Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.
[a] Each subject is counted once for each applicable specific important protocol deviation. A subject with multiple deviations within a category is counted once for that category.
[b] Included parent signature missing for optional pharmacodynamic marker testing (1 subject); C-SSRS assessment performed and/or signed by subject instead of delegated site staff (2 subjects); lack of PI oversight leading to missed informed consent for labs drawn (1 subject); and lack of PI oversight leading to wrong IP dispensation (1 subject)

Protocol deviations related to COVID-19 control measures were reported for 37 subjects (22.7%) in the apremilast group and 21 subjects (25.6%) in the placebo group at any time during study conduct. None of the COVID-19-related deviations were important protocol deviations.

Baseline data

Table 17. Baseline Demographics (ITT Population)

Parameter	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
Q1, Q3	9.0, 15.0	10.0, 15.0	9.0, 15.0
Min, Max	6, 17	6, 17	6, 17
Age category - n (%)			
6 to 11 years	34 (41.5)	67 (41.1)	101 (41.2)
12 to 17 years	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 (%)			
White	73 (89.0)	140 (85.9)	213 (86.9)
Black or African American	3 (3.7)	5 (3.1)	8 (3.3)
Asian	3 (3.7)	6 (3.7)	9 (3.7)
American Indian or Alaskan Native	0 (0.0)	2 (1.2)	2 (0.8)
Not collected or unknown	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)
Not reported	3 (3.7)	5 (3.1)	8 (3.3)
Unknown	0 (0.0)	5 (3.1)	5 (2.0)
Weight (kg)			
Mean	51.83	52.04	51.97
SD	22.172	21.123	21.435
Median	50.10	50.00	50.00
Q1, Q3	35.00, 62.30	38.40, 61.50	38.30, 61.80
Min, Max	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)
Baseline age and weight categories – n (%)			
6 to 11 years and ≥ 20 to < 50 kg	30 (36.6)	58 (35.6)	88 (35.9)
6 to 11 years and ≥ 50 kg	4 (4.9)	9 (5.5)	13 (5.3)
12 to 17 years and ≥ 20 to < 50 kg	10 (12.2)	22 (13.5)	32 (13.1)
12 to 17 years and ≥ 50 kg	38 (46.3)	74 (45.4)	112 (45.7)
BMI (kg/m^2)			
Mean	21.30	21.33	21.32
SD	5.631	5.197	5.335
Median	20.47	20.54	20.51
Q1, Q3	17.83, 23.47	17.65, 23.39	17.72, 23.39
Min, Max	12.7, 46.2	13.2, 46.7	12.7, 46.7
BMI category[a] - n (%)			
Underweight	4 (4.9)	4 (2.5)	8 (3.3)
Healthy weight	54 (65.9)	103 (63.2)	157 (64.1)
Overweight	8 (9.8)	25 (15.3)	33 (13.5)
Obesity	16 (19.5)	31 (19.0)	47 (19.2)

Table 18. Baseline Disease Characteristics (ITT Population)

Parameter	Placebo (N = 82)	Apremilast (N = 163)	Total (N = 245)
Duration of plaque psoriasis (years)			
Mean	3.99	4.27	4.18
SD	3.394	3.346	3.358
Median	2.67	3.22	3.08
Q1, Q3	1.12, 6.58	1.52, 6.87	1.40, 6.58
Min, Max	0.5, 14.4	0.5, 15.4	0.5, 15.4
Duration of plaque psoriasis categories (years)			
< 1	16 (19.5)	19 (11.7)	35 (14.3)
≥ 1 to < 2	19 (23.2)	35 (21.5)	54 (22.0)
≥ 2 to < 5	19 (23.2)	51 (31.3)	70 (28.6)
≥ 5	28 (34.1)	58 (35.6)	86 (35.1)
Baseline sPGA score - n (%)			
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	19.45	20.03	19.84
SD	7.936	8.159	8.073
Median	16.45	17.40	17.20
Q1, Q3	13.40, 22.80	13.80, 22.80	13.70, 22.80
Min, Max	12.0, 50.6	12.0, 47.7	12.0, 50.6
Baseline psoriatic involved BSA (%)			
Mean	30.79	31.91	31.54
SD	19.041	18.450	18.618
Median	24.00	27.00	26.00
Q1, Q3	17.00, 39.00	20.00, 39.00	18.00, 39.00
Min, Max	10.0, 88.0	10.0, 92.0	10.0, 92.0
Baseline CDLQI total score			
Mean	7.57	8.78	8.38
SD	4.992	5.803	5.566
Median	6.00	8.00	7.00
Q1, Q3	3.00, 10.00	4.00, 13.00	4.00, 12.00
Min, Max	0.0, 20.0	0.0, 27.0	0.0, 27.0
Number of prior phototherapies – n (%)			
0	66 (80.5)	136 (83.4)	202 (82.4)
1	16 (19.5)	26 (16.0)	42 (17.1)
2	0 (0.0)	1 (0.6)	1 (0.4)
Number of prior conventional systemic therapies - n (%)			
0	64 (78.0)	139 (85.3)	203 (82.9)
1	15 (18.3)	19 (11.7)	34 (13.9)
2	3 (3.7)	4 (2.5)	7 (2.9)
≥ 3	0 (0.0)	1 (0.6)	1 (0.4)
Number of prior biologic therapies - n (%)			
0	77 (93.9)	154 (94.5)	231 (94.3)
1	4 (4.9)	6 (3.7)	10 (4.1)
2	1 (1.2)	3 (1.8)	4 (1.6)
Number of prior systemic therapies – n (%)			
0	52 (63.4)	109 (66.9)	161 (65.7)
1	18 (22.0)	37 (22.7)	55 (22.4)
2	10 (12.2)	12 (7.4)	22 (9.0)
≥ 3	2 (2.4)	5 (3.1)	7 (2.9)

Numbers analysed

A total of 245 subjects were randomised, with 82 subjects randomised to the placebo group and 163 subjects randomised to the APR group. 163 subjects (100%) in the apremilast group and 80 subjects (97.6%) in the placebo group received at least 1 dose of investigational product. A total of 80 subjects were treated with apremilast 20mg bd and 83 were treated with 30mg bd.

A total of 221 subjects entered the apremilast extension phase. Of these, 149 subjects were originally randomized to the apremilast group and 72 subjects were originally randomized to the placebo group. Overall, 125 subjects (83.9%) in the apremilast group (as randomized) and 61 subjects (84.7%) in the placebo group (as randomized) and completed the study. The most frequent reason for discontinuation (≥ 3% of subjects overall) during the apremilast extension phase was lack of efficacy (5.0%).

Outcomes and estimation

Efficacy results

Table 19. sPGA Response at Week 16 (ITT Population)

Imputation Method	Placebo (N=82)	APR (N=163)	Treatment Comparison (APR - Placebo)
MI [a]			
n (%)	9.4 (11.5)	53.9 (33.1)	
95% CI (%)	4.2, 18.7	25.7, 40.5	
SE (%)	3.69	3.78	
Unadjusted Difference (%)			21.6
Adjusted Difference			
Difference (%) (2-sided 95% CI)			21.7 (11.2, 32.1)
2-sided p-value			<0.0001
SE (%)			5.33

Sensitivity Analyses

The results of the primary analysis were supported by multiple sensitivity analyses using additional imputation methods (LOCF, NRI) to assess the impact of missing data and showed that a greater proportion of subjects in the apremilast group achieved a sPGA response at week 16 compared with the placebo group across all of the sensitivity analyses.

LOCF (ITT population): 20.4% [95% CI: 10.5, 30.3]

NRI (ITT population): 20.4% [95% CI: 10.8, 29.9]

Consistent results were shown with the per-protocol population (adjusted treatment difference based on the MI method: 22.5% [95% CI: 12.1, 32.9]

Analysis of sPGA response adjusted by pooled sites and stratification factor at randomization resulted in an adjusted treatment difference based on the MI method of 21.8% (95% CI: 11.6, 32.1)

A sensitivity analysis excluding all subjects impacted by COVID-19 control measures in the placebo-controlled phase confirm that COVID-19 had minimal impact on the results (adjusted treatment difference based on the MI method: 19.9% [95% CI: 8.8, 31.1]). An additional sensitivity analysis where scores from visits impacted by COVID-19 were assigned as missing before analysis derivation confirmed that COVID-

19 had minimal impact on the results (adjusted treatment difference based on the MI method: 20.6% [95% CI: 10.5, 30.7]).

Secondary Efficacy Endpoints Major Secondary Endpoint –PASI-75 at Week 16

At week 16, 45.4% of subjects in the apremilast group and 16.1% of subjects in the placebo group achieved a PASI-75 response based on the MI method. The adjusted treatment difference was statistically significant (29.4% [95% CI: 17.8, 40.9]; p < 0.0001). Subjects who terminated early due to lack of efficacy before week 16 were assigned as non-responders for missed assessments; subjects who added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications before week 16 were also assigned as non-responders.

Table 20. PASI-75 Response at Week 16 (ITT Population, MI)

	Placebo (N = 82)	Apremilast (N = 163)	Treatment Comparison (Apremilast -Placebo)
n (%)	13.2 (16.1)	74.1 (45.4)	
95% CI (%)	7.7, 24.5	37.6, 53.3	
SE (%)	4.30	4.01	
Unadjusted Difference (%)			29.4
Adjusted Difference			
Difference (%) (2-sided 95% CI)			29.4 (17.8, 40.9)
2-sided p-value			< 0.0001
SE (%)			5.89

Results of PASI-75 were generally consistent for prespecified sensitivity analyses. Consistent results were shown with the ITT population using LOCF 29.6% [95% CI: 18.7, 40.4] and NRI 28.9% [95% CI: 18.3, 39.5].

For the Per-protocol population (adjusted treatment difference based on the MI method: 29.6% [95% CI: 18.0, 41.2]). Analysis of PASI-75 response adjusted by pooled site and stratification factor at randomization resulted in an adjusted treatment difference based on the MI method of 30.0% (95% CI: 18.4, 41.5).

A sensitivity analysis excluding all subjects impacted by COVID-19 control measures in the placebo-controlled phase confirm that COVID-19 had minimal impact on the results (adjusted treatment difference based on the MI method: 27.9% [95%CI: 15.5, 40.3]). An additional sensitivity analysis where scores from visits impacted by COVID-19 were assigned as missing before analysis derivation confirmed that COVID-19 had minimal impact on the results (adjusted treatment difference based on the MI method: 27.1% [95% CI: 15.8, 38.4]).

Other Secondary endpoints

Table 21. PASI-50 response rate

	Placebo (N = 82)	Apremilast (N = 163)	Treatment Comparison (Apremilast - Placebo)
n (%)	26.4 (32.1)	115.0 (70.5)	
95% CI (%)	21.7, 42.6	63.2, 77.9	
SE (%)	5.34	3.74	
Unadjusted difference (%)			38.4
Adjusted difference			
Difference (%) (2-sided 95% CI)			38.4 (25.6, 51.2)
2-sided p-value			< 0.0001
SE (%)			6.53

Table 22. PASI Percent Change from Baseline at Week 16

	Placebo (N = 82)	Apremilast (N = 163)	Treatment Comparison (Apremilast - Placebo)
n (%)	82 (100)	163 (100)	
Mean (SE)	-37.49 (3.866)	-64.52 (2.543)	
LS mean (SE)	-38.29 (3.753)	-65.25 (2.603)	
95% CI for LS mean	-45.65, -30.92	-70.36, -60.15	
Difference in LS mean (SE)			-26.97 (4.572)
2-sided 95% CI of difference			-35.93, -18.00
2-sided p-value			< 0.0001

Table 23. BSA Percent Change From Baseline at Week 16

	Placebo (N = 82)	Apremilast (N = 163)	Treatment Comparison (Apremilast - Placebo)
n (%)	82 (100)	163 (100)	
Mean (SE)	-20.56 (5.441)	-55.44 (3.428)	
LS Mean (SE)	-21.82 (5.104)	-56.59 (3.558)	
95% CI for LS Mean	-31.84, -11.81	-63.57, -49.61	
Difference in LS Mean (SE)			-34.77 (6.229)
2-sided 95% CI of Difference			-46.99, -22.55
2-sided p-value			< 0.0001

Table 24. CDLQI (0/1) response rate at Week 16

	Placebo (N = 76)	Apremilast (N = 148)	Treatment Comparison (Apremilast - Placebo)
n (%)	23.8 (31.3)	52.3 (35.4)	
95% CI (%)	20.3, 42.3	27.4, 43.3	
SE (%)	5.61	4.07	
Unadjusted difference (%)			4.1
Adjusted difference			
Difference (%) (2-sided 95% CI)			4.1 (-9.8, 18.0)
2-sided p-value			0.5616
SE (%)			7.06

Exploratory endpoints

At week 16, greater improvements were observed in the apremilast group as compared to the placebo group for multiple exploratory endpoints, including, but not limited to, PASI-90 response, whole body itch NRS response, and change from baseline in whole body itch NRS.

Subgroup Analyses

Subgroup analyses for sex, race, age, weight, region baseline disease severity and previous treatments were performed within the pivotal study.

Table 25. sPGA Response at week 16 by Subgroups (ITT Population MI)

Subgroup Factor Subgroup	Placebo (N = 82) n/m (%)[a]	Apremilast (N = 163) n/m (%)[a]	Adjusted Difference (%) (2-sided 95% CI)[b] (Apremilast - Placebo)
Sex			
Male	2.7/43 (6.3)	14.3/74 (19.3)	13.4 (0.8, 26.1)
Female	6.7/39 (17.1)	39.6/89 (44.5)	26.8 (10.5, 43.2)
Race			
White	8.2/73 (11.2)	47.4/140 (33.9)	22.9 (11.8, 34.1)
Non-White	1.2/9 (13.3)	6.5/23 (28.2)	12.3 (-16.2, 40.9)
Age			
6 to 11 years	3.7/34 (10.9)	33.2/67 (49.6)	38.7 (21.6, 55.7)
12 to 17 years	5.7/48 (11.8)	20.6/96 (21.5)	9.7 (-3.1, 22.5)
Baseline weight			
≥ 20 to < 50 kg	8.7/40 (21.8)	37.9/80 (47.4)	25.7 (7.5, 43.8)
≥ 50 kg	0.7/42 (1.6)	16.0/83 (19.2)	17.5 (7.2, 27.8)
Baseline age (years) and weight (kg)			
6 to 11 years and ≥ 20 to < 50 kg	3.7/30 (12.4)	30.9/58 (53.2)	40.8 (22.3, 59.4)
6 to 11 years and ≥ 50 kg	0.0/4 (0.0)	2.4/9 (26.2)	26.2 (-4.3, 56.8)
12 to 17 years and ≥ 20 to < 50 kg	5.0/10 (50.0)	7.0/22 (32.0)	-18.0 (-54.7, 18.7)
12 to 17 years and ≥ 50 kg	0.7/38 (1.8)	13.6/74 (18.4)	16.6 (5.7, 27.5)
Baseline BMI category			
Underweight	1.4/4 (34.0)	2.0/4 (50.0)	27.7 (-35.7, 91.1)
Healthy weight	6.8/54 (12.5)	36.4/103 (35.4)	22.9 (9.4, 36.4)
Overweight	0.1/8 (1.0)	11.0/25 (44.0)	43.4 (21.6, 65.2)
Obesity	1.2/16 (7.5)	4.4/31 (14.3)	5.8 (-12.2, 23.9)
Geographical region			
USA	3.6/20 (17.8)	10.5/38 (27.6)	9.1 (-12.7, 30.9)
Canada	0.0/3 (0.0)	8.3/13 (64.0)	63.4 (34.4, 92.4)
EU/rest of the world	5.8/59 (9.9)	35.1/112 (31.3)	21.8 (9.6, 34.1)
Duration of plaque psoriasis category			
< 5 years	7.3/54 (13.5)	42.5/105 (40.5)	25.6 (11.9, 39.2)
≥ 5 years	2.1/28 (7.6)	11.4/58 (19.6)	10.3 (-4.5, 25.0)
Baseline sPGA score			
3 (Moderate)	6.8/63 (10.7)	39.7/122 (32.5)	22.8 (11.1, 34.5)
4 (Severe)	2.6/19 (13.9)	14.2/41 (34.6)	16.4 (-6.6, 39.5)

Subgroup Factor Subgroup	Placebo (N = 82) n/m (%)[a]	Apremilast (N = 163) n/m (%)[a]	Adjusted Difference (%) (2-sided 95% CI)[b] (Apremilast - Placebo)
Baseline PASI category			
≤ 20	6.9/56 (12.4)	38.5/105 (36.7)	24.1 (11.0, 37.1)
> 20	2.5/26 (9.5)	15.4/58 (26.5)	17.9 (0.2, 35.7)
Baseline BSA category			
≤ 20%	3.9/36 (10.9)	15.2/48 (31.6)	20.9 (3.7, 38.0)
> 20%	5.5/46 (11.9)	38.7/115 (33.7)	21.1 (7.6, 34.6)
Baseline CDLQI total score category			
0 to 6	8.8/42 (21.0)	21.1/65 (32.5)	11.5 (-5.9, 28.9)
7 to 30	0.3/39 (0.8)	32.8/98 (33.4)	32.7 (22.3, 43.1)
Baseline Whole Body Itch NRS category			
0 to 4	5.4/33 (16.4)	16.8/54 (31.1)	14.2 (-4.1, 32.5)
5 to 10	3.7/48 (7.7)	37.1/109 (34.0)	27.1 (14.7, 39.4)
Baseline ScPGA category			
0 to 2	3.1/11 (28.0)	8.7/27 (32.3)	4.1 (-28.9, 37.2)
3 to 4	6.0/69 (8.8)	44.8/132 (33.9)	25.6 (14.8, 36.4)
Baseline sPGA-G score			
0 to 2	6.0/44 (13.7)	31.5/85 (37.0)	22.4 (6.9, 37.9)
3 to 4	3.1/36 (8.6)	22.0/74 (29.7)	22.8 (9.1, 36.6)
Prior phototherapies			
Used	3.4/16 (21.5)	4.8/27 (17.8)	-5.1 (-31.6, 21.5)
Never used	6.0/66 (9.0)	49.1/136 (36.1)	26.5 (15.4, 37.5)
Prior conventional systemic therapies			
Used	1.5/18 (8.2)	8.1/24 (33.7)	25.2 (1.0, 49.4)
Never used	7.9/64 (12.4)	45.8/139 (32.9)	21.0 (9.2, 32.8)
Prior biologic therapies			
Used	1.1/5 (22.4)	2.3/9 (25.8)	3.4 (-48.1, 54.8)
Never used	8.3/77 (10.8)	51.6/154 (33.5)	23.0 (12.4, 33.5)
Prior systemic therapies			
Used	1.6/30 (5.2)	12.3/54 (22.7)	17.2 (2.6, 31.9)
Never used	7.8/52 (15.1)	41.6/109 (38.2)	23.7 (9.7, 37.7)

a n/m = number of sPGA responders based on combined inference / number of subjects in subgroups

b Adjusted difference in proportions is the weighted average of the treatment differences across the strata using Cochran-Mantel-Haenszel weights. Two-sided 95% CI is based on the normal approximation to the weighted average. Stratification factors include baseline age group (6 to 11 years or 12 to 17 years).

Table 26. PASI-75 Response at Week 16 by Subgroups (ITT Population, MI) Study PPSO-003

Subgroup Factor Subgroup	Placebo (N = 82) n/m (%)[a]	Apremilast (N = 163) n/m (%)[a]	Adjusted Difference (%) (2-sided 95% CI)[b] (Apremilast - Placebo)
Sex			
Male	5.4/43 (12.7)	27.8/74 (37.6)	25.1 (9.1, 41.0)
Female	7.8/39 (19.9)	46.3/89 (52.0)	31.9 (15.1, 48.8)
Race			
White	11.9/73 (16.3)	68.6/140 (49.0)	32.8 (20.4, 45.1)
Non-White	1.3/9 (14.2)	5.5/23 (23.8)	7.7 (-22.0, 37.3)
Age			
6 to 11 years	4.6/34 (13.4)	35.0/67 (52.3)	38.9 (21.6, 56.2)
12 to 17 years	8.6/48 (18.0)	39.0/96 (40.7)	22.7 (7.3, 38.1)
Baseline weight			
≥ 20 to < 50 kg	8.6/40 (21.4)	41.9/80 (52.4)	30.8 (13.5, 48.2)
≥ 50 kg	4.6/42 (11.0)	32.2/83 (38.7)	27.7 (12.5, 42.8)
Baseline age and weight			
6 to 11 years and ≥ 20 to < 50 kg	4.6/30 (15.2)	30.7/58 (53.0)	37.8 (18.8, 56.7)
6 to 11 years and ≥ 50 kg	0.0/4 (0.0)	4.3/9 (48.0)	48.0 (13.8, 82.2)
12 to 17 years and ≥ 20 to < 50 kg	4.0/10 (40.0)	11.2/22 (50.9)	10.9 (-26.1, 47.9)
12 to 17 years and ≥ 50 kg	4.6/38 (12.2)	27.8/74 (37.6)	25.4 (9.1, 41.7)
Baseline BMI category			
Underweight	1.4/4 (35.0)	3.0/4 (75.0)	47.9 (-14.0, 100)
Healthy weight	8.6/54 (16.0)	44.6/103 (43.3)	27.3 (13.1, 41.6)
Overweight	0.6/8 (8.0)	17.0/25 (68.2)	60.1 (31.5, 88.7)
Obesity	2.5/16 (15.8)	9.4/31 (30.3)	14.2 (-11.4, 39.7)
Geographical region			
USA	6.2/20 (31.2)	16.5/38 (43.5)	12.0 (-15.1, 39.0)
Canada	0.0/3 (0.0)	8.0/13 (61.8)	61.8 (32.8, 90.8)
EU/rest of the world	7.0/59 (11.8)	49.5/112 (44.2)	32.5 (19.6, 45.4)
Duration of plaque psoriasis category			
< 5 years	8.2/54 (15.3)	48.9/105 (46.6)	30.5 (16.2, 44.8)
≥ 5 years	5.0/28 (17.7)	25.2/58 (43.4)	24.2 (4.3, 44.1)
Baseline sPGA score			
3 (Moderate)	7.9/63 (12.6)	55.7/122 (45.6)	33.4 (20.8, 46.0)
4 (Severe)	5.3/19 (27.8)	18.4/41 (44.9)	15.2 (-12.1, 42.5)

Subgroup Factor Subgroup	Placebo (N = 82) n/m (%)[a]	Apremilast (N = 163) n/m (%)[a]	Adjusted Difference (%) (2-sided 95% CI)[b] (Apremilast - Placebo)
Baseline PASI category			
≤ 20	9.1/56 (16.3)	50.9/105 (48.5)	32.1 (17.8, 46.5)
> 20	4.1/26 (15.7)	23.2/58 (39.9)	24.6 (4.3, 44.8)
Baseline BSA category			
≤ 20%	5.1/36 (14.2)	21.6/48 (45.0)	30.8 (11.1, 50.5)
> 20%	8.1/46 (17.6)	52.5/115 (45.6)	27.6 (12.8, 42.5)
Baseline CDLQI total score category			
0 to 6	10.4/42 (24.8)	30.0/65 (46.1)	21.3 (3.0, 39.6)
7 to 30	2.6/39 (6.6)	44.1/98 (45.0)	38.5 (24.8, 52.2)
Baseline Whole Body Itch NRS category			
0 to 4	6.4/33 (19.3)	25.0/54 (46.2)	27.0 (7.6, 46.4)
5 to 10	6.6/48 (13.8)	49.1/109 (45.1)	31.7 (17.3, 46.0)
Baseline ScPGA category			
0 to 2	2.6/11 (24.0)	14.0/27 (52.0)	28.3 (-4.6, 61.1)
3 to 4	10.3/69 (15.0)	59.7/132 (45.2)	30.4 (17.9, 42.9)
Baseline sPGA-G score			
0 to 2	7.8/44 (17.8)	44.7/85 (52.6)	34.4 (17.9, 51.0)
3 to 4	5.1/36 (14.2)	29.0/74 (39.2)	25.7 (9.6, 41.8)
Prior phototherapies			
Used	2.3/16 (14.5)	6.5/27 (24.0)	9.2 (-16.3, 34.7)
Never used	10.9/66 (16.5)	67.6/136 (49.7)	33.0 (20.2, 45.9)
Prior conventional systemic therapies			
Used	1.8/18 (9.8)	11.7/24 (48.7)	38.5 (12.2, 64.8)
Never used	11.4/64 (17.9)	62.4/139 (44.9)	27.1 (14.1, 40.0)
Prior biologic therapies			
Used	1.7/5 (34.4)	3.2/9 (36.0)	3.6 (-53.3, 60.5)
Never used	11.5/77 (14.9)	70.8/154 (46.0)	31.2 (19.5, 42.9)
Prior systemic therapies			
Used	3.4/30 (11.3)	18.8/54 (34.7)	23.1 (4.9, 41.3)
Never used	9.8/52 (18.8)	55.3/109 (50.8)	32.0 (17.3, 46.6)

Apremilast Extension Phase:

sPGA Response at Week 52

During the apremilast extension phase, 47.7% of subjects in the apremilast group (as randomized and entered the apremilast extension phase) and 44.4% of subjects in the placebo group (as randomized and entered the apremilast extension phase) achieved an sPGA response (defined as an sPGA score of clear [0] or almost clear [1] with 2-point reduction from baseline) at week 52.

Figure 18. sPGA Response Through Week 52 (ITT Population, NRI)

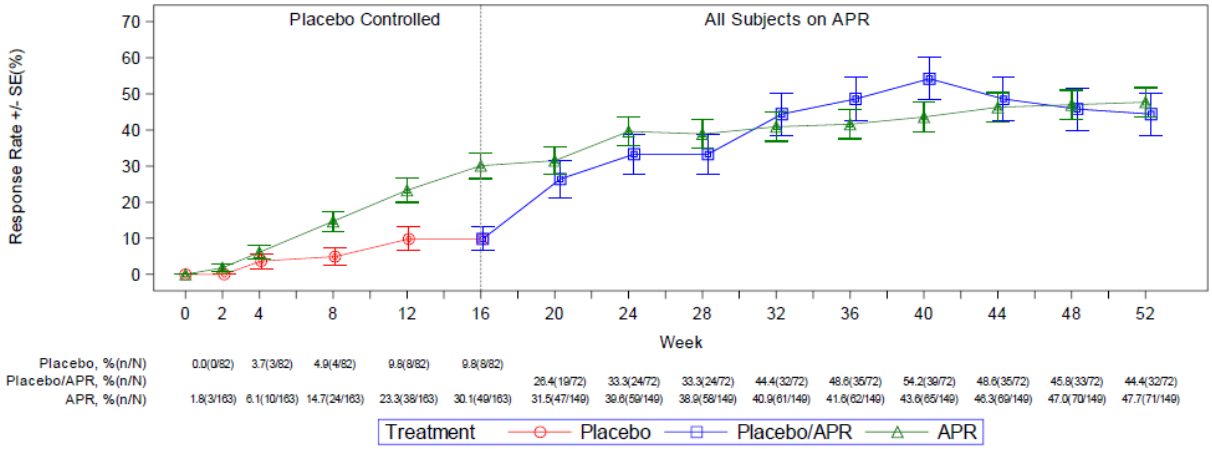


Figure 19. PASI-75 Response Through Week 52 (ITT Population, NRI)

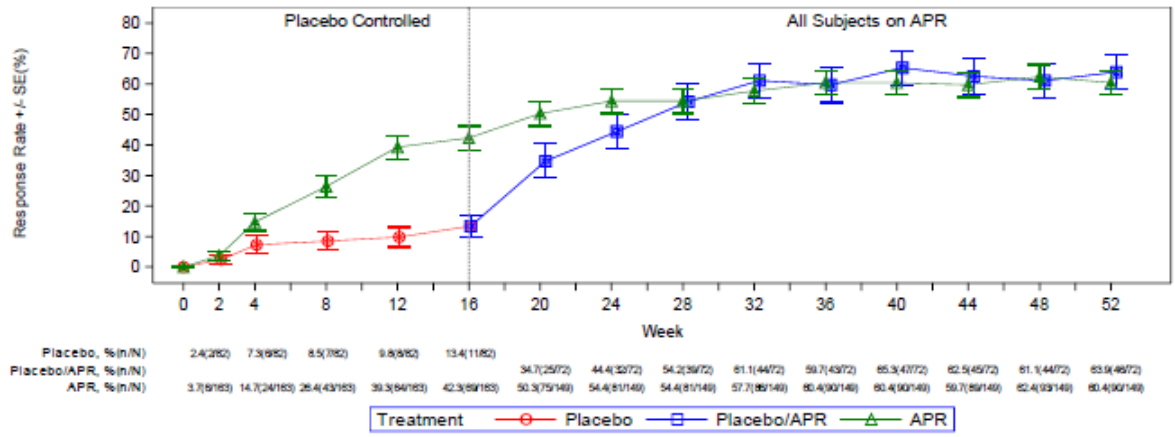


Figure 20. PASI-50 at Week 52 (ITT Population, NRI)

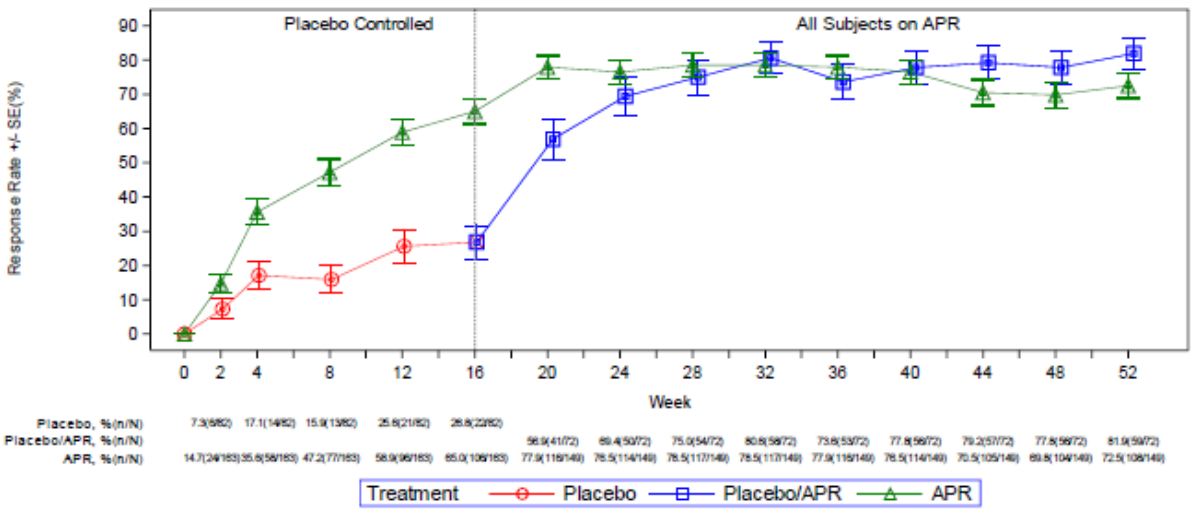
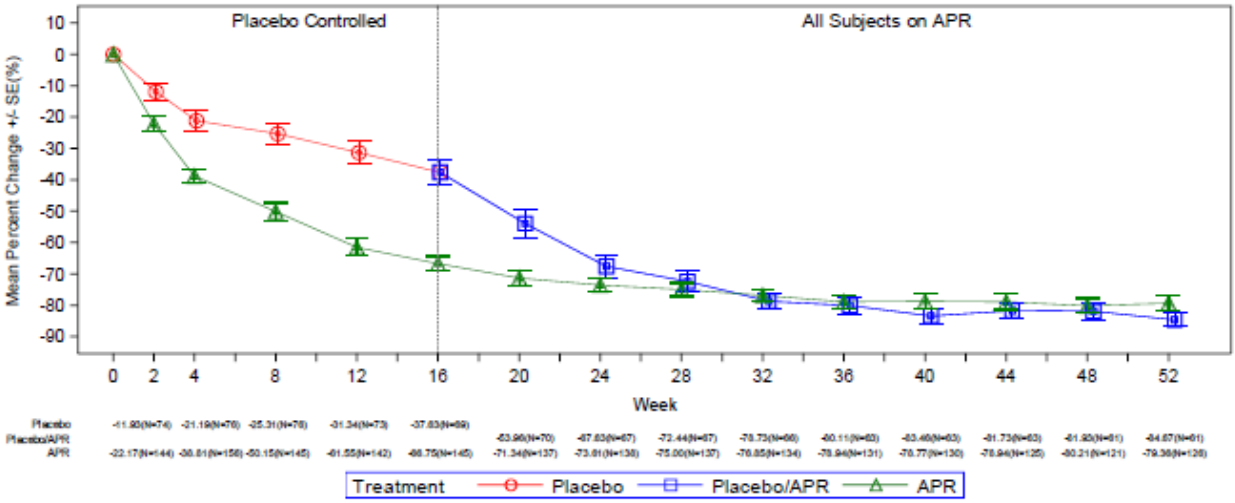


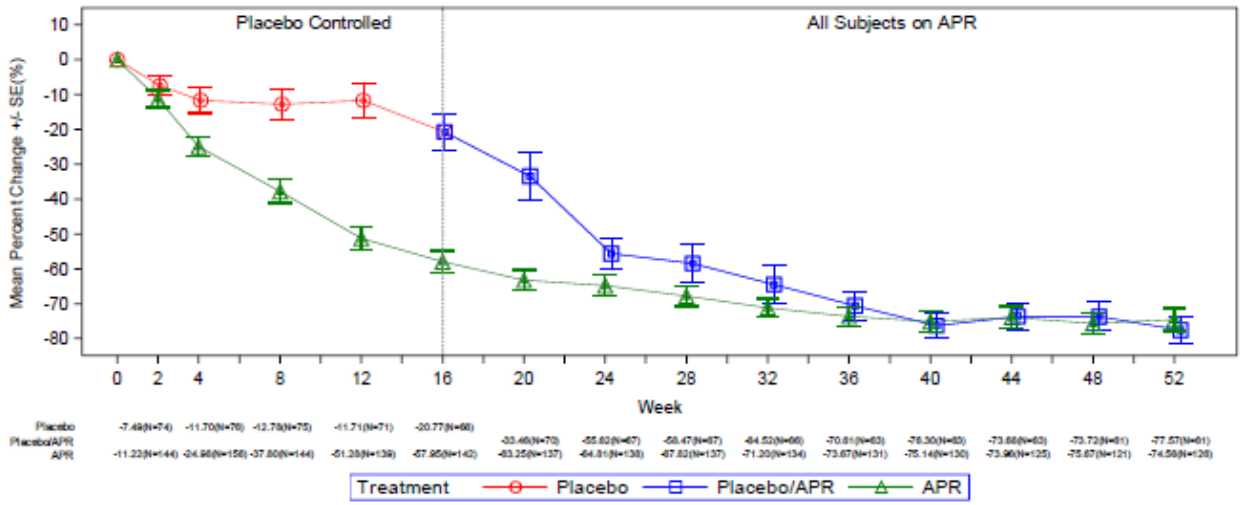
Figure 21. PASI Percent Change From Baseline at Week 52 (ITT Population, DAO)



BSA Percent Change from Baseline Through Week 52

The mean (SE) percent change from baseline in affected BSA (with reduction representing improvement) was -74.6% (3.3) in the apremilast group (as randomized and entered the apremilast extension phase) and -77.6% (3.7) in the placebo group (as randomized and entered the apremilast extension phase) at week 52.

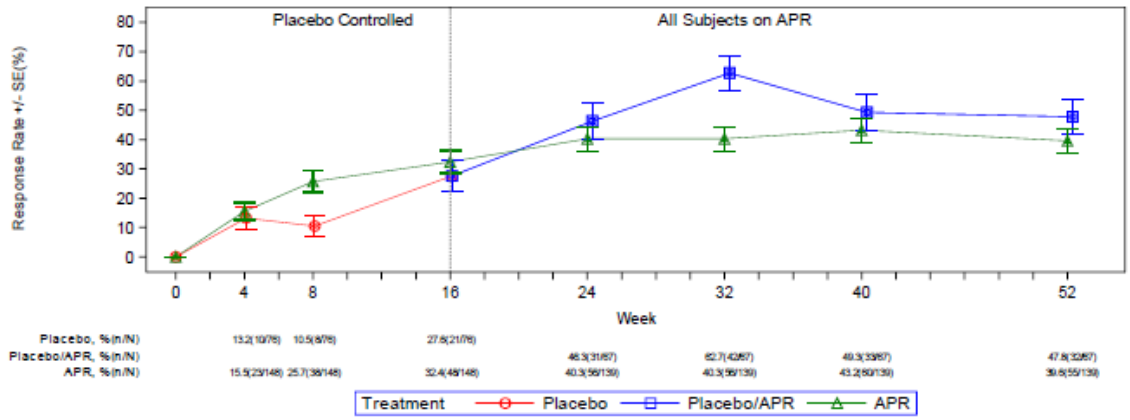
Figure 22. BSA Percent Change from Baseline Through Week 52 (ITT Population, DAO)



CDLQI Response at Week 52

During the apremilast extension phase, a CDLQI (0/1) response was achieved by 39.6% of subjects in the apremilast group (as randomized and entered the apremilast extension phase) and 47.8% of subjects in the placebo group (as randomized and entered the apremilast extension phase) at week 52.

Figure 23. CDLQI Response at Week 52 (ITT Population with Baseline Score ≥ 2, NRI)



APR = apremilast; CDLQI = Children's Dermatology Life Quality Index; ITT = intent-to-treat; NRI = nonresponder imputation
Included subjects who were randomized for the placebo-controlled phase and who entered the apremilast extension phase.

A CDLQI (0/1) response in the maintenance phase was generally maintained in the APR/APR treated group. From week 16 (32.4%) the responder rate increases slightly to 43.2% but reduces to 30.6% by week 52. For subjects who switched from placebo to APR, the treatment effect was more pronounced peaking at week 32 (16 weeks after starting APR) with a response rate of 62.7% reducing to 47.8% at week 52.

Exploratory analyses

For PASI-90, ScPGA, and whole-body itch NRS responses, response rates were generally maintained through week 52 for subjects originally randomized to apremilast who continued with apremilast treatment afterweek 16. Response rates increased for subjects originally randomized to placebo after initiation of apremilast treatment at week 16 through week 52. For subjects originally randomized to apremilast who continued with apremilast treatment after week 16, improvement in change from baseline in whole body itch NRS was maintained through week 52. Subjects originally randomized to placebo who were switched to apremilast at week 16 demonstrated improvement in change from baseline in whole body itch NRS from week 16 through week 52.

Ancillary analyses

None

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27. Summary of Efficacy for Study CC-10004-PPSO-003

Title: A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Apremilast (CC-10004) in Pediatric Subjects From 6 Through 17 Years of Age With Moderate to Severe Plaque Psoriasis	
Study identifier	CC-10004-PPSO-003 (Study 20200056; EudraCT Number: 2018-002918-12; NCT Number: NCT03701763)

Design	This was a phase 3, multicenter, randomized, placebo controlled, double blind study designed to evaluate the efficacy and safety of apremilast in paediatric subjects with moderate to severe plaque psoriasis. The study included a placebo-controlled treatment phase (weeks 0 to 16), an apremilast extension phase (weeks 16 to 52), and a 14-week observational follow-up phase.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks (weeks 0 to 16) not applicable 36 weeks (weeks 16 to 52)
Hypothesis	Superiority		
Treatments groups	Apremilast		**Treatment**: Subjects 20 to < 50 kg received apremilast 20 mg twice daily (BID) and subjects ≥ 50 kg received apremilast 30 mg BID, after an initial titration period. **Duration**: Placebo-controlled phase (weeks 0 to 16) and apremilast extension phase (weeks 16 to 52) **Number randomized**: 163 subjects
	Placebo		**Treatment**: Placebo BID **Duration**: placebo-controlled phase (weeks 0 to 16) **Treatment**: Subjects 20 to < 50 kg received apremilast 20 mg BID and subjects ≥ 50 kg received apremilast 30 mg BID, after an initial titration period. **Duration**: Apremilast extension phase (weeks 16 to 52) **Number randomized**: 82 subjects
Endpoints and definitions	Primary endpoint	Static Physician Global Assessment (sPGA) 0/1	Proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2 point reduction from baseline at week 16
	Major Secondary endpoint	At least a 75% reduction in Psoriasis Area and Severity Index (PASI-75)	Proportion of subjects who achieved PASI-75 from baseline at week 16
	Other Secondary endpoints	At least a 50% reduction in Psoriasis Area and Severity Index (PASI-50)	Proportion of subjects who achieved PASI-50 from baseline at week 16
		Psoriasis Area and Severity Index (PASI)	Percent change from baseline in total PASI score at week 16

		Body surface area (BSA)	Percent change from baseline in affected BSA at week 16
		Children's Dermatology Life Quality Index (CDLQI [0/1])	Proportion of subjects who achieved CDLQI (0/1) at week 16
		CDLQI	Change from baseline in CDLQI score at week 16
Database lock	05 May 2023		
Results and Analysis			
Analysis description		**Primary Analysis**	
Analysis population and time point description		Intent to treat at Week 16	
Descriptive statistics and estimate variability	Treatment group	Placebo	Apremilast
	Number of subjects	82	163
	sPGA Response n (%)	9.4 (11.5)	53.9 (33.1)
	95% CI (%)	4.2, 18.7	25.7, 40.5
Effect estimate per comparison	Primary endpoint: sPGA Response	Comparison groups	Apremilast -Placebo
		Adjusted difference	21.7
		2-sided 95% CI	11.2, 32.1
		2-sided p-value	< 0.0001
Effect estimate per comparison (continued)	Major Secondary endpoint: PASI-75 Response	Comparison groups	Apremilast -Placebo
		Adjusted difference	29.4
		2-sided 95% CI	17.8, 40.9
		2-sided p-value	< 0.0001
	Other Secondary: PASI-50 Response	Comparison groups	Apremilast -Placebo
		Adjusted difference	38.4
		2-sided 95% CI	25.6, 51.2
		2-sided p-valuea	< 0.0001
	Other Secondary: PASI Percent	Comparison groups	Apremilast -Placebo

	Change From Baseline		
		Difference in LS mean	-26.97
		2-sided 95% CI	-35.93, -18.00
		2-sided p-valuea	< 0.0001
	Other Secondary: BSA Percent Change From Baseline	Comparison groups	Apremilast -Placebo
		Difference in LS mean	-34.77
		2-sided 95% CI	-46.99, -22.55
		2-sided p-valuea	< 0.0001
	Other Secondary: CDLQI Response	Comparison groups	Apremilast -Placebo
		Adjusted difference	4.1
		2-sided 95% CI	-9.8, 18.0
		2-sided p-value[a]	0.5616
	Other Secondary: CDLQI Change From Baseline	Comparison groups	Apremilast -Placebo
		Difference in LS mean	-1.8
		2-sided 95% CI	-2.9, -0.8
		2-sided p-valuea	0.0009
	Exploratory: PASI-90 Response	Comparison groups	Apremilast-Placebo
		Adjusted difference	20.3
		2-sided 95% CI	12.1, 28.5
		2-sided p-valuea	0.0001

Notes	-

Supportive study

Study CC-10004-PPSO-004 (PPSO-004)

A Phase 3b, Multi-Center, Open-label, Long-term Extension Study of Apremilast (CC-10004) in Paediatric Subjects from 6 Through 17 Years of Age with Moderate to Severe Plaque Psoriasis.

This extension study is designed to allow subjects to continue to receive uninterrupted apremilast therapy for up to an additional 4 years, until apremilast becomes commercially available for paediatric plaque psoriasis, or until the subject turns 18 years of age (and can be switched to commercially available apremilast for adults), whichever occurs first. Eligible subjects could opt to enroll in this extension study after completing week 52 of Study PPSO-003. Subjects who chose not to participate in the long-term extension study, or discontinued Study PPSO-003 early, entered the observational follow-up phase of PPSO-003.

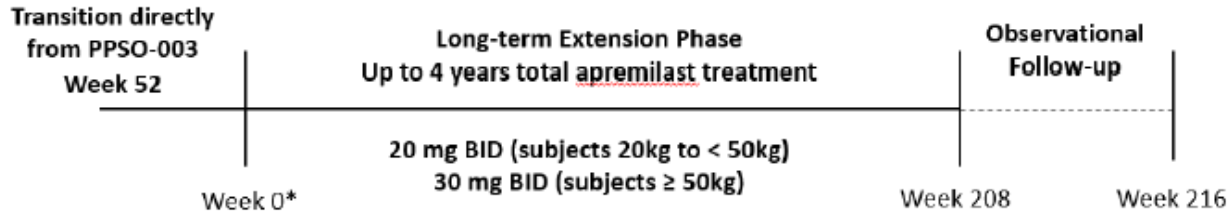
Methods

The study consists of 2 phases: a long-term extension phase (up to208 weeks) and an observational follow-up phase (8 weeks). Subjects may participate in the study for up to 216 weeks.

In this study, treatment was assigned by weight category at visit 1. Subjects weighing 20 to < 50 kg received apremilast 20 mg BID, and subjects weighing ≥ 50 kg received apremilast 30 mg BID. Subjects who begin the study receiving apremilast 20 mg BID and later record a body weight ≥ 50 kg are switched to apremilast 30 mg BID.

The study is ongoing. The analyses presented in this report are based on a database cutoff date of 27 March 2023, and a snapshot date of 10 May 2023. As of the data cutoff date of 27 March 2023, subjects received treatment for a mean (SD) of 48.5 (36.3) weeks in the long-term extension phase and 95.4 (36.9) weeks in the apremilast-exposure period (from Study PPSO-003 to Study PPSO-004).

Study Schema



BID = twice daily
* 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.

The primary objective of the study is to evaluate the long-term safety of apremilast in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis.

The secondary objective of the study is to evaluate the maintenance of effect as measured by static Physician Global Assessment (sPGA).

Interim Results

Disposition

A total of 160 subjects were enrolled in the long-term extension Study PPSO-004 from the core Study PPSO-003. Of these, 106 subjects were originally randomized to the apremilast group and 54 subjects were originally randomized to the placebo group. All subjects (100%) completed week 52 of the core study and received at least 1 dose of apremilast in the long-term extension study.

As of the data cutoff date, 101 subjects (63.1%) were continuing the study, and 59 subjects (36.9%) had discontinued from the study. The most frequent reasons for discontinuation (≥ 3% of subjects overall) during the long-term extension phase included the subject turned 18 years of age (17.5%), withdrawal by parent/guardian (6.9%), lack of efficacy (4.4%), and withdrawal by subject (3.1%). No subjects have completed the study.

Demography and Baseline Characteristics

Baseline demographics of the 160 subjects who continued onto the long-term extension Study PPSO-004 were similar to the 245 subjects enrolled in the core Study PPSO-004. Overall, 53.1% of subjects were female, 93.1% were white, and 85.0% were not Hispanic or Latino. The median (range) age at time of Study PPSO-004 start was 13 years (7, 17); 62 subjects (38.8%) were 6 to 11 years of age, and 98 subjects (61.3%) were 12 to 17 years of age. The median (range) weight was 50.7 kg (21.7, 141.4); most subjects (73.8%) had an age-appropriate healthy weight body mass index category.

Table 28. Baseline Disease Characteristics in Study PPSO-004 (Long-term Extension Treatment Population)

Parameter	Placebo/APR (N = 54)	APR/APR (N = 106)	Total (N = 160)
sPGA Score - n (%)			
0 (Clear)	15 (27.8)	24 (22.6)	39 (24.4)
1 (Almost Clear)	16 (29.6)	41 (38.7)	57 (35.6)
2 (Mild)	16 (29.6)	27 (25.5)	43 (26.9)
3 (Moderate)	7 (13.0)	13 (12.3)	20 (12.5)
4 (Severe)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	1 (0.9)	1 (0.6)
Duration of Plaque Psoriasis (years)			
Mean	4.80	4.88	4.86
SD	2.944	2.932	2.927
Median	3.70	3.80	3.76
Q1, Q3	2.38, 7.47	2.56, 6.75	2.54, 7.13
Min, Max	1.6, 12.5	1.6, 14.3	1.6, 14.3
Duration of Plaque Psoriasis Categories (years)			
< 1	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 to < 2	9 (16.7)	11 (10.4)	20 (12.5)
≥ 2 to < 5	26 (48.1)	56 (52.8)	82 (51.3)
≥ 5	19 (35.2)	39 (36.8)	58 (36.3)

APR = apremilast; sPGA = Static Physician Global Assessment
This table summarized value at first visit in the long-term extension study.
Placebo/apremilast refers to subjects who received placebo at the start and switched to apremilast at week 16 of the core study; apremilast/apremilast refers to subjects who received apremilast at the start of the core study.
Percentages are based on the number of subjects in each treatment group

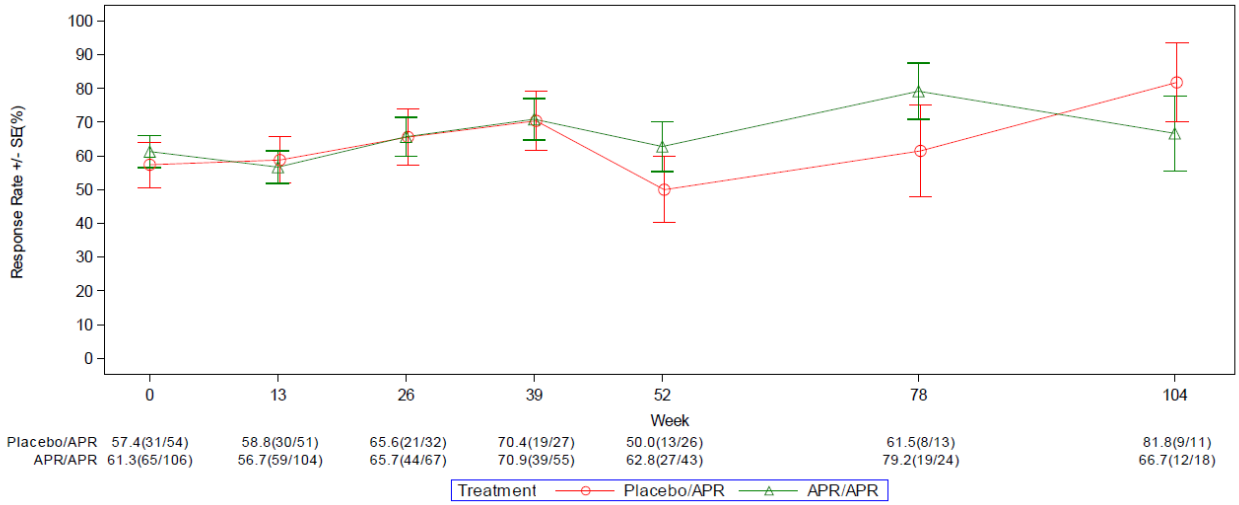
Efficacy was assessed as a secondary endpoint in this study.

Secondary Efficacy Endpoint - sPGA Response

Overall, the proportion of subjects achieving an sPGA response, using data as observed, at weeks 0, 26, and 52 were:

- week 0: 96/160 subjects (60.0%)
- week 26: 65/99 subjects (65.7%)
- week 52: 40/69 subjects (58.0%)

Figure 24. sPGA Response (PPSO-004) (Long-term Extension Treatment Population, DAO)



APR = apremilast; DAO = data as observed
Response rate (%) was calculated as 100*n/m where n = number of responders, m = number of subjects with observed score.
Placebo/apremilast refers to subjects who received placebo at the start and switched to apremilast at week 16 of the core study (PPSO-003); apremilast/apremilast refers to subjects who received apremilast at the start of the core study (PPSO-003).

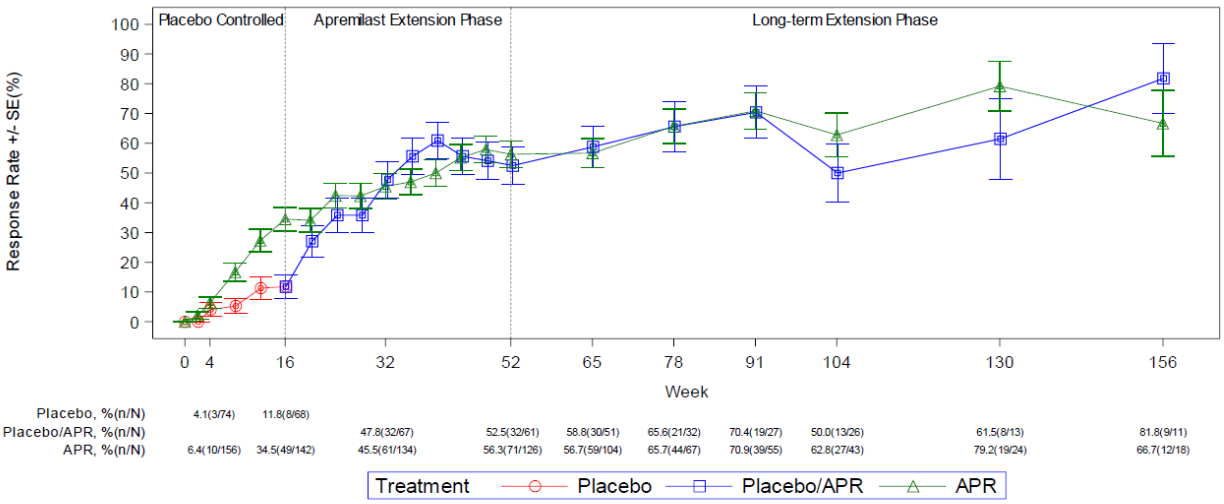
Table 29. sPGA Response by Time Point Through Week 52 in Study PPSO-004 (Long-term Extension Treatment Population, NRI and DAO)

	NRI			DAO		
	Apremilast Total (N=160)			Apremilast Total (N=160)		
Time Point	n/m (%)[a]	SE (%)	Two-sided 95% CI (%)[b]	n/m (%)[a]	SE (%)	Two-sided 95% CI (%)[b]
Week 0	96/160 (60.0)	3.87	(52.0, 67.7)	96/160 (60.0)	3.87	(52.0, 67.7)
Week 13	89/158 (56.3)	3.95	(48.2, 64.2)	89/155 (57.4)	3.97	(49.2, 65.3)
Week 26	65/111 (58.6)	4.68	(48.8, 67.8)	65/99 (65.7)	4.77	(55.4, 74.9)
Week 39	58/96 (60.4)	4.99	(49.9, 70.3)	58/82 (70.7)	5.02	(59.6, 80.3)
Week 52	40/86 (46.5)	5.38	(35.7, 57.6)	40/69 (58.0)	5.94	(45.5, 69.8)

Analysis performed across trials (pooled analyses and meta-analysis)

The sPGA response across the core Study PPSO-003 and the long-term extension Study PPSO-004 (as of the data cut-off date) is provided in Figure 25. Across both studies, sPGA response was defined as a score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline of the core study, PPSO-003. The figure includes the sPGA response data for all of the subjects who participated in Study PPSO-003, regardless of participation in PPSO-004, as well as the data from subjects who rolled over into PPSO-004.

Figure 25. The sPGA response across the core Study PPSO-003 and the long-term extension Study PPSO-004 (as of the data cut-off date). sPGA Response by Time Point (ITT Population, DAO)



APR = Apremilast. DAO = Data as Observed. ITT = Intent-to-Treat. sPGA = Static Physician Global Assessment.
Included subjects who were randomized at Week 0 of PPSO-003 and had assessment at the study visit.

Program: /userdata/stat/otezla/meta/snda_ped_psor_mod_sev_2023/analysis/sce/figures/f-spga-resp-w260.sas
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2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study Design

The efficacy and safety of apremilast in paediatric psoriasis is supported by one pivotal, randomised, double-blind, placebo-controlled Phase 3 study (PPSO-003) and an ongoing phase 3b, multi-centre, open-label long-term extension study of apremilast (PPSO-004). The general design features of this double-blind placebo- study are in accordance with the Paediatric Investigation Plan (PIP) for psoriasis (EMEA 00715 PIP03-11-M06). The study deviates from recommendations of the EU Guideline on psoriasis (CHMP/EWP/2454/02 corr) which recommends both a placebo and active control to determine clinical relevance of any treatment effect and to further clarify the place of apremilast in the paediatric treatment algorithm. A key feature of treatment with apremilast is its oral administration which could be of particular advantage for compliance in the paediatric population. The MAH justifies the placebo control design by referring to the clinical development programme for the first biologic medication approved for use in children. The MAH's rationale was followed by the CHMP and the issue not further pursued.

The EU Guideline on psoriasis (CHMP/EWP/2454/02 corr) requires evaluation of the durability of remission/response, relapse and rebound after the end of treatment. No randomised withdrawal phase was included in this study design. The MAH was asked to discuss any available evidence of durability of effect off treatment, including the duration of remission/response and time to rebound with reference to the 14-week observational follow-up phase for subjects who were responders who but opted not to continue in the long term study or discontinued the study early and the relevance of outcomes from randomized withdrawal data in adults to the paediatric population and comment on whether, as in adults, continuous treatment with a therapeutic dose of apremilast is necessary to maintain an appropriate efficacy response in paediatric subjects. In their response, the MAH presented an analysis for time to loss of sPGA and PASI-75 response for Study PPSO-003. Median time to loss of sPGA response at week 52 or early termination for all randomised paediatric subjects who entered the observational follow-up period was 14 weeks; median time to loss of PASI-75 response could not be estimated. The number of subjects

for which there is data available is small (n=10) as most subjects continued into the long-term extension study. Given the low number of subjects and the number of subjects censored, it was not possible to compare median time to loss of treatment effect between groups. The MAH concluded that given the similarities in the exposure response and clinical response between adults and children, a similar loss of efficacy would be expected in children and treatment should therefore be continued with a therapeutic dose to maintain efficacy. This is agreed by the CHMP.

An early escape option for subjects demonstrating a worsening of their psoriasis, measured as a ≥ 50% increase in PASI score from baseline, was permitted. These early escape subjects were allowed to use moderate-to high potency topical steroids but were considered non-responders for the purposes of statistical analysis which is an acceptable approach.

The inclusion and exclusion criteria are acceptable to the CHMP and adequately reflect the targeted patient population of patients with moderate to severe plaque psoriasis. The severity criteria for inclusion (PASI score ≥12, sPGA ≥3, and BSA involvement ≥10%) are the same as used in the pivotal apremilast adult studies. They align with the definition for moderate to severe psoriasis in the EU Guideline on psoriasis (CHMP/EWP/2454/02 corr). Approximately 30% of children are expected to have coexisting psoriatic arthritis with psoriasis. The impact of apremilast on this subgroup has not been evaluated. The EMA has deferred the obligation to submit results of studies with apremilast in paediatric psoriatic arthritis.

This pivotal study was conducted at 106 centres in 10 countries (Belgium, Canada, Czech Republic, France, Israel, Italy, Netherlands, Russia, Spain, and the United States). Centre effect was included in the sensitivity analysis.

The study population included paediatric patients who were inadequately controlled by or inappropriate for topical therapy for psoriasis and who were candidates for systemic therapy or phototherapy. Subjects who were inadequately controlled with topical steroids at baseline had moderate to severe plaque psoriasis at baseline screening defined by PASI score>/=12 BSA, affected by psoriasis >/=10% and SPGA score>/=3. Subjects were considered inadequately controlled on treatment if these inclusion criteria were met.

Subjects who were either treatment naïve or who had received phototherapy and/or systemic therapy were eligible for inclusion in the study.

Subjects were stratified by age and randomised to receive apremilast (APR) 20mg or APR 30 mg twice daily or identically-appearing placebo during the 16-week Placebo-controlled Phase based on weight (20mg: ≥ 20 and <50 kg and 30mg: ≥ 50 kg).

The blinding procedures of the double-blind treatment arms were acceptable. Blinding was maintained through week 52 in the extension phase. Although only subjects initially randomized to placebo were dose titrated during their first week of the apremilast-extension phase, all subjects received identically appearing titration or dummy titration cards and treatment cards at the week 16 visit.

Endpoints

Static Physician Global Assessment (sPGA) has been selected as the primary endpoint. This is a validated, standardised global score evaluating the severity of the disease at a given point in time, with psoriasis lesions evaluated for induration, erythema and presence of desquamation. PASI-75 was included as a key secondary endpoint in this study, which is acceptable to the CHMP. The pre-defined primary and key secondary endpoints are in accordance with the PIP and with the applicable Guideline requirements.

Endpoints for more difficult to treat areas such as scalp and genital psoriasis (ScPGA, sPGA-G) were included as exploratory endpoints. Nail parameters were not evaluated in the study. The MAH suggested that apremilast may have a value in treating psoriasis in areas that are considered difficult to treat. The patterns of psoriasis seen in children can include areas that are difficult to treat and along with management of

overall body psoriasis in children and adolescents, are important due to the cosmetic impact, which can contribute to the psychological and social distress of patients with psoriasis. The CHMP highlighted that any effect in difficult to treat areas would need to be substantiated, with efficacy data in these areas that should have been included as secondary endpoints.

Overall, the key study objectives and endpoints are acceptable to the CHMP.

Statistical Methodology

For the placebo-controlled phase (weeks 0 to 16), the analyses for efficacy endpoints were based on the intent-to-treat (ITT) population, defined as all subjects who were randomized. The primary and secondary efficacy endpoints were hierarchically ranked for testing, to control the overall type I error rate in claiming statistical significance at the 2-sided 0.05 significance level.

The sample size was based on the results of the adult Phase 3 and 3b studies with apremilast (PSOR-008, PSOR-009 and PSOR-010) which demonstrated positive treatment effects. The study had a 90% power to detect a 15% difference (20% versus 5%) for the proportion of subjects achieving sPGA response at Week 16, and 95% power to detect a 20% difference in PASI-75.

Disposition

A total of 245 subjects were randomised, with 82 subjects randomised to the placebo group and 163 subjects randomised to the APR group. A total of 163 subjects (100%) in the apremilast group and 80 subjects (97.6%) in the placebo group received at least 1 dose of investigational product.

A total of 80 subjects were treated with apremilast 20mg bd and 83 were treated with 30mg bd in the placebo-controlled phase of the study.

Completion rates in the placebo-controlled phase were high overall but were slightly higher in the total apremilast compared to the placebo group (91.4% vs 87.8% respectively). The most frequent reasons for discontinuation (≥ 3% of subjects in either treatment group [apremilast, placebo]) during the placebo-controlled phase included withdrawal by parent/guardian (3.1%, 3.7%) and adverse event (3.1%, 1.2%).

A total of 221 (90.2% of the total population) subjects entered the apremilast extension phase of whom >80% completed the extension phase. In this phase, the most frequent reason for discontinuation (≥ 3% of subjects overall) during the apremilast extension phase was lack of efficacy (5.0%). This was broadly comparable across the placebo/apremilast and apremilast/apremilast groups. 5.4% of the apremilast/apremilast group were withdrawn by parent compared with 1.4% of the PLB/APR group. With respect to cases of 'withdrawal by parent', the MAH has provided reassuring data that the reason for withdrawal was not linked to an adverse reaction or event.

There was an imbalance in the proportion of study participants with protocol deviations, 9.2% in the apremilast group and 17.1% in the placebo group having at least 1 important protocol deviation for the entire study. This imbalance was mainly due to investigational product (IP) oversight issues. These deviations did not impact the overall interpretation of the efficacy results, as assessed by the per-protocol population. Most of the issues arose due to incorrect dispensing and none had any clinical sequelae reported.

Baseline Demographics and Disease Characteristics

Patient demographics were generally balanced across treatment groups. However, a slightly higher proportion of subjects in the apremilast group compared with the placebo group were female compared to male (54.6% vs 47.6%).

There were some small imbalances in baseline disease characteristics. The three main indices of disease activity were balanced across treatment arms for placebo and apremilast respectively (sPGA 76.8 vs 74.8;

PASI 19.5 vs 20.03 BSA 30.8 vs 31.9). The CHMP considered the observed imbalances small and unlikely to impact on the study outcomes.

The psoriasis-related therapies previously used by subjects prior to enrolment in the study were generally well balanced across treatment groups. Most subjects had no prior treatment with phototherapy (82.4%), conventional systemic therapy (82.9%), biologic therapy (94.3%), or systemic therapy (65.7%). Conventional systemic therapy for psoriasis is described in the protocol and included but was not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, and fumaric acid esters. In the adult application, systemic therapy referred to a combination of conventional and biological therapy. However, the number of subjects treated with 'systemic therapy' exceeds the sum of subjects treated with conventional systemic and biologic therapies so it was unclear how the numbers for 'systemic therapy' were calculated in this application. The MAH clarified that the number of subjects treated with systemic therapy also includes those who received treatment with antihistamines as well as conventional systemic and biologic therapies. Therefore, the number was greater than the sum of those subjects who had received systemic and biologic therapies.

The majority of subjects had no treatment with systemic therapy or phototherapy. Of the approximately 35% of patients who had a history of previous systemic therapy, it was unclear if all or a proportion of study participants failed or were intolerant of study treatment. The MAH provided further details of previous therapies and of the number of subjects who had prior systemic therapy (n=84) and of those who had 1, 2 or greater lines of therapy. The reasons for discontinuation of prior systemic therapy included treatment failure, lost response, partial response, lost insurance, adverse event course completed and end of clinical trial. In total, 30, i.e. 12.2% of subjects failed previous systemic therapies. This confirms that only a small percentage of the population studied in the pivotal clinical trial had failed prior systemic therapies. Adult psoriasis patients in Studies PSOR-008 and 009 had higher levels of prior systemic and phototherapies which impacts comparison of outcomes across the paediatric and adult populations.

Efficacy data and additional analyses

Primary endpoint

The primary endpoint measured the proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline. The treatment effect for the total apremilast group compared to placebo was 21.7% (95% CI 11.2, 32.1; p-value < 0.0001). The treatment effect is larger than the assumption made at the planning stage of the study (power to detect a 15% difference (20% versus 5%) between the apremilast arm and the placebo arm for the proportion of subjects achieving sPGA response at Week 1). This is slightly higher than the treatment effect seen in key secondary endpoint in adults (sPGA Response at Week 16 pooled analysis FAS: 17.2%). However, the CHMP noted that the adult population in studies PSOR 008 and 009 were more heavily pretreated than the paediatric population.

Key secondary endpoint

The key secondary efficacy endpoint in both studies was the proportion of subjects achieving at least a 75% reduction from baseline in the PASI score (PASI-75) at Week 16. Statistically significant treatment effects were seen with total apremilast for the key secondary endpoint. 45.4% of subjects in the apremilast group and 16.1% of subjects in the placebo group achieved a PASI-75 response. The adjusted treatment difference was statistically significant (29.4% [95% CI: 17.8, 40.9]; p < 0.0001). The results of the primary and secondary analysis were also supported by multiple sensitivity analyses using additional imputation methods (LOCF, NRI) to assess the impact of missing data. Analysis of sPGA

response adjusted by pooled sites and stratification factor at randomization were generally consistent across these prespecified sensitivity analyses.

Other secondary endpoints

Nominally statistically significant improvements in PASI 50, PASI Percent Change from Baseline and BSA percent change following treatment with apremilast compared with placebo were evident at 16 weeks. The PASI-50 response at week 16 was 32.1% and 70.5% for the placebo and apremilast treated groups respectively. The PASI percent change from baseline was -38.3 vs -65.3 (Difference: -27.0 (95% CI -35.9, -18.0 p-value < 0.0001) for the placebo and apremilast treated groups, respectively.

At Week 16, the mean percent changes (improvement) from baseline in BSA involvement for the APR BID and placebo treatment groups were –21.8% and -56.6%, respectively, treatment difference -34.8 (95% CI -47.0, -22.6; p-value < 0.0001), in study PPSO-003. Results on the CDLQI indicated a mixed picture on patient reported quality of life. The mean CDLQI Total Scores at baseline were approximately 7 in the pivotal study indicating a mild/moderate impact of psoriasis on the subjects' quality of life. No statistically significant difference was seen in CDLQI (0/1) response scores between the treatment arms. 35.4% of subjects in the apremilast group and 31.3% of subjects in the placebo group at week 16 (treatment difference 4.1% (95%CI: -9.8, 18.0; p = 0.56]). Nominally significant improvement was however observed in CDLQI change from baseline at week 16 change from baseline at week 16 was -1.8 (95% CI: -2.9, -0.8; p = 0.0009.)

Subgroup Analyses

Subgroup analyses based on age stratum, weight category and previous exposure to systemic therapy were presented for sPGA and PASI-75.

The results of sPGA response at week 16 across the subgroups presented were generally in favour of apremilast except for the sPGA endpoint in 2 subgroups (subjects 12 to 17 years and ≥ 20 to < 50 kg and subjects with prior phototherapy), where the treatment effect favoured placebo. The magnitude of the treatment effect was variable across and within the subgroups. The percentage of sPGA responders were lower in males than females, non-whites compared to whites and subjects from USA.

The dosing recommendations by weight are supported by subgroup analyses, although significant variability in the observed treatment effect was observed by weight and age. For the following subgroups, adolescents age 12-17, subjects with duration of psoriasis >5 yrs, Baseline sPGA 4 (severe), Baseline ScPGA 0-2, baseline CDLQI 0-6, whole body itch NRS 0-4, underweight and obesity, 12 to 17 years and ≥ 20 to < 50 kg and non-white subgroups, the confidence interval included zero. The CHMP noted that the size of these subgroups is in some cases very small. In addition, the lack of stratification and powering make it difficult to interpret these results. The lack of efficacy in the 12-17 year age group seems to be mainly driven by lack of effect in the age 12-17 and ≥ 20 to < 50 kg subgroup which suggests a reduced effect in underweight adolescents. The treatment effect is most evident in children under 6 to 11 with BW <5 0 kgs. However, the CHMP noted that for children age 6-11 with weight >50kg, the CI interval for the treatment effect included 0. The variable outcomes in the sub-group analyses for the primary efficacy parameter sPGA and for PASI75 raised the question of plausibility. The MAH was requested to further discuss these imbalances, e.g. greater sPGA responders rates in females compared to males, the variable magnitude of the treatment effect across and within age and weight subgroups, e.g. the treatment effect is most evident in children under 6 to 11 years of age with BW<50 kgs, whereas there is a lack of effect in the age 12-17 and ≥ 20 to < 50 kg subgroup. The MAH was also asked to discuss a possible role of underdosing and overdosing in these outcomes. There was a treatment effect for both sexes when compared to placebo and the effect was of greater magnitude in girls. There is no biologically plausible reason for the greater response in girls and

the MAH considers that the differences in observed effect was due to random variation associated with the small number of subjects in each group. This is agreed by the CHMP.

The MAH presented the sPGA and PASI-75 results in each age cohort and for each weight group. The response to both endpoints is favourable in all groups except for adolescence between 12-17 years and between >20kg and < 50kg. The MAH explained that this may be due to the higher response to placebo in this age group and that the observed response to treatment in this age group was consistent with other treated groups i.e. of the order of 32%. The MAH could not explain why the response to placebo might be higher for this age and weight cohort. For children in this age group i.e. 12-17 years who were <20 kg or >50kg, the response favoured the treated group. For PASI-75, the treatment difference favoured apremilast in all treatment groups. The MAH concluded that given the small number of subjects in each subgroup and the wide confidence intervals around each result, the observed group where the response to placebo was greater, does not change the overall conclusion that there is an effective response in paediatric subjects to treatment. In addition, although age was not a covariate in the population PK model, none of the demographic covariates used such as body weight and sex resulted in a difference in apremilast exposure requiring dose adjustment. There was no evidence in the study of overdosing or underdosing affecting response outcomes. The MAH could not fully explain the observed difference in response in children aged between 12-17 years. The observed difference may be due to an enhanced placebo response in this age group or to the limited numbers in each subgroup. The data overall trends towards a response to treatment when PASI-75 is taken into account. The MAH will continue to monitor in the PSUR reports lack of efficacy in this adolescent group. Upon the CHMP's request, the MAH also presented efficacy outcomes by actual treatment received overall (all subjects who received 20mg or 30mg of apremilast). For subjects who received 20mg with baseline weight 20kg to <50 kg the adjusted treatment difference for the proportion of subjects achieving a response was 25.7% (7.5-43.8%) for static sPGA. For those who received 30mg with a baseline weight >/=50kg, the adjusted treatment difference for the proportion of subjects achieving a response was 17.5% (7.2-27.8%) for sPGA. Only 2 subjects randomised to apremilast received the wrong dose. The MAH also presented results per dose for age, weight and BMI subgroups. Consistent with the previous subgroup analysis, the adjusted differences generally favoured apremilast across age, weight and BMI.

The majority of subjects had no prior treatment with systemic treatment or phototherapy. For the subgroup of patients who had used prior phototherapy the treatment difference for the primary outcome sPGA(0,1) was -5.1% in favour of placebo CI (95% CI –31.6, 21.5).

For subjects who used prior biologic therapies the treatment effect in favour of apremilast was 3.4% and the CI included 0 (95% CI –48.1, 54.8). Again, the numbers in these subgroups are very small but it does raise an uncertainty regarding the efficacy of apremilast in subjects who have been pretreated with these therapies.

Subgroup analyses were also conducted by PASI-75 Response at Week 16. The treatment effect favoured apremilast for PASI-75 across all subgroups evaluated, but similar to the sPGA analysis for a number of subgroups including subjects with a history of prior phototherapy, prior biologic therapy the confidence interval included zero.

The majority of patients in this pivotal study were systemic treatment naïve and treatment with apremilast appears to have been their first systemic treatment. The MAH initially proposed an indication for use in children which recommends second line use after at least one other systemic therapy or phototherapy, which was not agreed by the CHMP. The MAH was asked to consider and justify an indication more in line with the PPSO-003 study population (e.g. *for the use in children from 6 years of age who are candidates for systemic therapy)*. Such a target population would also include patients who have a contraindication, have an inadequate response, or are intolerant to at least one other systemic therapy or phototherapy. Therefore, the MAH was also asked to discuss if efficacy and safety could be extrapolated from adults for

these subgroups. In their response, the MAH revised the indication in accordance with the inclusion criteria of the pivotal study PPSO-003, in which most subjects enrolled had not used a systemic therapy or phototherapy prior to enrolment i.e. *for use in patients who are candidates for systemic therapy*. To support the use of apremilast in paediatric patients with an inadequate response to other systemic therapy or phototherapy, the MAH adequately justified extrapolation of safety and efficacy response from studies in adults. The justification provided by the MAH includes that both adults and children over 6 years of age have a similar clinical presentation and the PK exposure response relationship is similar in both groups. The MAH also presented data comparing efficacy in children and adults with prior systemic therapy: sPGA responders were compared in the adult and paediatric groups at 16 weeks. The adjusted difference to placebo in subjects with 0 prior systemic therapies or phototherapy was 28.7% (14.5,42.9) in children and 19.1% (13.0,25.2) in adults and in subjects with >/= 1 prior therapy was 11.1% (-3.7,25.9) in paediatric subjects and 18.4 % (11.9-25.0) in adults with 1 prior therapy. The CHMP noted that the number of subjects in the paediatric groups is small (n=67) compared to that in the adult group with 1 prior systemic therapy (n=237) and the confidence interval around the values are wide and crosses 0 for the paediatric group with >/=1 prior systemic or phototherapy. In subjects with prior failed therapy (i.e. >/=1 prior failed systemic or phototherapy), the response appears higher in adult subjects 24.4% (15.8,33.0) compared to paediatric subjects 5% (-22.8,32.8). However, the number of paediatric subjects (n=21) is small compared to the adult group and therefore no firm conclusions can be drawn from the available data. The PASI-75 response at week 16 shows a similar trend. The best response was seen in children without any prior therapies 37% (21.2,52.8). The response observed in children with prior therapy and with prior failed therapy was less than that observed in adults with prior therapy and prior failed therapy. However, as pointed out previously, the number of children with prior therapy is small compared to the data available/number of adults with prior therapy. The overall trend in the data is towards an increase in the number of responders compared to placebo in children who had or had not received prior systemic treatment or phototherapy, with a greater response observed in those who had not received prior systemic therapy or phototherapy. The MAH pointed also the similar safety profile for apremilast in the paediatric and adult clinical studies. The CHMP concluded that the available data support the use of apremilast in paediatric patients with an inadequate response to other systemic therapy or phototherapy.

The CHMP noted also that the paediatric inclusion criteria specify inclusion of children with a cut-off from age 6 years weighing at least 20 kg. This weight threshold falls within the 50th and the 25th centile for 6-year-old boys and at approximately the 50th centile for 6 year-old girls. The posology excludes subjects < 20 kg weight whereas a non-negligible proportion of subjects in the lower age range will have a weight < 20 kg. The MAH was requested to address this inconsistency and to discuss whether a weight restriction should be addressed in the indication (e.g. children ≥ 20 kg in weight) in addition to the age restriction or if the issue could best be addressed in the posology section. The MAH agreed to include a weight restriction in the indication i.e. for children weighing at least 20 kg. This is in line with the population in the pivotal clinical trial and in line with EMA guidance on when it is relevant to include bodyweight limit in the wording of a paediatric indication EMA/268908/2023.

Based on the above, the MAH proposed the following revised indication, which is agreed by the CHMP:

Otezla is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years and weighing at least 20 kg who are candidates for systemic therapy.

A treatment effect in favour of apremilast (sPGA and PASI) was noted in subjects with scalp psoriasis and with genital psoriasis which suggests that apremilast may have a role in treating psoriasis in difficult locations. However, these endpoints were only included as exploratory endpoints in the study and no firm conclusions on efficacy can be drawn.

Maintenance of effect

Study PPSO-003 evaluated up to 52 weeks of treatment with apremilast in paediatric subjects with moderate to severe plaque psoriasis. Eligible subjects who completed the apremilast extension phase and opted to enrol in the long-term extension study PPSO-004 are being evaluated for up to an additional 208 weeks, for up to a total of 5 years.

The sPGA response rates and PASI 75 response rates for subjects originally randomized to apremilast 20 mg and 30 BID were generally maintained through Week 52 in study PPS-0003. Subjects originally randomized to placebo demonstrated sPGA response and PASI 75 following initiation of apremilast treatment. However, it took until week 28 to achieve a level of response similar to that seen for subjects originally randomized to apremilast at baseline. Nevertheless, a consistent pattern of improvement (from Week 16 to Week 52) was seen among patients switching from placebo to apremilast at Week 16. Response rates achieved by Week 16 were generally maintained or increased further during maintenance treatment.

Among subjects who continued receiving apremilast in the long-term extension study PPS-0004, there is some evidence of maintenance of effect, as measured by proportion of subjects achieving an sPGA response of clear (0) or almost clear (1) with at least a 2-point reduction from baseline over time.

2.4.3. Conclusions on the clinical efficacy

Efficacy has been demonstrated for paediatric patients 6 years and above and weighing at least 20 kg with moderate to severe plaque psoriasis at 16 weeks and up to 52 weeks. The primary endpoint and key secondary endpoint for the pivotal study was statistically significant, improvement in sPGA and PASI 75, at 16 weeks and compared to placebo was shown, however better results were observed in patients naive to biological treatment or phototherapy. The treatment effect exceeded or was comparable to that seen in adults. However, adult psoriasis patients in studies PSOR-008 and 009 had higher levels of prior systemic and phototherapies, which impacts comparison of outcomes across the paediatric and adult populations.

The CHMP concluded that the clinical efficacy has been demonstrated for use of Otezla in the following indication:

Otezla is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years and weighing at least 20 kg who are candidates for systemic therapy.

2.5. Clinical safety

Introduction

Otezla (apremilast) has been authorised for the treatment of moderate to severe chronic plaque psoriasis in adult patients since 2015. The most commonly reported adverse reactions with Otezla in the adult population are gastrointestinal (GI) disorders including diarrhoea and nausea. The gastrointestinal adverse reactions generally occur within the first 2 weeks of treatment and usually resolve within 4 weeks. The other most commonly reported adverse reactions include upper respiratory tract infections, headache, and tension headache and are mostly mild to moderate in severity. Hypersensitivity reactions are uncommonly observed.

Other important risks associated with apremilast in the adult population (included in Section 4.4 of the SmPC) include an increased risk of psychiatric disorders (including insomnia, depression, suicidal ideation and behaviour, suicide, that have been observed in patients with or without history of depression), use in severe renal impairment with reduced dosing advised, and unexplained and clinically significant weight loss.

For the proposed extension of the moderate to severe plaque psoriasis indication to children and adolescents from 6 to 17 years, the analysis of the safety profile of apremilast in this population is primarily based on the results from the phase 3 Study PPSO-003, supported by the results from the phase 2 Study PPSO-001. Interim safety data from the long-term extension phase 3b, Study PPSO-004, are also presented to provide additional information on the long-term safety of apremilast in paediatric subjects.

Safety data from Study PPSO-003 are also presented side-by-side with pooled safety data from the prior pivotal placebo-controlled psoriasis studies in adults, CC-10004-PSOR-008 (ESTEEM 1) and CC-10004-PSOR-009 (ESTEEM 2), to compare the safety profile of apremilast in the adult and paediatric moderate to severe plaque psoriasis populations.

Patient exposure

Study PPSO-003

This completed pivotal phase 3 study consisted of a 16-week double-blind placebo-controlled treatment phase (weeks 0 to 16) in which paediatric subjects were randomized in a 2 (apremilast):1 (placebo) ratio, a 36-week apremilast extension phase (weeks 16 to 52) with subjects receiving placebo in the first treatment phase being titrated to the appropriate weight-based dosage of apremilast at week 16.

Treatment assignment was stratified by baseline age group (6 to 11 years or 12 to 17 years). Subjects 20 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.

In Study PPSO-003, safety data are presented for both the placebo-controlled phase and the apremilast-exposure period. Safety analyses for the placebo-controlled phase were based on the safety population (ie, all subjects who were randomized and received at least 1 dose of investigational product). Safety analyses for the apremilast-exposure period were based on apremilast subjects as treated (subjects who were treated with at least 1 dose of apremilast [all subjects who were initially randomized to apremilast or switched to apremilast at week 16 and received at least 1 dose of apremilast]).

The median age of subjects was 13 years; 101 subjects (41.2%) were 6 to 11 years of age and 144 subjects (58.8%) were 12 to 17 years of age. Median weight was 50.0 kg. Most children 6 to 11 years of age weighed ≥ 20 to < 50 kg, while most adolescents 12 to 17 years of age weighed ≥ 50 kg. Most subjects had no prior treatment with phototherapy (82.4%), conventional systemic therapy (82.9%), biologic therapy (94.3%), or systemic therapy (65.7%). From a safety evaluation perspective, there were no clinically meaningful differences observed across treatment groups with respect to demographics, prior treatments, and baseline disease characteristics. Baseline disease characteristics were consistent with a population with moderate to severe disease.

Placebo-controlled phase

A total of 245 subjects were enrolled (163 subjects were randomized to the apremilast group and 82 subjects were randomized to the placebo group). All 163 subjects (100%) in the apremilast group and 80 subjects (97.6%) in the placebo group received at least 1 dose of investigational product. In the apremilast and placebo groups, 149 subjects (91.4%) and 72 subjects (87.8%), respectively, completed the placebo-controlled phase. The most frequent reasons for discontinuation (≥ 3% of subjects in either treatment group [apremilast, placebo]) during the placebo-controlled phase included withdrawal by parent/guardian (3.1%, 3.7%) and adverse event (3.1%, 1.2%).

Subjects received treatment for a mean (SD) of 15.3 (3.0) weeks in the apremilast group and 15.2 (2.7) weeks in the placebo group (Table 28).

Table 30. Treatment Duration in the Placebo-controlled Phase (Weeks 0 to 16) (Safety Population)

Parameter	Placebo (N = 80)	Apremilast (N = 163)	Total (N = 243)
Treatment duration (weeks)[a]			
Mean	15.24	15.34	15.31
SD	2.649	2.977	2.868
Median	16.00	16.00	16.00
Q1, Q3	15.90, 16.10	15.90, 16.30	15.90, 16.10
Min, Max	3.7, 17.0	1.7, 18.0	1.7, 18.0
Treatment duration categories (weeks) - n (%)			
< 4	2 (2.5)	5 (3.1)	7 (2.9)
≥ 4 to < 8	1 (1.3)	3 (1.8)	4 (1.6)
≥ 8 to < 12	4 (5.0)	5 (3.1)	9 (3.7)
≥ 12 to < 16	20 (25.0)	33 (20.2)	53 (21.8)
≥ 16	53 (66.3)	117 (71.8)	170 (70.0)
Exposure category - n (%)			
≥ 1 day	80 (100)	163 (100)	243 (100)
≥ 4 weeks	78 (97.5)	158 (96.9)	236 (97.1)
≥ 8 weeks	77 (96.3)	155 (95.1)	232 (95.5)
≥ 12 weeks	73 (91.3)	150 (92.0)	223 (91.8)
≥ 16 weeks	53 (66.3)	117 (71.8)	170 (70.0)

IP = investigational product
[a] Treatment duration (in weeks) is calculated from the date of the first dose of IP at week 0/visit 2 to either the date 1 day before the first dose date in the apremilast extension phase for the IP dispense at week 16/visit 7, or the date of the last dose of IP in the study for subjects who discontinue in the phase.

Apremilast-exposure period

A total of 235 subjects were included in the apremilast-exposure period, defined as all subjects who received at least 1 dose of apremilast in the placebo-controlled phase and/or the apremilast extension phase. Of these, 119 subjects received apremilast 30 mg BID and 116 subjects received apremilast 20 mg BID. Overall, 186 apremilast-treated subjects (79.1%) completed the study, while 49 subjects (20.9%) discontinued treatment. The most frequent reasons for discontinuation (≥ 3% of subjects overall) during the apremilast-exposure period were withdrawal by parent/guardian (6.0%), lack of efficacy (4.7%), adverse event (3.8%), and withdrawal by subject (3.0%).

Overall, for the apremilast-exposure period, subjects had a mean (SD) exposure of 41.9 (13.7) weeks.

Table 31. Study PPSO-003 Treatment Duration in the Apremilast-exposure Period (Apremilast Subjects as Treated)

Parameter	20 mg BID (N=116)	30 mg BID (N=119)	Apremilast Total (N=235)
Treatment Duration (weeks)[a]			
n	116	119	235
Mean	42.79	41.09	41.93
SD	13.425	13.898	13.664
Median	51.70	51.30	51.70
Q1, Q3	36.10, 52.10	35.70, 52.00	36.00, 52.00
Min, Max	2.3, 58.9	1.7, 57.0	1.7, 58.9
Treatment Duration Categories (weeks) - n (%)			
< 4	2 (1.7)	3 (2.5)	5 (2.1)
>= 4 to < 8	3 (2.6)	3 (2.5)	6 (2.6)
>= 8 to < 12	3 (2.6)	2 (1.7)	5 (2.1)
>= 12 to < 16	0 (0.0)	1 (0.8)	1 (0.4)
>= 16 to < 20	3 (2.6)	2 (1.7)	5 (2.1)
>= 20 to < 24	0 (0.0)	4 (3.4)	4 (1.7)
>= 24 to < 28	2 (1.7)	1 (0.8)	3 (1.3)
>= 28 to < 32	1 (0.9)	2 (1.7)	3 (1.3)
>= 32 to < 36	8 (6.9)	17 (14.3)	25 (10.6)
>= 36 to < 40	26 (22.4)	19 (16.0)	45 (19.1)
>= 40 to < 44	1 (0.9)	5 (4.2)	6 (2.6)
>= 44 to < 48	1 (0.9)	0 (0.0)	1 (0.4)
>= 48 to < 52	16 (13.8)	12 (10.1)	28 (11.9)
>= 52	50 (43.1)	48 (40.3)	98 (41.7)
Exposure Category - n (%)			
>= 1 day	116 (100)	119 (100)	235 (100)
>= 4 weeks	114 (98.3)	116 (97.5)	230 (97.9)
>= 8 weeks	111 (95.7)	113 (95.0)	224 (95.3)
>= 12 weeks	108 (93.1)	111 (93.3)	219 (93.2)
>= 16 weeks	105 (90.5)	104 (87.4)	209 (88.9)
>= 24 weeks	105 (90.5)	104 (87.4)	209 (88.9)
>= 32 weeks	102 (87.9)	101 (84.9)	203 (86.4)
>= 36 weeks	94 (81.0)	84 (70.6)	178 (75.7)
>= 40 weeks	68 (58.6)	65 (54.6)	133 (56.6)
>= 48 weeks	66 (56.9)	60 (50.4)	126 (53.6)
>= 52 weeks	50 (43.1)	48 (40.3)	98 (41.7)

BID = twice daily
The 20 mg BID, 30 mg BID, and apremilast total groups include data during the apremilast treatment for subjects who received apremilast 20 mg BID, 30 mg BID, and either 20 or 30 mg BID regardless of whether the apremilast started at week 0 or week 16.
[a] Treatment duration for apremilast-exposure period is calculated from the date of the first dose of apremilast, which is the date of the first dose of apremilast after randomization at week 0/visit 2 or switched to apremilast at week 16/visit 7, to the last apremilast dose date for subjects who discontinue in the first 52 weeks or who complete the study at week 52/visit 16.

Study PPSO-002

This completed phase 2 open-label study's objectives included assessment of the safety, tolerability, and pharmacokinetics (PK) of apremilast in paediatric subjects with moderate to severe plaque psoriasis and was the first study of apremilast in children and adolescents aged 6 to 17 years.

The study had a 50-week open-label treatment period, comprised of an initial 2-week PK treatment period and a 48-week extension period, followed by an observational follow-up period with visits 4, 8, and 52 weeks after the last dose of apremilast. Subjects received weight-based dosing of apremilast throughout the treatment period. A staggered, stepwise approach by age range and weight (starting with older and heavier subjects) per dosing regimen was adopted, with doses for younger and lower body weight subjects adjusted based on safety and PK data from older and heavier subjects. Dose titration was not implemented in this study.

A total of 42 subjects were enrolled. Twenty-one adolescents (12 to 17 years of age) in Group 1 (13 subjects at APR 20 BID and 8 subjects at APR 30 BID), and 21 children (6 to 11 years of age) in Group 2 (APR 20 BID). All 42 subjects were included in the safety analysis set (all enrolled subjects who received at least 1 dose of apremilast).

A total of 31 (73.8%) subjects completed the Treatment Period. Overall, 11 subjects (26.2%) discontinued treatment, 6 subjects (28.6%) in Group 1 and 5 subjects (23.8) in Group 2. The most common reason for discontinuation in Group 1 was withdrawal by subject (4 subjects, 19.0%), and the most common reasons

for discontinuation in Group 2 were adverse event (2 subjects, 9.5%) and withdrawal by subject (2 subjects, 9.5%). Mean treatment duration was 42.49 weeks for group 1 and 41.31 weeks for group 2; 15/21 (71.4%) subjects in group 1 and 16/21 (76.2%) subjects in group 2 received at least 48 weeks of study treatment.

Study PPSO-004

All eligible subjects who completed the apremilast extension phase of Study PPSO-003 had the option of enrolling in Study PPSO-004, a separate phase 3b open-label long-term safety study.

The study consists of 2 phases: a long-term extension phase (up to 208 weeks) and an observational follow up phase (8 weeks). Treatment was assigned by weight category at visit 1. Subjects weighing 20 to < 50 kg received apremilast 20 mg BID, and subjects weighing ≥ 50 kg received apremilast 30 mg BID. Subjects who began the study receiving apremilast 20 mg BID and later record a body weight ≥ 50 kg are switched to apremilast 30 mg BID. This study is ongoing, and the analyses presented are based on interim data, with a database cutoff date of 27 March 2023 and a snapshot date of 10 May 2023. The submitted interim analysis CSR, as amended, is dated 18 September 2023.

In Study PPSO-004, safety data are presented for the long-term extension phase and the apremilast-exposure period. Safety analyses for both analysis periods were based on the long-term extension treatment population (all subjects who received at least 1 dose of apremilast in the extension study). The long-term extension phase includes safety data starting from the first apremilast dose date in the extension study (Study PPSO-004). The apremilast-exposure period includes safety data starting from the first apremilast dose date in the core study (Study PPSO-003) for all subjects who received at least 1 dose of apremilast in the extension study.

A total of 160 subjects were enrolled in the long-term extension study (Study PPSO-004) from the core study (Study PPSO-003). All subjects (100%) were treated through week 52 of the core study and received at least 1 dose of apremilast in the long-term extension study. As of the data cutoff date, 101 subjects (63.1%) were continuing the study, and 59 subjects (36.9%) had discontinued from the study. The most frequent reasons for discontinuation (≥ 3% of subjects overall) during the long-term extension phase included the subject turned 18 years of age (17.5%), withdrawal by parent/guardian (6.9%), lack of efficacy (4.4%), and withdrawal by subject (3.1%). No subjects have completed the study.

Results for the overall extend of exposure are summarized for the long-term extension phase and the apremilast-exposure period through the database cutoff date. In the long-term extension phase, subjects received treatment for a mean (SD) of 48.5 (36.3) weeks. For the apremilast-exposure period, subjects had a mean (SD) exposure of 95.4 (36.9) weeks (Table 30).

Table 32. Study PPSO-004 Treatment Duration in the Apremilast-exposure Period (From Study PPSO 003 to Study PPSO-004) (Long-term Extension Treatment Population)

Parameter	APR Total (N=160)
Treatment Duration (weeks)[a]	
n	160
Mean	95.38
SD	36.891
Median	85.15
Q1, Q3	65.10, 130.30
Min, Max	38.1, 193.3
Treatment Duration Categories (weeks) - n (%)	
< 1	0 (0.0)
≥ 1 to < 16	0 (0.0)
≥ 16 to < 32	0 (0.0)
≥ 32 to < 48	1 (0.6)
≥ 48 to < 52	13 (8.1)
≥ 52 to < 65	21 (13.1)
≥ 65 to < 78	29 (18.1)
≥ 78 to < 91	27 (16.9)
≥ 91 to < 104	9 (5.6)
≥ 104 to < 130	19 (11.9)
≥ 130 to < 156	21 (13.1)
≥ 156 to < 182	18 (11.3)
≥ 182 to < 208	2 (1.3)
≥ 208 to < 234	0 (0.0)
≥ 234 to < 260	0 (0.0)
≥ 260	0 (0.0)
Exposure Category - n (%)	
≥ 1 day	160 (100)
≥ 16 weeks	160 (100)
≥ 32 weeks	160 (100)
≥ 48 weeks	159 (99.4)
≥ 52 weeks	146 (91.3)
≥ 65 weeks	125 (78.1)
≥ 78 weeks	96 (60.0)
≥ 91 weeks	69 (43.1)
≥ 104 weeks	60 (37.5)
≥ 130 weeks	41 (25.6)
≥ 156 weeks	20 (12.5)
≥ 182 weeks	2 (1.3)
≥ 208 weeks	0 (0.0)
≥ 234 weeks	0 (0.0)
≥ 260 weeks	0 (0.0)

APR = apremilast
[a] Treatment duration is calculated from the first APR dose date in Study PPSO-003 to the last APR dose date in Study PPSO-004 for completed subjects or to the latest study date for ongoing subjects.

Adverse events

Study PPSO-003

A treatment-emergent adverse event (TEAE) or adverse event (AE) in the placebo-controlled phase was defined as an adverse event with a start date on or after the first IP dose date in placebo-controlled phase and before the first dose date in apremilast extension phase or within 28 days of the last dose date for subjects who only received placebo-controlled phase treatment. A TEAE in the apremilast-exposure period was defined as an adverse event with a start date on or after the first apremilast dose date and within 28 days of the last apremilast dose date. Therefore, TEAEs reported for subjects treated with apremilast in the placebo-controlled phase were also included in the apremilast-exposure period analysis.

Serious adverse events (SAEs) were defined as per protocol. Severity of AEs/SAEs were assigned by the investigator as mild, moderate, or severe. The relationship between the administration of the IP and the occurrence of an AE/SAE as 'not suspected' or 'suspected' was determined by the investigator as per protocol.

In addition to the crude subject incidence of events, the exposure-adjusted incidence rate, EAIR, (per 100 subject-years) was also calculated. EAIR per 100 SY was 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).

Summary of overall TEAEs

An overview of TEAEs reported for the placebo-controlled phase and in the apremilast-exposure period are provided in Table 31 and Table 32, respectively.

Table 33. Overview of Treatment-emergent Adverse Events in the Placebo controlled Phase (Week 0 to 16) (Safety Population)

	Placebo (N = 80, SY = 23.4)		20 mg BID (N = 80, SY = 23.7)		30 mg BID (N = 83, SY = 24.3)		Apremilast Total (N = 163, SY = 47.9)	
	n (%)	EAIR/ 100 SY	n (%)	EAIR/ 100 SY	n (%)	EAIR/ 100 SY	n (%)	EAIR/ 100 SY
Subjects with any TEAE	33 (41.3)	201.3	58 (72.5)	576.4	51 (61.4)	417.7	109 (66.9)	489.4
Subjects with any drug-related TEAE	12 (15.0)	55.7	36 (45.0)	240.2	34 (41.0)	216.4	70 (42.9)	228.0
Subjects with any severe TEAE	1 (1.3)	4.3	2 (2.5)	8.5	0 (0.0)	0.0	2 (1.2)	4.2
Subjects with any serious TEAE	1 (1.3)	4.3	2 (2.5)	8.5	0 (0.0)	0.0	2 (1.2)	4.2
Subjects with any serious drug-related TEAE	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Subjects with any TEAE leading to drug interruption	2 (2.5)	8.6	6 (7.5)	25.8	3 (3.6)	12.7	9 (5.5)	19.2
Subjects with any TEAE leading to drug withdrawal	1 (1.3)	4.3	3 (3.8)	12.7	2 (2.4)	8.3	5 (3.1)	10.5
Subjects with any TEAE leading to death	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0

BID = twice daily; EAIR = exposure-adjusted incidence rate; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; SY = subject-years; TEAE = treatment-emergent adverse event
A TEAE in the placebo-controlled phase is an adverse event with a start date on or after the first IP dose date in placebo-controlled phase and before the first dose date in apremilast extension phase or within 28 days of the last dose date for subjects who only received placebo-controlled phase treatment. Adverse events are coded using MedDRA version 25.1.
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).

Table 34. Overview of Treatment-emergent Adverse Events in the Apremilast exposure Period (Apremilast Subjects as Treated)

	20 mg BID (N = 116, SY = 95.1)		30 mg BID (N = 119,SY = 93.7)		Apremilast Total (N = 235,SY = 188.9)	
	n (%)	EAIR/100 SY	n (%)	EAIR/100 SY	n (%)	EAIR/100 SY
Subjects with Any TEAE	88 (75.9)	255.1	80 (67.2)	197.8	168 (71.5)	224.2
Subjects with Any Drug-related TEAE	45 (38.8)	72.9	47 (39.5)	75.3	92 (39.1)	74.1
Subjects with Any Severe TEAE	2 (1.7)	2.1	2 (1.7)	2.2	4 (1.7)	2.1
Subjects with Any Serious TEAE	2 (1.7)	2.1	2 (1.7)	2.2	4 (1.7)	2.1
Subjects with Any Serious Drug-related TEAE	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Subjects with Any TEAE Leading to Drug Interruption	10 (8.6)	10.9	6 (5.0)	6.6	16 (6.8)	8.8
Subjects with Any TEAE Leading to Drug Withdrawal	5 (4.3)	5.3	4 (3.4)	4.3	9 (3.8)	4.8
Subjects with Any TEAE Leading to Death	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0

BID = twice daily; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; SY = subject-years; TEAE = treatment-emergent adverse event
A TEAE in the apremilast-exposure period is an adverse event with a start date on or after the first apremilast dose date and within 28 days of the last apremilast dose date. Adverse events are coded using MedDRA version 25.1.
Subject incidence is 100 times the number (n) of subjects reporting the event divided by N.
EAIR per 100 subject-years is defined as 100 times the number (n) of subjects reporting the specific event divided by subject-years within the period (up to the first event start date for subjects reporting the event).

Common TEAEs

Common TEAEs, those with subject incidence ≥ 5% in any treatment group by SOC and PT are reported for the placebo-controlled phase and apremilast-exposure period in Table 33 and Table 34, respectively.

Table 35. Treatment-emergent Adverse Events With Subject Incidence ≥ 5% in Any Treatment Group by System Organ Class and Preferred Term in the Placebo controlled Phase (Weeks 0 to 16) (Safety Population)

System Organ Class Preferred Term	Placebo (N = 80, SY = 23.4)		20 mg BID (N = 80, SY = 23.7)		30 mg BID (N = 83, SY = 24.3)		Apremilast Total (N = 163, SY = 47.9)	
	n (%)	EAIR/ 100 SY	n (%)	EAIR/ 100 SY	n (%)	EAIR/ 100 SY	n (%)	EAIR/ 100 SY
Number of subjects reporting TEAEs	33 (41.3)	201.3	58 (72.5)	576.4	51 (61.4)	417.7	109 (66.9)	489.4
Gastrointestinal disorders								
Diarrhoea	8 (10.0)	36.7	15 (18.8)	74.3	17 (20.5)	86.0	32 (19.6)	80.1
Nausea	2 (2.5)	8.6	15 (18.8)	74.2	17 (20.5)	85.3	32 (19.6)	79.7
Abdominal pain	8 (10.0)	37.0	23 (28.8)	128.0	9 (10.8)	40.7	32 (19.6)	79.8
Vomiting	2 (2.5)	8.7	16 (20.0)	77.7	13 (15.7)	60.7	29 (17.8)	69.0
Dyspepsia	0 (0.0)	0.0	3 (3.8)	13.1	7 (8.4)	31.3	10 (6.1)	22.1
Abdominal pain upper	4 (5.0)	17.8	5 (6.3)	22.2	4 (4.8)	17.1	9 (5.5)	19.6
General disorders and administration site conditions								
Pyrexia	1 (1.3)	4.3	7 (8.8)	31.6	3 (3.6)	12.7	10 (6.1)	21.9
Infections and infestations								
Nasopharyngitis	3 (3.8)	13.1	5 (6.3)	22.0	5 (6.0)	21.2	10 (6.1)	21.6
Influenza	1 (1.3)	4.3	5 (6.3)	21.9	2 (2.4)	8.4	7 (4.3)	15.0
Infections and infestations								
COVID-19	5 (6.3)	22.1	2 (2.5)	8.6	3 (3.6)	12.7	5 (3.1)	10.7
Nervous system disorders								
Headache	4 (5.0)	17.8	12 (15.0)	57.0	5 (6.0)	21.7	17 (10.4)	38.6

BID = twice-daily; EAIR = exposure-adjusted incidence rate; IP = investigational product; SY = subject-years; TEAE = treatment-emergent adverse event
Includes preferred terms where at least 5% subjects with at least 1 TEAE in 1 treatment group.
A TEAE in the placebo-controlled phase is an adverse event with a start date on or after the first IP dose date in placebo-controlled phase and before the first dose date in apremilast extension phase or within 28 days of the last dose date for subjects who only received placebo-controlled phase treatment. Adverse events are coded using Medical Dictionary for Regulatory Activities version 25.1.
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 SY within the phase (up to the first event start date for subjects reporting the event).

Table 36. Study PPSO-003 Treatment-emergent Adverse Events With Subject Incidence ≥ 5% in Any Treatment Group by System Organ Class and Preferred Term in the Apremilast-exposure Period (Apremilast Subjects as Treated)

System Organ Class Preferred Term	20 mg BID (N = 116, SY = 95.1)		30 mg BID (N = 119, SY = 93.7)		Apremilast Total (N = 235, SY = 188.9)	
	n (%)	EAIR/ 100 SY	n (%)	EAIR/ 100 SY	n (%)	EAIR/ 100 SY
Number of subjects reporting TEAEs	88 (75.9)	255.1	80 (67.2)	197.8	168 (71.5)	224.2
Gastrointestinal disorders						
Nausea	29 (25.0)	37.4	23 (19.3)	29.9	52 (22.1)	33.7
Diarrhoea	25 (21.6)	32.3	23 (19.3)	30.6	48 (20.4)	31.5
Abdominal pain	32 (27.6)	44.0	13 (10.9)	15.3	45 (19.1)	28.5
Vomiting	27 (23.3)	34.6	17 (14.3)	20.4	44 (18.7)	27.3
Abdominal pain upper	9 (7.8)	10.1	4 (3.4)	4.4	13 (5.5)	7.2
Dyspepsia	3 (2.6)	3.3	9 (7.6)	10.4	12 (5.1)	6.7
Abdominal distension	6 (5.2)	6.5	5 (4.2)	5.6	11 (4.7)	6.1
General disorders and administration site conditions						
Pyrexia	11 (9.5)	12.6	3 (2.5)	3.3	14 (6.0)	7.8
Infections and infestations						
Nasopharyngitis	12 (10.3)	13.5	8 (6.7)	8.9	20 (8.5)	11.2
Influenza	9 (7.8)	10.1	4 (3.4)	4.4	13 (5.5)	7.2
COVID-19	6 (5.2)	6.5	5 (4.2)	5.5	11 (4.7)	6.0
Nervous system disorders						
Headache	17 (14.7)	20.3	8 (6.7)	9.2	25 (10.6)	14.6
Skin and subcutaneous tissue disorders						
Psoriasis	6 (5.2)	6.4	13 (10.9)	14.3	19 (8.1)	10.3

BID = twice-daily; EAIR = exposure-adjusted incidence rate; IP = investigational product; SY = subject-years; TEAE = treatment-emergent adverse event
Includes PT where at least 5% subjects with at least 1 TEAE in 1 treatment group.
A TEAE in the apremilast-exposure period is an adverse event with a start date on or after the first apremilast dose date and within 28 days of the last apremilast dose date. Adverse events are coded using Medical Dictionary for Regulatory Activities version 25.1.
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 SY within the period (up to the first event start date for subjects reporting the event).

Study PPSO-001

An overview of all reported TEAEs in the safety population are reported in Table 37. TEAEs are reported by group 1, group 2 and both groups combined, and within each group by dosage regimen.

Table 37. Overview of Treatment-emergent Adverse Events (Safety Population)

	Group 1 (Adolescents[a])			Group 2 (Children[b])	Group 1 and 2		
	APR 20 BID (N = 13)	APR 30 BID (N = 8)	Total (N = 21)	APR 20 BID (N = 21)	APR 20 BID (N = 34)	APR 30 BID (N =8)	Total (N = 42)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects With any TEAE	13 (100)	7 (87.5)	20 (95.2)	20 (95.2)	33 (97.1)	7 (87.5)	40 (95.2)
Subjects With any Drug-related TEAE	11 (84.6)	6 (75.0)	17 (81.0)	17 (81.0)	28 (82.4)	6 (75.0)	34 (81.0)
Subject With any Severe TEAE	1 (7.7)	0	1 (4.8)	1 (4.8)	2 (5.9)	0	2 (4.8)
Subjects With any Serious TEAE	0	0	0	1 (4.8)	1 (2.9)	0	1 (2.4)
Subjects With any TEAE Leading to Drug Interruption	1 (7.7)	0	1 (4.8)	4 (19.0)	5 (14.7)	0	5 (11.9)
Subjects With any TEAE Leading to Drug Withdrawal	0	0	0	2 (9.5)	2 (5.9)	0	2 (4.8)
Subjects With any TEAE Leading to Death	0	0	0	0	0	0	0

APR 20 BID = apremilast 20 mg twice daily; APR 30 BID = apremilast 30 mg twice daily; TEAE = treatment-emergent adverse event.
[a] Adolescents are 12 to 17 years of age.
[b] Children are 6 to 11 years of age.
A TEAE was an adverse event with a start date on or after the date of the first dose of apremilast and no later than 28 days after the last dose of apremilast.
The N value is the number of subjects in the Safety Population. Each subject was counted once for each applicable category. Subject incidence was 100 times the number (n) of subjects reporting the event divided by N.

Common TEAEs with a subject incidence ≥ 5% overall by PT are presented in Table 38.

Table 38. Study PPSO-001 Adverse Events With Subject Incidence ≥ 5% Overall by Preferred Term (Safety Population)

	Group 1 (Adolescents[a])			Group 2 (Children[b])	Group 1 and 2		
	APR 20 BID (N = 13)	APR 30 BID (N = 8)	Total (N = 21)	APR 20 BID (N = 21)	APR 20 BID (N = 34)	APR 30 BID (N = 8)	Total (N = 42)
Preferred Term[c]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects With any TEAE	13 (100)	7 (87.5)	20 (95.2)	20 (95.2)	33 (97.1)	7 (87.5)	40 (95.2)
Nausea	8 (61.5)	4 (50.0)	12 (57.1)	10 (47.6)	18 (52.9)	4 (50.0)	22 (52.4)
Headache	7 (53.8)	1 (12.5)	8 (38.1)	11 (52.4)	18 (52.9)	1 (12.5)	19 (45.2)
Abdominal Pain	6 (46.2)	1 (12.5)	7 (33.3)	11 (52.4)	17 (50.0)	1 (12.5)	18 (42.9)
Nasopharyngitis	6 (46.2)	3 (37.5)	9 (42.9)	7 (33.3)	13 (38.2)	3 (37.5)	16 (38.1)
Diarrhoea	6 (46.2)	4 (50.0)	10 (47.6)	5 (23.8)	11 (32.4)	4 (50.0)	15 (35.7)
Vomiting	4 (30.8)	1 (12.5)	5 (23.8)	8 (38.1)	12 (35.3)	1 (12.5)	13 (31.0)
Gastroenteritis	2 (15.4)	1 (12.5)	3 (14.3)	5 (23.8)	7 (20.6)	1 (12.5)	8 (19.0)
Abdominal Pain Upper	2 (15.4)	1 (12.5)	3 (14.3)	4 (19.0)	6 (17.6)	1 (12.5)	7 (16.7)
Cough	3 (23.1)	1 (12.5)	4 (19.0)	2 (9.5)	5 (14.7)	1 (12.5)	6 (14.3)
Abdominal Distension	1 (7.7)	1 (12.5)	2 (9.5)	3 (14.3)	4 (11.8)	1 (12.5)	5 (11.9)
Oropharyngeal Pain	2 (15.4)	0	2 (9.5)	3 (14.3)	5 (14.7)	0	5 (11.9)
Decreased Appetite	2 (15.4)	1 (12.5)	3 (14.3)	1 (4.8)	3 (8.8)	1 (12.5)	4 (9.5)
Dyspepsia	2 (15.4)	1 (12.5)	3 (14.3)	1 (4.8)	3 (8.8)	1 (12.5)	4 (9.5)
Pyrexia	1 (7.7)	1 (12.5)	2 (9.5)	2 (9.5)	3 (8.8)	1 (12.5)	4 (9.5)
Urinary Tract Infection	1 (7.7)	2 (25.0)	3 (14.3)	0	1 (2.9)	2 (25.0)	3 (7.1)
Gastroenteritis Viral	2 (15.4)	0	2 (9.5)	1 (4.8)	3 (8.8)	0	3 (7.1)
Influenza	2 (15.4)	0	2 (9.5)	1 (4.8)	3 (8.8)	0	3 (7.1)
Dysmenorrhoea	2 (15.4)	0	2 (9.5)	1 (4.8)	3 (8.8)	0	3 (7.1)
Eosinophil Count Increased	0	0	0	3 (14.3)	3 (8.8)	0	3 (7.1)
Protein Urine Present	1 (7.7)	0	1 (4.8)	2 (9.5)	3 (8.8)	0	3 (7.1)
Insomnia	2 (15.4)	0	2 (9.5)	1 (4.8)	3 (8.8)	0	3 (7.1)

APR 20 BID = apremilast 20 mg twice daily; APR 30 BID = apremilast 30 mg twice daily; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAE = treatment-emergent adverse event.
[a] Adolescents are 12 to 17 years of age.
[b] Children are 6 to 11 years of age.
[c] Preferred terms were coded using the MedDRA (Version 22.0). Preferred terms were sorted in descending order based on group 1 and group 2 total incidence.
A TEAE was an adverse event with a start date on or after the date of the first dose of apremilast and no later than 28 days after the last dose of apremilast.
The N value is the number of subjects in the Safety Population. Each subject was counted once for each applicable specific TEAE and a subject with multiple TEAEs within an SOC was counted once for that SOC. Subject incidence was 100 times the number (n) of subjects reporting the event divided by N.

Study PPSO-004

An overview of TEAEs reported for the long-term extension phase and in the apremilast-exposure period are provided in Table 39 and 40, respectively.

Table 39. Overview of Treatment-emergent Adverse Events in Study PPSO-004 (Long-term Extension Treatment Population)

	APR Total (N=160, SY=148.8)	
	n (%)	EAIR/100 SY
Subjects with Any TEAE	55 (34.4)	51.7
Subjects with Any Drug-related TEAE	13 (8.1)	9.4
Subjects with Any Severe TEAE	3 (1.9)	2.0
Subjects with Any Serious TEAE	4 (2.5)	2.7
Subjects with Any Serious Drug-related TEAE	0 (0.0)	0.0
Subjects with Any TEAE Leading to Drug Interruption	10 (6.3)	7.2
Subjects with Any TEAE Leading to Drug Withdrawal	4 (2.5)	2.7
Subjects with Any TEAE Leading to Death	0 (0.0)	0.0

APR = apremilast; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; SY = total subject-years of exposure to investigational product; TEAE = treatment-emergent adverse event
A TEAE in PPSO-004 is an adverse event with a start date on or after the first dose date in PPSO-004 and no later than 28 days after the last dose date in PPSO-004.
Adverse events were coded using MedDRA version 25.1.
Each subject is counted once for each applicable category. Subject incidence is 100 times the number (n) of subjects reporting the event divided by N.
Exposure-adjusted incidence rate per 100 subject-years is defined as 100 times the number (n) of subjects with the specific event divided by subject-years in PPSO-004 (up to the first event start date for subjects reporting the event).

Table 40. Overview of Treatment-emergent Adverse Events in the Apremilast-exposure Period (From Study PPSO-003 to Study PPSO-004) (Long-term Extension Treatment Population)

	APR Total (N=160, SY=292.5)	
	n (%)	EAIR/100 SY
Subjects with Any TEAE	121 (75.6)	127.1
Subjects with Any Drug-related TEAE	55 (34.4)	27.8
Subjects with Any Severe TEAE	3 (1.9)	1.0
Subjects with Any Serious TEAE	5 (3.1)	1.7
Subjects with Any Serious Drug-related TEAE	0 (0.0)	0.0
Subjects with Any TEAE Leading to Drug Interruption	18 (11.3)	6.7
Subjects with Any TEAE Leading to Drug Withdrawal	4 (2.5)	1.4
Subjects with Any TEAE Leading to Death	0 (0.0)	0.0

APR = apremilast; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; SY = total subject-years of exposure to investigational product; TEAE = treatment-emergent adverse event
A TEAE in the apremilast-exposure period is an adverse event with a start date on or after the first apremilast dose date in PPSO-003 and within 28 days of the last dose date in PPSO-004.
Adverse events were coded using MedDRA version 25.1.
Each subject is counted once for each applicable category. Subject incidence is 100 times the number (n) of subjects reporting the event divided by N.
Exposure-adjusted incidence rate per 100 subject-years is defined as 100 times the number (n) of subjects reporting the specific event divided by subject-years within the period (up to the first event start date for subjects reporting the event).

Throughout the long-term extension phase, there were no adverse events reported for ≥ 5% of subjects. The most frequently reported (≥ 3% of subjects) adverse events were 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%). Common TEAEs, those with subject incidence ≥ 5% in any treatment group by SOC and PT are reported for the apremilast-exposure period in Table 41.

Table 41. Table 1 Treatment-emergent Adverse Events with Subject Incidence ≥ 5% by System Organ Class and Preferred Term in the Apremilast-exposure Period (From Study PPSO-003 to Study PPSO-004) (Long-term Extension Treatment Population)

System Organ Class Preferred Term	APR Total (N=160, SY=292.5)	
	n (%)	EAIR/100 SY
Number of subjects reporting treatment-emergent adverse events	121 (75.6)	127.1
Gastrointestinal disorders		
Diarrhoea	38 (23.8)	16.7
Abdominal pain	36 (22.5)	15.9
Nausea	35 (21.9)	15.0
Vomiting	31 (19.4)	12.7
Abdominal pain upper	11 (6.9)	4.0
Dyspepsia	10 (6.3)	3.6
General disorders and administration site conditions		
Pyrexia	11 (6.9)	4.1
Infections and infestations		
COVID-19	15 (9.4)	5.5
Respiratory tract infection viral	14 (8.8)	5.1
Influenza	12 (7.5)	4.4
Nasopharyngitis	12 (7.5)	4.3
Nervous system disorders		
Headache	19 (11.9)	7.3
Skin and subcutaneous tissue disorders		
Psoriasis	11 (6.9)	3.8

APR = apremilast; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; SY = total subject-years of exposure to investigational product; TEAE = treatment-emergent adverse event
Includes preferred terms where at least 5% subjects with at least 1 TEAE in 1 treatment arm.
A TEAE in the apremilast-exposure period is an adverse event with a start date on or after the first apremilast dose date in PPSO-003 and within 28 days of the last dose date in PPSO-004.
Adverse events were coded using MedDRA version 25.1.
Each subject is counted once for each applicable category. Subject incidence is 100 times the number (n) of subjects reporting the event divided by N.
Exposure-adjusted incidence rate per 100 subject-years is defined as 100 times the number (n) of subjects reporting the specific event divided by subject-years within the period (up to the first event start date for subjects reporting the event).

TEAE comparison between paediatric and adult studies

Adverse events are presented from both the paediatric pivotal Study PPSO-003, and from the 2 pivotal phase 3 studies (CC-10004-PSOR-008 and CC-10004-PSOR-009) that supported the indication in adults with moderate to severe plaque psoriasis in Table 42 and Table 43.

Table 42. Adverse Events with Subject Incidence ≥ 5% in any Treatment Group by SOC/PT in Placebo-controlled Phase (Weeks 0 16) (Adult and Paediatric Psoriasis Phase 3 Studies: Safety Population)

	Adult Phase 3 Studies				Pediatric Phase 3 Study			
	Placebo (N=418, Subj-yrs=116.5)		Apremilast 30 mg BID (N=832, Subj-yrs=236.8)		Placebo (N=80, Subj-yrs=23.4)		Apremilast 20 or 30 mg BID (N=163, Subj-yrs=47.9)	
System Organ Class Preferred Term	n (%)	EAIR/100 Subj-yrs	n (%)	EAIR/100 Subj-yrs	n (%)	EAIR/100 Subj-yrs	n (%)	EAIR/100 Subj-yrs
Any TEAEs	239 (57.2)	350.3	573 (68.9)	536.4	33 (41.3)	201.3	109 (66.9)	489.4
Gastrointestinal disorders								
Diarrhoea	28 (6.7)	25.5	148 (17.8)	74.2	8 (10.0)	36.7	32 (19.6)	80.1
Nausea	28 (6.7)	25.3	138 (16.6)	68.2	2 (2.5)	8.6	32 (19.6)	79.7
Abdominal pain	6 (1.4)	5.2	17 (2.0)	7.3	8 (10.0)	37.0	32 (19.6)	79.8
Vomiting	7 (1.7)	6.1	31 (3.7)	13.4	2 (2.5)	8.7	29 (17.8)	69.0
Dyspepsia	4 (1.0)	3.5	25 (3.0)	10.8	0 (0.0)	0.0	10 (6.1)	22.1
Abdominal pain upper	4 (1.0)	3.5	18 (2.2)	7.7	4 (5.0)	17.8	9 (5.5)	19.6
General disorders and administration site conditions								
Pyrexia	5 (1.2)	4.3	3 (0.4)	1.3	1 (1.3)	4.3	10 (6.1)	21.9
Infections and infestations								
Nasopharyngitis	29 (6.9)	25.9	61 (7.3)	26.8	3 (3.8)	13.1	10 (6.1)	21.6
Influenza	7 (1.7)	6.1	7 (0.8)	3.0	1 (1.3)	4.3	7 (4.3)	15.0
COVID-19	0 (0.0)	0.0	0 (0.0)	0.0	5 (6.3)	22.1	5 (3.1)	10.7
Upper respiratory tract infection	27 (6.5)	23.9	70 (8.4)	30.9	0 (0.0)	0.0	2 (1.2)	4.2
Nervous system disorders								
Headache	14 (3.3)	12.4	48 (5.8)	21.2	4 (5.0)	17.8	17 (10.4)	38.6
Tension headache	14 (3.3)	12.4	61 (7.3)	27.5	0 (0.0)	0.0	0 (0.0)	0.0

Note: TEAE = Treatment-emergent adverse event. SOC/PT = System organ class/Preferred term. Subj-yrs = Total subject years of exposure to investigational product (IP). Safety population included subjects who received at least one dose of IP.
Adult Phase 3 studies included CC-10004-PSOR-008 and PSOR-009. Adverse events were coded using MedDRA version 14; Pediatric Phase 3 study included CC-10004-PPSO-003 (20200056). Adverse events were coded using MedDRA version 25.1. A TEAE was an adverse event with a start date on or after the date of the first dose of IP and no later than 28 days after the last dose of IP. TEAEs for placebo-controlled phase (weeks 0 to 16) were included. Each subject was counted once for each applicable category. Subject incidence was 100 times the number (n) of subjects reporting the event divided by N. Exposure-adjusted incidence rate (EAIR) per 100 subject-years was 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

Table 43. Adverse Events with Subject Incidence ≥ 5% in any Treatment Group in Apremilast Exposure Period (Weeks 0 to 52) (Adult and Paediatric Psoriasis Phase 3 Studies: Apremilast Subjects as Treated)

	Adult Phase 3 Studies		Pediatric Phase 3 Study	
	Apremilast 30 mg BID (N=1184, Subj-yrs=900.1)		Apremilast 20 or 30 mg BID (N=235, Subj-yrs=188.9)	
System Organ Class Preferred Term	n (%)	EAIR/100 Subj-yrs	n (%)	EAIR/100 Subj-yrs
Subjects with Any TEAE	936 (79.1)	317.2	168 (71.5)	224.2
Gastrointestinal disorders				
Nausea	185 (15.6)	23.9	52 (22.1)	33.7
Diarrhoea	205 (17.3)	26.9	48 (20.4)	31.5
Abdominal pain	34 (2.9)	3.9	45 (19.1)	28.5
Vomiting	57 (4.8)	6.5	44 (18.7)	27.3
Abdominal pain upper	28 (2.4)	3.2	13 (5.5)	7.2
Dyspepsia	42 (3.5)	4.8	12 (5.1)	6.7
Abdominal distension	9 (0.8)	1.0	11 (4.7)	6.1
General disorders and administration site conditions				
Pyrexia	5 (0.4)	0.6	14 (6.0)	7.8
Infections and infestations				
Nasopharyngitis	166 (14.0)	20.4	20 (8.5)	11.2
Upper respiratory tract infection	183 (15.5)	22.9	4 (1.7)	2.1
Infections and infestations				
Influenza	23 (1.9)	2.6	13 (5.5)	7.2
COVID-19	0 (0.0)	0.0	11 (4.7)	6.0
Nervous system disorders				
Headache	74 (6.3)	8.6	25 (10.6)	14.6
Tension headache	106 (9.0)	12.9	0 (0.0)	0.0
Skin and subcutaneous tissue disorders				
Psoriasis	27 (2.3)	3.0	19 (8.1)	10.3

BID= twice a day, EAIR= exposure-adjusted incidence rate, N = number of subjects, n = number of subjects with a TEAE, TEAE = treatment-emergent adverse event, Subj-yrs = total subject years of exposure to investigational product.
Apremilast subjects as treated included subjects who received at least one dose of apremilast.
Adult phase 3 studies included CC-10004-PSOR-008 and PSOR-009. Data for the first 52 weeks of apremilast exposure were included regardless of when apremilast exposure started (week 0 or week 16). Adverse events were coded using MedDRA version 14.
Pediatric phase 3 study included CC-10004-PPSO-003 (20200056). Data for apremilast exposure of the whole study through Week 52 visit were included regardless of when apremilast exposure started (week 0 or week 16). Adverse events were coded using MedDRA version 25.1.
A TEAE was an adverse event with a start date on or after the date of the first dose of apremilast and no later than 28 days after the last dose of apremilast.
Each subject was counted once for each applicable category. Subject incidence was 100 times the number (n) of subjects reporting the event divided by N. Exposure-adjusted incidence rate per 100 subject-years was 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

Serious adverse event/deaths/other significant events

Study PPSO-003

Serious adverse events

During the placebo-controlled phase, serious adverse events were reported for 2 subjects (1.2%) in the apremilast group and 1 subject (1.3%) in the placebo group. No preferred term was reported for more than 1 subject. The preferred terms were psoriasis, autonomic nervous system imbalance, iron deficiency anaemia, sinus tachycardia, and wandering pacemaker in the apremilast group and testicular appendage torsion in the placebo group.

For the apremilast-exposure period, serious adverse events were reported for 4 subjects (1.7%), which included the SAEs reported in the apremilast arm of the placebo-controlled phase. No preferred term was reported for more than 1 subject. The preferred terms were psoriasis, status migrainosus, autonomic nervous system imbalance, appendicitis, iron deficiency anaemia, sinus tachycardia, and wandering pacemaker.

For all SAEs reported in the study, no serious adverse events in the gastrointestinal disorders system organ class were reported, and the investigator considered the adverse event relationship to IP to be 'not suspected'.

Deaths

There were no deaths reported in the study.

Gastrointestinal Events

Gastrointestinal adverse events, defined as adverse events in the gastrointestinal disorders system organ class, were reported for 78 subjects (47.9%) in the apremilast group and 16 subjects (20.0%) in the placebo group. The most frequently reported (≥ 5% of subjects in any group) gastrointestinal adverse events (apremilast, placebo) were diarrhoea (19.6%, 10.0%), abdominal pain (19.6%, 10.0%), nausea (19.6%, 2.5%), vomiting (17.8%, 2.5%), abdominal pain upper (5.5%, 5.0%), and dyspepsia (6.1%, 0.0%). No adverse events of anorexia were reported during the placebo-controlled phase.

No severe or serious gastrointestinal adverse events were reported during the placebo-controlled phase.

Gastrointestinal adverse events leading to discontinuation of IP during the placebo-controlled phase were reported for 5 subjects (3.1%) in the apremilast group and 0 subjects (0.0%) in the placebo group. The preferred terms included abdominal pain (3 subjects [1.8%]) and abdominal pain upper, nausea, and vomiting (each 1 subject [0.6%]).

Data from Stool Diaries for diarrhoea, defined as ≥ 3 liquid or watery stools in a day, were also presented by frequency, duration, and symptoms. The frequency of diarrhoea generally decreased over the course of treatment during the placebo-controlled phase for subjects in the apremilast group.

Gastrointestinal adverse events were reported for 113 subjects (48.1%) during the apremilast-exposure period. The most frequently reported (≥ 5% of subjects) gastrointestinal adverse events were nausea (22.1%), diarrhoea (20.4%), abdominal pain (19.1%), vomiting (18.7%), abdominal pain upper (5.5%), and dyspepsia (5.1%). No adverse events of anorexia were reported.

Severe gastrointestinal adverse events were reported for 1 subject (0.4%); the preferred term was abdominal pain. No serious gastrointestinal adverse events were reported.

Gastrointestinal adverse events leading to discontinuation of investigational product during the apremilast-exposure period were reported for 7 subjects (3.0%); the most frequently reported (≥ 2 subjects) adverse events leading to treatment discontinuation were abdominal pain and vomiting (each 3 subjects [1.3%]).

Psychiatric Events

No suicidal ideation or behaviour was reported based on results from the Columbia-Suicide Severity Rating Scale (C-SSRS) during the placebo-controlled phase. However, 1 subject (1.3%) in the placebo group had an adverse event of suicidal ideation that led to discontinuation of investigational product compared with no subjects in the apremilast group. Other adverse events reported in the psychiatric disorders system organ class during the placebo-controlled phase (apremilast, placebo) included insomnia (0.6%, 1.3%), anxiety (0.6%, 0.0%), and sleep disorder (0.6%, 0.0%). No adverse events with the preferred term depression were reported during the placebo-controlled phase.

No suicidal ideation or behaviour was reported based on results from the C-SRRS during the apremilast-exposure period.

Physical findings

Weight, height, BMI:

The MAH states that during the placebo-controlled period, no notable differences between treatment groups were observed for changes from baseline in body weight, height, or body mass index during the placebo-controlled phase. The median percent changes from baseline to end of the 16-week placebo-controlled phase for the apremilast and placebo groups, respectively, were 0.00% and 3.07% for weight, 0.39% and 0.60% for height, and -0.92% and 2.04% for body mass index.

The majority of subjects who were within the age-appropriate healthy BMI range at baseline remained in their age-appropriate BMI range throughout the placebo-controlled phase (97.1% apremilast, 92.3% placebo)

At any visit during the 16-week placebo-controlled phase, 2 subjects randomized to apremilast (one in each treatment arm) had weight decreases > 10% from baseline weight (maximum 13.0%) measured before or on the date of randomization.

The median percent changes from baseline to end of the apremilast-exposure period were 2.17% for weight, 1.27% for height, and -0.93% for body mass index.

At any visit during the apremilast-exposure period, 14 subjects had weight decreases > 10% from baseline weight (defined as the last value measured before or on the date of randomization [subjects randomized to apremilast] or the date of the week 16 visit [subjects randomized to placebo who switched to apremilast at week 16]), which included 1 subject originally randomized to placebo and 2 subjects originally randomized to apremilast who continued on the study beyond week 16 and received apremilast.

Weight decrease in 13 of these 14 subjects occurred during the treatment period and the maximum decrease was 14.3%. One subject had a weight decrease >10% from baseline (11.4%) during the observational follow-up phase. Subjects that experienced weight decrease of > 10% from baseline weight were evenly distributed between apremilast 20 mg BID and 30 mg BID treatment arms.

Tanner staging:

Tanner Staging results were consistent with the expected development for boys and girls aged 6 to 17 years during the apremilast-exposure period.

Psoriasis Flare and Rebound

Psoriasis flare was reported for 2 subjects (1.2%) in the apremilast group and 3 subjects (3.8%) in the placebo group. During the apremilast-exposure period, psoriasis flare was reported for 18 subjects (7.7%).

Psoriasis rebound, defined as an adverse event of psoriasis that started after the last dose date for subjects who received treatment in the study, was reported for 4 subjects (9.1%) after apremilast treatment.

Hypersensitivity

No PTs were reported for hypersensitivity during the apremilast-exposure period.

Study PPSO-001

Serious adverse events

One subject receiving APR 20 BID in Group 2 experienced an SAE of moderate syncope that was not suspected to be related to IP.

Death

No death was reported.

Gastrointestinal events

The incidence of TEAEs SOC GI disorders PTs diarrhoea, nausea, abdominal pain, and vomiting was high in Groups 1 and 2. Notwithstanding the small number of subjects in the APR 30 mg BID arm of Group 1, there was a notable imbalance in the incidence rates of these PTs between treatment regimens, with significantly higher rates reported in the APR 20 mg BID arm.

One TEAE SOC GI disorder was reported as severe: One (7.7%) subject receiving APR 20 BID in Group 1 experienced 1 severe TEAE each of headache and abdominal pain on study Day 1 that resolved the next day; both TEAEs were suspected to be related to IP.

Onset of diarrhoea and nausea were reported to mostly have occurred within the first month of treatment and generally resolved within 3 days.

No dose titration was implemented in this study.

Psychiatric events

One subject in Group 1 (APR 20 BID) answered "yes" to "Wish to be dead" and "yes" to "Engaged in non-suicidal self-injurious behaviour" in the C-SSRS scale at Week 32. The subject was discontinued. Subsequent psychiatric evaluations were negative, and there was no risk of suicide. The other 41 subjects answered "no" at all time points up to the end of treatment.

There were 3 reported TEAEs of PT insomnia (mild or moderate), in 2 subjects in Group 1 and 1 subject in Group 2. All were in APR 20 MG BID treatment arms. One subject, a 7-year-old subject, withdrew after experiencing multiple TEAEs (crying, headache, and sleep disorder) on study Day 2 that were suspected to be related to investigational product (IP).

There were two reported TEAEs of PT anxiety (mild) and no reported TEAEs of PT depression during the study.

Physical findings

Weight, height, BMI:

Mean and median weight increased from Baseline over time. Three subjects in Group 1 had >10% weight loss from Baseline. These were reported to be due to the following reasons: 1 subject increased physical activity, 1 subject was counselled to lose weight, and 1 subject lost weight intentionally.

Tanner staging:

Tanner Staging assessment was consistent with the expected development for boys and girls ages 6 to 17 years.

Hypersensitivity

There were no reported TEAEs of hypersensitivity.

Study PPSO-004

Serious adverse events

Serious adverse events were reported for 4 subjects (2.5%) in the long-term extension phase (from safety data starting from the first apremilast dose date in this extension study). Serious adverse events reported were phimosis, abdominal pain, headache, and acute kidney injury (1 subject each). One subject (0.6%) had a serious adverse event in the gastrointestinal disorders system organ class (abdominal pain).

Case narratives have been provided for all subjects. In each case, the investigator considered the AE relationship to IP to be 'not suspected'. No action was taken with the IP.

Death

No deaths have been reported in this ongoing study.

Gastrointestinal events

TEAEs by SOC GI disorder and PT for the long-term extension treatment phase were reported as follows:

System Organ Class	APR Total (N=160,Subj-yrs=148.8)	
Preferred Term	n (%)	EAIR/100 Subj-yrs
Number of subjects reporting treatment-emergent adverse events	55 (34.4)	51.7
Gastrointestinal disorders	16 (10.0)	11.8
Vomiting	7 (4.4)	4.8
Abdominal pain	5 (3.1)	3.5
Nausea	5 (3.1)	3.5
Diarrhoea	3 (1.9)	2.1
Abdominal pain upper	2 (1.3)	1.3
Constipation	2 (1.3)	1.4
Dyspepsia	1 (0.6)	0.7
Food poisoning	1 (0.6)	0.7
General disorders and administration site conditions	5 (3.1)	3.4
Pyrexia	2 (1.3)	1.4

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TEAE = Treatment-emergent adverse event. SOC/PT = System organ class/Preferred term. APR = Apremilast. Subj-yrs = Total subject years of exposure to investigational product.
A TEAE in PPSO-004 is an adverse event with a start date on or after the first dose date in PPSO-004 and no later than 28 days after the last dose date in PPSO-004.
Adverse events are coded using MedDRA version 25.1.
Each subject is counted once for each applicable category. Subject incidence is 100 times the number (n) of subjects reporting the event divided by N.
Exposure-adjusted incidence rate (EAIR) per 100 subject-years is defined as 100 times the number (n) of subjects with the specific event divided by subject-years in PPSO-004 (up to the first event start date for subjects reporting the event).

All events were reported as mild to moderate. One event PT 'abdominal pain syndrome' in a subject (APR 20 mg BID) was categorised as an SAE. The investigator considered the AE relationship to IP to be 'not suspected'. No action was taken with the IP.

One event of PT abdominal pain upper and one event of PT vomiting were reported in two different subjects, both receiving APR 20 mg BID, and resulted in withdrawal from the study. The formed was 'not suspected' to be related to the IP. The latter was 'suspected' to be related to the IP.

Psychiatric events

No suicidal ideation or behaviour was reported on the C-SSRS during the long-term extension phase. No adverse events with the preferred term depression, suicidal ideation, or suicidal behaviour were reported during the long-term extension phase. Other adverse events reported in the SOC psychiatric disorders during the long-term extension phase included anxiety (n=2; 1.3%), mental disorder (n=1; 0.6%) and tic (n=1; 0.6%). All events were reported as mild or moderate. One event of anxiety and the event of mental disorder were considered to have a 'suspected' relationship to the IP.

The adverse event mental disorder led to discontinuation of the investigational product in one subject. The event occurred in an 8-year-old female, with medical history of 'affect lability', 'attention deficit hyperactivity disorder' and 'bicuspid aortic valve'. The subject received apremilast (20 mg BID) during the double-blind phase and continued to receive apremilast until the event 'other psychiatric event, a nervous breakdown [mental disorder]' of moderate intensity occurred at Day 477 after first dose. Then, the IP was discontinued. No treatment was reported. The event ended the day after with an outcome of recovered/ resolved.

Physical findings

Weight, height, BMI:

Three subjects had weight decreases > 10% at any visit from baseline weight, as measured before or on the date of the first dose of apremilast in the long-term extension study (PPSO-004), with the maximum weight loss being 13.6%. Of these, 1 subject had weight loss > 10% at their last visit in the long-term extension study.

Tanner staging:

Tanner Staging assessment was consistent with the expected development for boys and girls ages 6 to 17 years during the apremilast-exposure period.

Psoriasis Flare and Rebound

Psoriasis flare was reported for 5 subjects (3.1%) in the long-term extension phase. Psoriasis rebound was not reported for any subjects. During the apremilast-exposure period, any psoriasis flare was reported in 12 subjects (7.5%): psoriasis was reported for 11 subjects (6.9%), and guttate psoriasis was reported for 1 subject (0.6%). Psoriasis rebound was not reported for any subjects.

Hypersensitivity

Although, no preferred terms were reported for hypersensitivity in the study, 5 events were identified from the hypersensitivity standardized MedDRA query. All events were mild, and none were serious.

Laboratory findings

Study PPSO-003

No clinically meaningful mean changes from baseline in laboratory values were noted in the double-blind, placebo-controlled phase for haematology and serum chemistry. No clinically meaningful shifts in laboratory parameters (low, normal, high) were noted at any postbaseline visits in the double-blind, placebo-controlled phase for haematology and serum chemistry. Overall, marked laboratory abnormalities reported during the placebo-controlled phase were infrequent. The only marked laboratory abnormality reported for ≥ 10% of subjects in any group during the placebo-controlled phase was haemoglobin > 150 g/L (apremilast: 18.5%; placebo: 22.8%). None of the laboratory abnormalities reported as adverse events were serious, none led to interruption or discontinuation of apremilast, and none were not considered clinically meaningful.

No clinically meaningful mean changes from baseline in laboratory values were noted in the apremilast-exposure period for haematology and serum chemistry. No clinically meaningful shifts in laboratory parameters (low, normal, high) were noted at any postbaseline visits in the apremilast-exposure period for haematology and serum chemistry. The marked laboratory abnormality reported for ≥ 10% of subjects were haemoglobin > 150 g/L (23.5%), potassium > 5.4 mmol/L (13.6%), and phosphate < 1.03 mmol/L (12.8%). Of note, the frequency of haemoglobin > 150 g/L in the apremilast-exposure period (23.5%) is similar to the frequency in the placebo group in the double-blind, placebo-controlled phase (22.8%). One subject experienced elevated creatinine leading to discontinuation of apremilast during the extension phase; the event was nonserious and was not associated with any other adverse events. None of the other laboratory abnormalities reported as adverse events led to dose discontinuation or interruption, and none were serious. The laboratory abnormalities reported during the apremilast-exposure period were not considered clinically meaningful.

Study PPSO-001

No clinically meaningful mean changes in haematology variables or chemistry variables were observed. Overall, marked laboratory abnormalities (laboratory values that may have clinical relevance) were infrequent during the study. One subject (4.8%) in group 2 experienced an adverse event of eosinophilia that led discontinuation of investigational product and was not suspected to be related to investigational product.

Study PPSO-004

In the long-term extension phase, the only marked laboratory abnormality reported in ≥ 10% of subjects was haemoglobin > 150 g/L (16.9%). This was not considered clinically meaningful.

No clinically meaningful mean changes from baseline in laboratory values were noted in the apremilast-exposure period for haematology and serum chemistry. No clinically meaningful shifts in laboratory parameters (low, normal, high) were noted at any postbaseline visits in the apremilast-exposure period for haematology and serum chemistry. The marked laboratory abnormalities reported in ≥ 10% of subjects were haemoglobin > 150 g/L (23.8%), potassium > 5.4 mmol/L (19.4%), phosphate < 1.03 mmol/L (15.6%), phosphate > 1.94 mmol/L (12.5%), and neutrophils < 1.5 (12.5%). The marked laboratory abnormalities were not considered clinically meaningful. No adverse events that were laboratory abnormalities were serious or led to dose interruption or discontinuation.

Safety in special populations

Intrinsic factors

Adverse events were analysed by intrinsic factor subgroups of age, sex, and race in Study PPSO-003. No meaningful differences were observed in the types of adverse events reported across subgroups of age, sex, and race.

Use in pregnancy and lactation

There were no pregnancies reported in Study PPSO-001, Study PPSO-003, or Study PPSO-004. No new information on use of apremilast in pregnancy and lactation is available for this submission.

Subjects with renal impairment

No data from paediatric patients with severe renal impairment are available from Study PPSO-001, Study PPSO-003, or Study PPSO-004.

Discontinuation due to adverse events

Study PPSO-003

During the placebo-controlled phase, adverse events leading to discontinuation of investigational product were reported for 5 subjects (3.1%) in the apremilast group and 1 subject (1.3%) in the placebo group.

The only preferred term reported for more than 1 subject was abdominal pain (apremilast: 3 subjects [1.8%]; placebo: 0 subjects [0.0]. One subject (1.3%) in the placebo group had an adverse event of suicidal ideation that led to drug withdrawal compared with 0 subjects (0.0%) in the apremilast group.

For the apremilast-exposure period, adverse events leading to discontinuation of investigational product were reported for 9 subjects (3.8%). The most frequently reported (≥ 2 subjects) adverse events leading to discontinuation were abdominal pain and vomiting (each 3 subjects [1.3%]).

Study PPSO-001

Two (4.8%) subjects experienced a TEAE leading to study drug withdrawal in Study PPSO-001. One subject withdrew after experiencing mild TEAEs of crying, headache, and sleep disorder on study Day 2 that were suspected to be related to investigational product (IP). One subject withdrew after experiencing a severe TEAE of eosinophilia on study Day 196 that was not suspected to be related to IP.

Study PPSO-004

In the long-term extension phase of the study, adverse events leading to discontinuation of investigational product were reported for 4 subjects (2.5%). PTs were abdominal pain upper, vomiting, mental disorder, and psoriasis. None were reported as severe or as an SAE.

Post marketing experience

Adult patients

As of 20 March 2023, the overall cumulative exposure to apremilast is estimated to be 858 164 patients from all geographic areas, which includes worldwide commercial exposure (848 111 patients, including 846059 in Amgen territories and 2 052 patients in Amgen business partner territories), company-sponsored study exposure (10038 subjects), and early access programme exposure (15 patients).

The safety profile of apremilast in the post-marketing setting remains similar to that observed in the registrational psoriasis and psoriatic arthritis clinical programme. The adverse events most frequently reported post-approval have been gastrointestinal (diarrhoea, nausea, vomiting, and abdominal discomfort) and nervous system disorders (headache). The reporting rates for events of interest in the postmarketing setting have not changed since apremilast was launched. No new relevant safety concern with respect to reporting rates or event information has been identified.

Paediatric patients

Otezla is not authorised in any country for use in children. The MAH received postmarketing reports of adverse events in children who received apremilast for various conditions off-label. The MAH's Global Safety Database was searched for reports of postmarking adverse events in patients less than 18 years of age from all reporting sources received from the first marketing approval of apremilast on 21 March 2014 to 20 March 2023. A total of 1389 paediatric cases in the postmarketing setting were identified. A total of 2481 adverse events (serious and nonserious) from these cases were reviewed. The most frequently reported adverse event preferred term for these cases was off-label use.

As per the MAH, overall, similar types of adverse events were observed between the paediatric and adult populations.

2.5.1. Discussion on clinical safety

In this procedure, the MAH applied to extend the indications of apremilast to include the use in the paediatric population with moderate to severe plaque psoriasis from 6 years and above. The analysis of the safety profile of apremilast in paediatric subjects with moderate to severe plaque psoriasis is primarily based on the results from phase 3 Study PPSO-003 and supported by results from phase 2 Study PPSO-001. Interim safety data from the long-term extension phase 3b, Study PPSO-004, are presented to provide additional information on the long-term safety of apremilast in paediatric subjects with moderate to severe plaque psoriasis.

In Study PPSO-003, exposure to apremilast 20 mg BID (N=116) and 30 mg BID (N=119) dosage regimens was well balanced, with a mean treatment duration of 42.79 and 41.09 weeks, respectively. The number of subjects exposed to ≥ 52 weeks treatment for the 20 mg BID and 30 mg BID arms was n=50 (43.1 %) and n=48 (40.3%), respectively. Adherence to treatment was good with 79.1% of subjects completing the study, and low rates of discontinuation due to adverse events.

Interim safety data from the long-term extension Study PPSO-004, were presented in support of the long-term safety of apremilast in paediatric subjects. As of the data cutoff date, 101 subjects (63.1%) were continuing the study and discontinuation due to adverse events was low. Subjects in the apremilast-exposure period (from Study PPSO 003 to Study PPSO-004) had a mean treatment duration of 95.4 weeks.

A total of 277 paediatric subjects received apremilast in the paediatric clinical studies (phase 2 [42 subjects] and phase 3 [235 subjects]; phase 3b includes 160 subjects from Study PPSO-003]). Overall, the extent of exposure and submitted safety database are considered adequate to characterise the safety profile of apremilast in the paediatric population for the proposed indication, and to allow for comparison to pooled safety data from the pivotal adult phase 3 studies. Further long-term data will be available from Study PPSO-004.

In Study PPSO-003, adverse events were reported for 66.9% subjects in the apremilast group in the placebo-controlled phase and for 71.5% subjects in the apremilast-exposure period. The majority of TEAEs were mild to moderate in severity. Serious adverse events were reported for 4 subjects, with none being considered related to the IP. No fatal events were reported. Adverse events leading to discontinuation were low.

The most frequently reported adverse events throughout the phase 3 study were diarrhoea, abdominal pain, nausea, vomiting, and headache. This is overall consistent with the known safety profile of apremilast in the adult population. As TEAE incidence was also presented by EAIR per 100 subject years, it was evident that there was no increasing incidence of any particular TEAE with exposure to apremilast.

Imbalances in reported TEAEs were observed in the phase 3 study between apremilast treatment arms (APR 20 mg BID and APR 30 mg BID), including those in SOC GI disorders and PTs abdominal pain, vomiting and abdominal pain upper, and SOC nervous system disorders and PT headache, with a higher incidence in subjects weighing less than 50 kg. Upon the CHMP's request, the MAH discussed the imbalance in GI disorders between apremilast and placebo, the greatest difference being in the population who received the 20mg dose. This imbalance did not lead to great weight loss in the lower weight population. No PI update was needed since the risk of GI disturbances with the use of apremilast is already captured in section 4.8 of the SmPC. The MAH discussed also the imbalance in nervous system disorders. In the placebo-controlled phase, the overall incidence of nervous system disorders adverse events was higher in subjects who received apremilast 20 mg BID compared with subjects who received apremilast 30 mg BID (20% vs 7.2%). All events, excluding one, were non-serious. No events led to treatment discontinuation. No PI update was recommended since headache is captured in section 4.8 of the SmPC as a 'very common' adverse reaction.

Interim data from the phase 3b study is consistent with that from the phase 3. The most frequently reported adverse events in the long-term extension phase were COVID-19, vomiting, abdominal pain, headache, nausea, psoriasis, and respiratory tract infection viral. Unlike the phase 3 study, TEAEs were not presented by treatment group (20 mg or 30 mg BID). Based on EAIR per 100 subject years, there is no evidence of an increased incidence of severe TEAEs, serious TEAEs, or TEAEs leading to drug withdrawal with longer term exposure to apremilast.

Data from the phase 2 study did not identify any new safety signals. The most frequently reported TEAEs by preferred term were nausea, headache, abdominal pain, viral upper respiratory tract infection, diarrhoea, and vomiting. Similar to that of the phase 3 study, imbalances between apremilast treatment arms were observed. The phase 2 study was largely a dose-finding study, subject numbers were small, and no dose titration was implemented.

In terms of adverse events of particular interest, including psychiatric events (suicidal ideation or behaviour, depression, anxiety, sleep disorders etc), hypersensitivity, psoriasis flare and rebound, no safety concerns in the paediatric population were identified in the pivotal or supporting studies.

From a gastrointestinal safety perspective, in line with the established safety profile in adults, GI-related TEAEs were most commonly reported in the phase 3 study. Despite the high incidence, only one was reported as severe. None were reported as a serious adverse event. Seven subjects (3.0%) were withdrawn from the apremilast exposure period due to a GI-related TEAE. EAIR per 100 subject years and stool diaries showed GI-events tended to occur earlier in treatment and decline with time.

In terms of assessment of growth and development, in all studies, Tanner Staging results were consistent with the expected development for boys and girls aged 6 to 17 years during the apremilast-exposure period. No notable differences between treatment groups were observed for changes from baseline in body weight, height, or body mass index during the study, and the majority of subjects who were within the age-appropriate healthy BMI range at baseline remained in their age-appropriate BMI range throughout the apremilast-exposure period of the study. However, during the phase 3 study and the long-term extension period of the phase 3b study, at any visit during the apremilast-exposure period, 14 and 3 subjects, respectively, had weight decreases $>$ 10% from baseline weight. The CHMP noted that 'body weight loss' is already captured in the warning section 4.4 of the SmPC of the existing product information for the adult population. However, the CHMP requested an update the warning to highlight the need for monitoring in paediatric patients with borderline or low body weight, to which the MAH agreed.

Safety data from Study PPSO-003 were also presented side-by-side with pooled safety data from the prior pivotal placebo-controlled psoriasis studies in adults to compare the safety profile of apremilast in the adult and paediatric moderate to severe plaque psoriasis populations. Whilst the MAH has stated that safety data presented from the phase 3 study are consistent with the pooled adult safety data, imbalances (higher incidence in the paediatric population) for GI and nervous system related TEAEs were observed. As discussed previously, no PI updates were recommended following review of these imbalances.

No safety data were submitted in support of use in a paediatric population with impaired renal function. Recommendations to reduce dosing in severe renal impairment have been supported by model-based simulations based on data from adults with severe renal impairment (CC-10004-Study CP-019) and from non-renally impaired paediatric subjects in Study PPSO-003. The CHMP acknowledged the absence of data for use in paediatrics with impaired renal function. Nevertheless, the CHMP agreed to recommend reduced dosing recommendations for paediatric patients with severe renal impairment where the recommended dosages are apremilast 20 mg once daily for patients weighing 20 kg to less than 50 kg and 30 mg once daily for patients weighing at least 50 kg. For initial dosage titration in these patients, it is recommended that apremilast be titrated as per Table 2 in section 4.2 of the SmPC for the AM schedule for the appropriate body weight category and to skip the PM dose. Caution on use in *severe renal*

impairment in section 4.4 of the SmPC has been expanded to include reduced dosing recommendations for the paediatric population with reference to revised sections 4.2 and 5.2 of the SmPC.

Safety data on use of apremilast beyond 1 year in paediatric patients are limited but will be monitored through routine pharmacovigilance and additional data provided from the ongoing phase 3b study PPSO-004.

2.5.2. Conclusions on clinical safety

The safety profile of Otezla in children and adolescents, from 6 through 17 years, with moderate to severe plaque psoriasis, based on the submitted safety database, is overall consistent with that observed in the adult population. No new safety signals have been identified.

No concerns relating to adverse events of particular interest, including psychiatric events and hypersensitivity reactions were raised by submitted data. Evaluation of the clinical consequences and management of 'body weight loss' in the paediatric population was provided. The MAH highlights that there were no paediatric participants with low BMI at the end of the study and that some of those who had >10% body weight loss were classed as obese at baseline. The MAH highlights that there does not appear to be an impact on growth. Adequate warning is implemented in SmPC Section 4.4 to highlight the need for monitoring in paediatric patients with borderline or low body weight.

Regarding the use of apremilast in paediatric patients with severe renal impairment, dosage adjustment of reduced dosing and warning are appropriately reflected in the SmPC Sections 4.2, 4.4 and 5.2.

Safety data on use of apremilast beyond 1 year in paediatric patients are limited but will be monitored through routine pharmacovigilance and additional data provided from the ongoing phase 3b study.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 15.2 is acceptable.

Safety concerns

Important identified risks	• Serious events of hypersensitivity • Suicidality • Serious events of depression
Important potential risks	• Vasculitis • Malignancies • Serious events of anxiety and nervousness

	• Serious infections including opportunistic infections and transmission of infections through live vaccines • MACE and tachyarrhythmia • Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast
Missing information	• Long-term safety

MACE = major adverse cardiovascular event

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Apremilast PsA Registry in the UK – BSRBR-PsA (CC-10004-PSA-012) Safety Outcomes for Psoriatic Arthritis Patients Treated with Otezla in the British Society for Rheumatology Biologics Register in Psoriatic Arthritis (BSRBR-PsA) Ongoing	To collect long-term data on specified AESIs in real world setting.	• Serious events of hypersensitivity • Suicidality • Serious events of depression • Vasculitis • Malignancies • Serious events of anxiety and nervousness • Serious infections including opportunistic infections and transmission of infections through live vaccines • MACE and tachyarrhythmia • Long-term safety	Final protocol for BSRBR-PsA registry: Enrollment initiated: 1-year report submission date: 2-year report submission date: 3-year report submission date: 4-year report submission date: 5-year report due date: 7-year report due date:	16 October 2018 Q4 2018 23 June 2020 21 June 2021 07 June 2022 21 June 2023 24 June 2024 Q3 2026

AESI = adverse event of special interest; BSRBR = British Society for Rheumatology Biologics Register; MACE = major adverse cardiac events; PsA = psoriatic arthritis; UK = United Kingdom

Risk minimisation measures

No additional risk minimisation measures.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated.

As a consequence of the new pack sizes, to introduce two new pack sizes (27 film-coated tablets (4 x 10 mg, 23 x 20 mg) and 14 film-coated tablets (14 x 20mg), in a pack size of 56 tablets), sections 6.5 and 8

of the SmPC are updated.

The Package Leaflet has been updated accordingly. Changes were also made to the PI to bring it in line with the current QRD template.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Malta.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The new indication with this application is for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years and weighing at least 20 kg who are candidates for systemic therapy. The proposed modifications to the package leaflet, do not alter the instructions for the safe usage of Otezla. The previous user tested report approved as part of the adult indication still applies to the amended Package Leaflet (PL). The following reasons have been given, and are accepted, for relying on the existing user testing report:

- The MAH confirms there are no changes to the design and layout information as a result of this variation.
- The MAH confirms the concept and style of writing and language used is same as the previous approved PL.
- The MAH confirms the key messages for safety are still carried in the same style and can be understood in the same manner as in the previously approved PL.
- The MAH confirms the updates do not affect the layout of critical safety sections of the PL.
- The MAH confirms there is no complexity of language used in the updated text and the style of language is similar to the previously approved PL.
- The MAH confirms the updated text can be clearly translated into other EU languages.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Psoriasis is a chronic, inflammatory skin disorder that is estimated to affect up to 2.5% of the world's population (Christophers, 2001[15]). The worldwide prevalence of psoriasis in children ranges from 0% to 1.37%. In Europe, the prevalence of paediatric psoriasis ranges between 0.17% and 1.5% (Peris et al, 2022[16]). European populations have a higher prevalence than African and Asian populations (Michalek et al, 2017[17]).

Plaque psoriasis is the most common form of the disease in both adults and children, characterized by erythematous plaques with silvery white scales (Lebwohl, 2003[18]; Weinstein and Menter, 2003[19]). The

[15] Christophers E. Psoriasis - epidemiology and clinical spectrum. Clin Exp Dermatol. 2001 Jun;26(4):314-20.
[16] Peris, Ketty, et al. "Update on the management of pediatric psoriasis: an Italian consensus." Dermatology and Therapy 12.8 (2022): 1753-1775.
[17] Michalek IM, Loring B, John SM A systemic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017 Feb;31(2):205-212.
[18] Lebwohl M. Psoriasis. Lancet. 2003;361:1197-1204.
[19] Weinstein GD, Menter MA. An overview of psoriasis. In: eds. Weinstein GD, Gottlieb AB. Therapy of moderate to severe psoriasis. New York, NY. National Psoriasis Foundation. 2003; 1-28.

symptoms of psoriasis, including, but not limited to, scaling, flaking, itching, soreness, and pain of the skin, can have considerable detrimental effects on a patient's quality of life, ability to function in daily activities, and overall social and societal engagement (Armstrong et al, 2012[20]). In addition, psoriasis in both adults and children is associated with a variety of comorbid conditions such as psoriatic arthritis, obesity, dyslipidaemia, metabolic syndrome, and cardiovascular disease (Menter et al, 2020[21]; Elmets et al, 2019[22]).

3.1.2. Available therapies and unmet medical need

The treatment options for paediatric patients with plaque psoriasis remain limited. Current therapeutic options include topical agents for mild, localized psoriasis, phototherapy for older children and adolescents with extensive areas of involvement or refractory plaque disease, and systemic medications for more extensive or refractory disease (Marqueling and Cordoro, 2013[23]; Shah, 2013[24]; Vogel et al, 2012[25]). Systemic medications utilized in children with moderate to severe plaque psoriasis include conventional therapies, such as methotrexate, retinoids, and cyclosporine, or biologics. However, fewer therapies, including antibody therapies across mechanisms of action, are approved for paediatric patients with moderate to severe plaque psoriasis compared with adults.

Systemic therapies approved for paediatric patients with moderate to severe plaque psoriasis include biologic medications. However, injection site reactions, infections, reactivation of tuberculosis, congestive heart failure, and new onset or exacerbation of demyelinating diseases may be safety concerns of these agents. Baseline and regular monitoring are advised for these biological therapies. In addition, fear of needles is common in children and can contribute to negative experiences with the use of biologics (McMurtry et al, 2016[26]).

As a result of the limitations of the treatment landscape, many children are treated off-label with the same agents approved for adults (Stahle et al, 2010[27]), despite limited safety and efficacy information to support the use of these agents in a paediatric population. Thus, there remains an unmet need for effective systemic therapies that offer convenient oral dosing and a favourable benefit-risk profile for the treatment of paediatric patients with moderate to severe plaque psoriasis.

3.1.3. Main clinical studies

The paediatric development program was designed to evaluate the efficacy, safety, and pharmacokinetics of apremilast in paediatric patients with moderate to severe plaque psoriasis. The programme includes the following clinical studies:

- Study CC-10004-PPSO-001 (20200171; hereafter referred to as PPSO-001): A Phase 2, Multicenter, Open Label Study to Assess the Safety, Tolerability and Pharmacokinetics of Apremilast (CC-10004) in Paediatric Subjects with Moderate to Severe Plaque Psoriasis (completed)

[20] Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation survey data 2003-2011. PLoS One. 2012;7(12):e52935.
[21] Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology- National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. J Am Acad Dermatol. 2020 Jan;82(1):161-201.
[22] Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol. 2019 Apr;80(4):1073-1113.
[23] Marqueling AL, Cordoro KM. Systemic treatments for severe pediatric psoriasis: a practical approach. Dermatol Clin. 2013 Apr;31(2):267-88.
[24] Shah KN. Diagnosis and treatment of pediatric psoriasis: Current and future. Am J Clin Dermatol. 2013 Jun;14(3):195-213.
[25] Vogel SA, Yentzer B, Davis SA, Feldman SR, Cordoro KM. Trends in pediatric psoriasis outpatient health care delivery in the United States. Arch Dermatol. 2012;148(1):66-71.
[26] McMurtry CM, Taddio A, Noel M, et al. Exposure-based interventions for the management of individuals with high levels of needle fear across the lifespan: a clinical practice guideline and call for further research. Cogn Behav Ther. 2016 Apr;45(3):217- 35.
[27] Ståhle M, Atakan N, Boehncke WH, et al. Juvenile psoriasis and its clinical management: a European expert group consensus. J Dtsch Dermatol Ges. 2010 Oct;8(10):812-818.

- Study CC-10004-PPSO-003 (20200056; hereafter referred to as PPSO-003): A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Apremilast (CC-10004) in Paediatric Subjects from 6 through 17 Years of Age with Moderate to Severe Plaque Psoriasis (completed)
- Study CC-10004-PPSO-004 (20200057; hereafter referred to as PPSO-004): A Phase 3B, Multi-Center, Open-Label Long-Term Extension Study of Apremilast (CC-10004) in Paediatric Subjects from 6 through 17 Years of Age with Moderate to Severe Plaque Psoriasis (ongoing)

3.2. Favourable effects

The primary endpoint of sPGA response at week 16 was achieved in study PPSO-003. In the ITT population, 33.1% of subjects in the apremilast group and 11.5% of subjects in the placebo group achieved an sPGA response of clear (0) or almost clear (1) with at least a 2-point reduction from baseline based on the MI method. The adjusted treatment difference was statistically significant (21.7% [95% CI: 11.2, 32.1]; $p < 0.0001$).

The key secondary endpoint of PASI-75 response at week 16 was also achieved. At week 16, 45.4% of subjects in the apremilast group and 16.1% of subjects in the placebo group achieved a PASI-75 response based on the MI method. The adjusted treatment difference was statistically significant (29.4% [95% CI: 17.8, 40.9]; $p < 0.0001$).

Other Secondary Endpoints (PASI-50 response at week 16, PASI percent change from baseline at week 16, CDLQI total score change from baseline at week 16) showed a nominally statistically significant improvement in the apremilast treatment group compared to placebo.

During the apremilast extension phase, 47.7% of subjects in the apremilast group (as randomized and entered the apremilast extension phase) and 44.4% of subjects in the placebo group (as randomized and entered the apremilast extension phase) achieved an sPGA response at week 52 (NRI analysis).

A total of 60.4% of subjects in the apremilast group (as randomized and entered the apremilast extension phase) and 63.9% of subjects in the placebo group (as randomized and entered the apremilast extension phase) achieved a PASI-75 response at week 52. Subjects who transitioned from placebo to apremilast during the apremilast extension phase showed improvements in all efficacy measures similar to those in the treatment group who received apremilast during the entire study.

The sPGA treatment effect compared to placebo in both the paediatric Study PPSO-003 (21.7%; 95% CI 11.2% to 32.1%) and the adult phase 3 studies (apremilast adjusted difference in response rate with placebo (17.2%; 95% CI 13.9% to 20.6%) are overall comparable. The treatment effect in adolescents aged 12-17 years and ≥50kg was most similar to the adult study outcome (treatment effect compared to placebo adjusted difference 16.6% (95% CI 7.2 to 27.8).

Similarly, a significantly greater PASI-75 response rate was reported in the apremilast group as compared to the placebo group in both the paediatric Study PPSO-003 (29.4% 95% CI 17.8% to 40.9%) and the adult phase 3 studies (adjusted difference 26.2%; 95% CI 22.4% to 30.0%).

3.3. Uncertainties and limitations about favourable effects

The population included in the pivotal study PPS0-003 was paediatric patients 6 years and above who were inadequately controlled by or inappropriate for topical therapy for psoriasis and who were candidates for systemic therapy or phototherapy. The majority of participants randomised in this study were systemic treatment naïve. The MAH initially proposed a second-line indication after systemic therapy or phototherapy not in line with the inclusion criteria of the pivotal study, this was not agreed by the CHMP. Upon the CHMP's

request, the MAH revised the wording of the indication in accordance with the inclusion criteria of the pivotal study i.e. for use in patients who are candidates for systemic therapy. A broader indication reflects the population studied in the pivotal clinical trial, Study PPSO-003, in which most subjects had not used a systemic therapy or phototherapy prior to enrolment. To support the use of apremilast in paediatric patients with an inadequate response to other systemic therapy or phototherapy, the MAH justified extrapolation of safety and efficacy response from studies in adults that both adults and children over 6 years of age have a similar clinical presentation and the PK exposure response relationship is similar in both groups. To further support a similar clinical response in adults and children, the MAH presented data comparing efficacy in children and adults with prior systemic therapy. This is agreed by the CHMP.

Further, the CHMP noted that the paediatric inclusion criteria specify inclusion of children with a cut-off from age 6 years weighing at least 20 kg. This weight threshold falls within the 50th and the 25th centile for 6-year-old boys and at approximately the 50th centile for 6-year-old girls. The posology excludes subjects < 20 kg weight whereas a non-negligible proportion of subjects in the lower age range will have a weight < 20 kg. The MAH agreed to include a weight restriction in the indication i.e. for children weighing at least 20 kg. This is in line with the population in the pivotal clinical trial and in line with EMA guidance on when it is relevant to include bodyweight limit in the wording of a paediatric indication EMA/268908/2023.

The dosing recommendations by weight are supported by subgroup analyses, although significant variability in the observed treatment effect was observed by weight and age. This variability by age group underlines the importance of weight-based posology for apremilast.

The presented sub-group analyses for the primary efficacy parameter sPGA and for PASI75 response show imbalances. This raised the question of plausibility of the effect.

Therefore, the MAH was requested to further discuss these imbalances, e.g. greater sPGA responders rates in females compared to males, the variable magnitude of the treatment effect across and within age and weight subgroups, e.g. the treatment effect is most evident in children under 6 to 11 years of age with BW<50kgs, whereas there is a lack of effect in the age 12-17 and ≥ 20 to < 50 kg subgroup. The MAH was also asked to discuss the possible role of underdosing and overdosing in these outcomes**.** The MAH could not fully explain the observed difference in response in children aged between 12-17 years. The observed difference may be due to an enhanced placebo response in this age group or to the limited numbers in each subgroup. The data overall trends towards a response to treatment when PASI-75 is taken into account. The MAH will continue to monitor in the PSUR reports of lack of efficacy in in this adolescent group.

Responders to treatment were not randomised either to active drug or to placebo to characterise the duration of remission/response and time to rebound. Given the similarities in the exposure response and clinical response between adults and children, the CHMP accepted the MAH's position that a similar loss of efficacy would be expected in children and that treatment should be continued with a therapeutic dose to maintain efficacy.

Among subjects who continued receiving apremilast in the long-term extension study, the interim data available indicate evidence of maintenance of effect.

Efficacy of apremilast in psoriasis affecting the nails, palms and soles was not evaluated.

3.4. Unfavourable effects

The safety profile of apremilast is consistent in the adult and paediatric moderate to severe plaque psoriasis populations. No new risks have been identified in the paediatric population.

Although the incidence of TEAEs was high (71.5% in the apremilast-exposure period of the pivotal phase 3 study), the majority of TEAEs were mild or moderate in severity and the incidence of SAEs was low. EAIRs per 100 subject years did not show an increase in the incidence of TEAEs with prolonged exposure to apremilast.

The most commonly reported adverse reactions in phase 3 clinical trials in adults and in paediatrics were gastrointestinal disorders, including diarrhoea, nausea, and abdominal pain. No serious gastrointestinal adverse events were reported in the paediatric phase 3 study.

The paediatric safety database has not raised additional concerns relating to the important identified risks and important potential risks.

Apremilast was generally well tolerated in the pivotal phase 3 and ongoing phase 3b studies as seen by the low discontinuation rates due to adverse events.

3.5. Uncertainties and limitations about unfavourable effects

Observed imbalances in the incidence of TEAEs between the apremilast 20 mg BID and 30 BID treatment arms of the pivotal phase 3 study have given rise to concern that there may be greater risk associated with use in the lower weight (less than 50 kg) population with respect to certain gastrointestinal and nervous system related TEAEs. The side-by-side comparison of adult and paediatric data highlighted imbalance in the incidence of gastrointestinal and nervous system related TEAEs, with a higher incidence noted in the paediatric population. Adult psoriasis patients in Studies PSOR-008 and 009 had higher levels of prior systemic and phototherapies which impacts comparison of outcomes across the paediatric and adult populations. No PI update was recommended since the risk of GI disturbances with the use of apremilast is already captured in section 4.8 of the SmPC and headache is captured in section 4.8 of the SmPC as a 'very common' adverse reaction. During the phase 3 study and the long-term extension period of the phase 3b study, at any visit during the apremilast-exposure period, 14 and 3 subjects, respectively, had weight decreases > 10% from baseline weight. As data is collected up to 52 weeks, the long term impact of >10% weight loss in this group is unclear. The existing warning on body weight loss in SmPC Section 4.4 is updated to highlight the need for monitoring in paediatric patients with borderline or low body weight.

Limitations include sparse safety data in patients with renal impairment, patients with hepatic impairment, and use in conjunction with live vaccination.

Although longer term safety data (over one year) is limited, the ongoing phase 3b study will capture safety data in the long-term extension phase of up to 208 weeks on treatment. Safety data on longer term use in paediatric patients will be monitored through routine pharmacovigilance

3.6. Effects Table

Table 44. Effects Table for apremilast in the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years and weighing at least 20 kg who are candidates for systemic therapy.

Effect	Short description	Unit	Treatment (20 or 30 mg BID (N = 163))	Control (Placebo (N=82))	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	Treatment (20 or 30 mg BID (N = 163))	Control (Placebo (N=82))	Uncertainties / Strength of evidence	References
sPGA	sPGA response defined as an sPGA score of clear [0] or almost clear [1] with ≥ 2 point reduction from baseline at week 16	%	33.1	11.5	p < 0.0001	StudyPPS0-003
PASI-75	Proportion of subjects achieving ≥ 75% reduction from baseline in the PASI score at week 16	%	45.4	16.1	p < 0.0001	StudyPPS0-003
BSA	Percent change from baseline at week 16	%	-56.6	-21.8	Nominal p< 0.0001	StudyPPS0-003
CDLQI	Response at Week 16	%	35.4	31.3	Nominal p = 0.5616	
Unfavourable Effects						
AE rate WK 16	Placebo- controlled phase	%	72.5 (APR 20 mg BID) 61.4 (APR 30 mg BID)	41.3%	-	PPSO-003
AE rate WK 52	Open label extension APR exposure phase	%	75.9 (APR 20 mg BID) 67.2 (APR 30 mg BID)	n/a	-	PPSO-003
AE rate WK 52	Select PTs abdominal pain, vomiting, abdominal pain upper, headache in APR exposure phase	%	27.6, 23.3, 7.8, 14.7 (20 mg BID); 10.9, 14.3, 3.4, 6.7 (30 mg BID)	n/a	-	PPSO-003
AE rate WK 16	PPS0-003 v adult phase 3 studies * (pooled)	%	66.9 (APR total)	68.9	-	Paediatric v adult data
AE rate WK 52	PPS0-003 v adult phase 3 studies * (pooled), open label extension phase	%	71.5 (APR total)	79.1	-	Paediatric v adult data
AE rate WK 52	Select PTs abdominal pain, vomiting, dyspepsia, headache	%	19.6, 17.8, 6.1, 10.4 (APR total)	2., 3.7, 3.0, 5.8	-	Paediatric v adult data

Effect	Short description	Unit	Treatment (20 or 30 mg BID (N = 163))	Control (Placebo (N=82))	Uncertainties / Strength of evidence	References
	PPS0-003 v adult phase 3 studies * (pooled), open label extension phase					

Abbreviations: AE=adverse events; APR = apremilast, PT= preferred term; BID = twice daily; n/a not applicable

* Notes: Adult Phase 3 studies included CC-10004-PSOR-008 and PSOR-009 with 30 mg BID posology in all treated.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The response rates for sPGA (0,1) and PASI 75, the primary and key secondary efficacy endpoints for apremilast in the treatment of moderate to severe plaque psoriasis among paediatric patients are statistically significant. Improvements in patient reported quality of life outcomes were inconsistent across CLDQI endpoints. The response rates for sPGA (0,1) and PASI 75 in paediatric patients who received apremilast (total apremilast) exceeds or is comparable to the response rates in adult patients with psoriasis, treated with 30mg bid in phase 3 Studies PSOR-008 and PSOR-009. Subjects < 20 kg weight were excluded from this study. No efficacy or safety data is available for this subgroup. The agreed indication excludes patients weighing less than 20 kg.

Efficacy in terms of sPGA (0,1) and PASI-75 was maintained or improved in the apremilast extension phase up to 52 weeks. Subjects who transitioned from placebo to apremilast during the apremilast extension phase showed improvements in all efficacy measures, similar to those in the treatment group who received apremilast during the entire study. However, durability of effect after treatment withdrawal has not been evaluated in this paediatric population. Given the similarities in the exposure response and clinical response between adults and children, the CHMP agrees that a similar loss of efficacy would be expected in children and that treatment should be continued with a therapeutic dose to maintain efficacy.

The safety profile observed in paediatric patients is largely consistent with previous experience in adult patients. During the clinical development programme of apremilast in paediatric patients, there were cases of weight decreases > 10% from baseline weight. Therefore, adequate warning is implemented in SmPC Section 4.4 to highlight the need for monitoring in paediatric patients with borderline or low body weight.

Regarding the use of apremilast in paediatric patients with severe renal impairment, dosage adjustment of reduced dosing and warning are appropriately reflected in the SmPC Sections 4.2, 4.4 and 5.2.

3.7.2. Balance of benefits and risks

The single pivotal study provides evidence of efficacy of apremilast in the treatment of paediatric moderate to severe plaque psoriasis. The proposed posology in children is weight based. Efficacy was demonstrated across both weight bands (≥ 20 to < 50 kg and ≥ 50 kg subgroups) for the apremilast 20 mg and 30 mg treated population and was more favourable in the lower weight subgroup. Efficacy was greater in younger

children (age 6 to 11 years) across both weight subgroups compared to adolescents (>12yrs). The observed variability in response by age/weight groups underlines the importance of weight-based dosing.

The MAH initially proposed a second-line indication in children >6yrs who have a contraindication, have an inadequate response, or are intolerant to at least one other systemic therapy or phototherapy. However, apremilast was evaluated primarily in patients who were candidates for systemic therapy or phototherapy. The posology excludes subjects < 20 kg weight whereas a non-negligible proportion of subjects in the lower age range of the initially proposed indication would have a weight < 20 kg. Upon the CHMP's request, the MAH agreed to revise the indication to children and adolescents from the age of 6 and weighing at least 20 kg who are candidates for systemic therapy.

Whilst an increased incidence of certain TEAEs was observed in lower weight patients (less than 50kg) in the paediatric population, and in the paediatric population compared to the adult population, the overall safety profile appears generally consistent between paediatrics and adult. Adequate warning is implemented in SmPC Section 4.4 to highlight the need for monitoring in paediatric patients with borderline or low body weight.

The proposed new pack sizes are in line with the posology for the extended indication for paediatric psoriasis and are considered to be acceptable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Otezla is positive in the following indication:

Otezla is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years and weighing at least 20 kg who are candidates for systemic therapy.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	A, I, IIIA and IIIB
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules,	Type IAin	A, I, IIIA and IIIB

	etc.) in a pack - Change within the range of the currently approved pack sizes		

- Type II (C.I.6.a): Extension of indication to include the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years and weighing at least 20 kg who are candidates for systemic therapy, based on final results from study CC-10004-PPSO-003 as well as results from studies CC-10004-PPSO-001 and CC-10004-PPSO-004. CC-10004-PPSO-003 is a phase 3, multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of apremilast in paediatric subjects from 6 through 17 years of age with moderate to severe plaque psoriasis. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 15.2 of the RMP is agreed. In addition, MAH took the opportunity to introduce editorial changes to the PI, to bring it in line with the current QRD template and to update the list of local representative (Malta) in the Package Leaflet.
- 2 Type IA (B.II.e.5.a.1): Update of sections 6.5 and 8 of the SmPC to introduce two new pack sizes within approved range as a result of the indication update (initiation pack of 27 film-coated tablets (4 x 10 mg, 23 x 20 mg) and 14 film-coated tablets (14 x 20mg) in a pack size of 56 tablets).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) A, I, IIIA, IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-C-000715-PIP03-11-M06 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMEA/H/C/003746/II/0044/G