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Original article

Apremilast monotherapy for long-term treatment of active psoriatic arthritis in DMARD-naïve patients

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Abstract

Objectives. Apremilast monotherapy was evaluated up to 5 years in PALACE 4 (fourth PsA Long-term Assessment of Clinical Efficacy study) DMARD-naïve patients with PsA.

Methods. Patients with active PsA were randomized (1:1:1) to placebo, apremilast 30 mg or apremilast 20 mg twice a day. Placebo patients were rerandomized to apremilast at week 16 or 24. Double-blind apremilast continued to week 52, with a 4-year open-label extension (≤260 weeks of exposure). Analyses through week 260 were based on observed data.

Results. A total of 527 patients were treated. Among patients randomized to apremilast 30 mg at baseline, 45.5% completed week 260. At study end, 24.8% reported conventional synthetic DMARD or steroid use for any reason. At week 260, 65.8%/39.0%/20.3% of apremilast 30 mg patients achieved ACR20/ACR50/ACR70 responses, respectively. PsA sign and symptom improvements were sustained up to week 260 with continued treatment, including reductions in swollen (84.8%) and tender (76.4%) joint counts. Among apremilast 30 mg patients with baseline enthesitis or dactylitis, 71.2% achieved a Maastricht Ankylosing Spondylitis Enthesitis Score of 0 and 95.1% achieved a dactylitis count of 0. Over 50% of patients achieved a HAQ Disability Index minimal clinically important difference (≥0.35). In patients with ≥3% baseline psoriasis-involved body surface area, 60.3% and 47.6% achieved ≥50% and ≥75% improvement in Psoriasis Area and Severity Index scores, respectively. Patients continuing apremilast 20 mg also demonstrated consistent, sustained improvements. The most common adverse events were diarrhoea, nausea, headache, upper respiratory tract infection and nasopharyngitis. No new safety concerns were observed long term.

Conclusions. Apremilast led to sustained PsA efficacy up to 260 weeks and was well tolerated.

Trial registration. ClinicalTrials.gov (http://clinicaltrials.gov), NCT01307423.

Key words: spondylarthropathies (including psoriatic arthritis), clinical trials and methods, cytokines and inflammatory mediators, biological therapies, DMARDs

Rheumatology key messages

- Improvements in PsA signs and symptoms with apremilast were sustained with continued therapy over 260 weeks.
- Apremilast demonstrated a favourable safety profile and was generally well tolerated up to 260 weeks.
- These findings are consistent with those previously observed with apremilast in DMARD-experienced patients.

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CLINICAL SCIENCE

Introduction

Treatment goals for the long-term control of PsA symptoms include: reduction in swollen joint count (SJC) and tender joint count (TJC); improvement in enthesitis, dactylitis and physical function; and decrease in skin disease [1, 2]. The fourth PsA Long-term Assessment of Clinical Efficacy (PALACE 4) study evaluated the efficacy and safety of apremilast for the treatment of active PsA among patients who were naïve to DMARDs (conventional synthetic or biologic), and included an open-label extension period to evaluate the effects of long-term exposure to apremilast [3]. We now report the final long-term efficacy and safety data for PALACE 4 in DMARD-naïve patients with active PsA who received apremilast for up to 260 weeks.

Methods

Study design

The parallel-group study had an overall duration up to 5 years. The study design has been previously described [3]. Briefly, patients were randomized (1:1:1) to placebo, apremilast 30 mg twice a day or apremilast 20 mg twice a day; the apremilast dose was titrated over the first week. Patients randomized to placebo were rerandomized to apremilast 30 mg twice a day or 20 mg twice a day at week 16 (early escape) or week 24. At week 52, patients could enter a long-term, open-label extension phase for up to four additional years; after week 52, patients who experienced worsening of arthritic symptoms of PsA were allowed treatment changes, including i.m. CS injections, short courses of oral CS or the addition of one conventional synthetic DMARD (csDMARD) (MTX, SSZ, LEF, HCQ or chloroquine).

Patients

As previously described [3], eligible patients were adults ($\geq$18 years of age) with a documented diagnosis of PsA for $\geq$3 months and had three or more swollen joints and three or more tender joints and met the Classification Criteria for PsA (CASPAR) [4]. Patients must not have received any prior treatment with csDMARDs or biologics.

Efficacy assessments

Efficacy endpoints included the proportions of patients achieving ACR20, ACR50 and ACR70 responses, modified for PsA (e.g. inclusion of the distal IP and MTP joints to the total joint counts) [5, 6]. Joint and physical function were evaluated by changes from baseline in SJC, TJC and HAQ Disability Index (HAQ-DI), as well as the achievement of a minimal clinically important difference score of $\geq$0.35 [7]. Additional assessments included resolution of enthesitis, measured by the achievement of a Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [8] of 0 among those with enthesitis at baseline, and resolution of dactylitis, measured by achievement of dactylitis count of 0 among those with dactylitis at baseline. Skin assessments included the proportion of patients with $\geq$50% and $\geq$75% improvement from baseline Psoriasis Area and Severity Index (PASI-50 and PASI-75) score in patients with psoriasis involving $\geq$3% of the body surface area.

Safety assessments

Safety assessments included collection of adverse events (AEs), clinical laboratory evaluation, physical examination and vital signs at each visit, and 12-lead ECG at baseline, and at scheduled visits during each treatment phase and in the event of early termination/withdrawal. AEs were classified using the Medical Dictionary for Regulatory Activities, version 14.0.

Statistical analysis

Efficacy data were analysed descriptively by time point through week 260, based on observed data without imputation for missing data. Safety outcomes were analysed descriptively for all patients who received at least one dose of apremilast and are presented for the apremilast treatment periods from weeks 0 to $\leq$52 (relative to the first dose of apremilast), weeks $>$52 to $\leq$104, weeks $>$104 to $\leq$156, weeks $>$156 to $\leq$208 and weeks $>$208. Standardized incidence ratios (SIRs) were used to report the occurrence of basal cell carcinoma and squamous cell carcinoma of skin and were calculated relative to age-adjusted National Cancer Institute rates reported [9, 10].

Ethics and informed consent

The PALACE 4 study (NCT01307423) was conducted in accordance with the declaration of Helsinki's general ethical principles and received approval from the institutional review board (IRB) at each study site (main IRB approval site, Schulman Associates IRB, 4445 Lake Forest Drive, Suite 300, Cincinnati, OH, USA). Informed written consent was obtained from each patient before any study-related procedure.

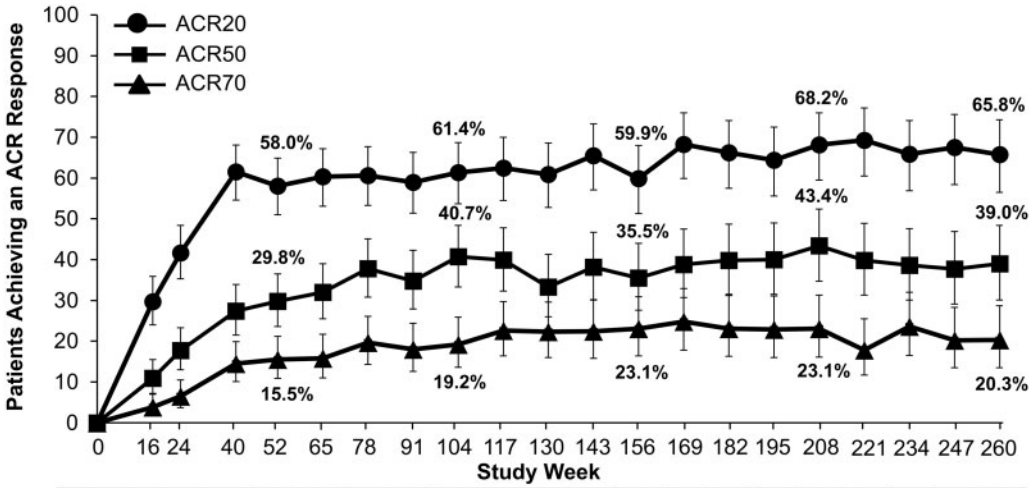
Results

Patients

A total of 528 patients were randomized; one patient was randomized in error and did not receive any study medication. The modified intent-to-treat population excluded this patient and comprised 527 patients (placebo: $n = 176$; apremilast 30 mg: $n = 176$; apremilast 20 mg: $n = 175$). Baseline patient demographics and disease characteristics have been described previously [3] and were comparable across treatment groups. Among patients randomized to apremilast 30 mg or 20 mg at baseline, 45.5% (80/176) and 40.6% (71/175) completed week 260, respectively. In all, 248 patients had $\geq$208 weeks of exposure to apremilast (30 mg: $n = 130$;

20 mg: $n = 118$). Among patients who were randomized to placebo at baseline and switched to apremilast 30 mg or 20 mg at week 16 or 24, 52.6% (41/78) and 48.1% (37/77) completed week 260, respectively. Over the apremilast exposure period, reasons for discontinuation included AEs (10.1%), lack of efficacy (12.1%), non-compliance with study drug (1.4%), withdrawal by patient (23.4%), lost to follow-up (4.0%), protocol violation

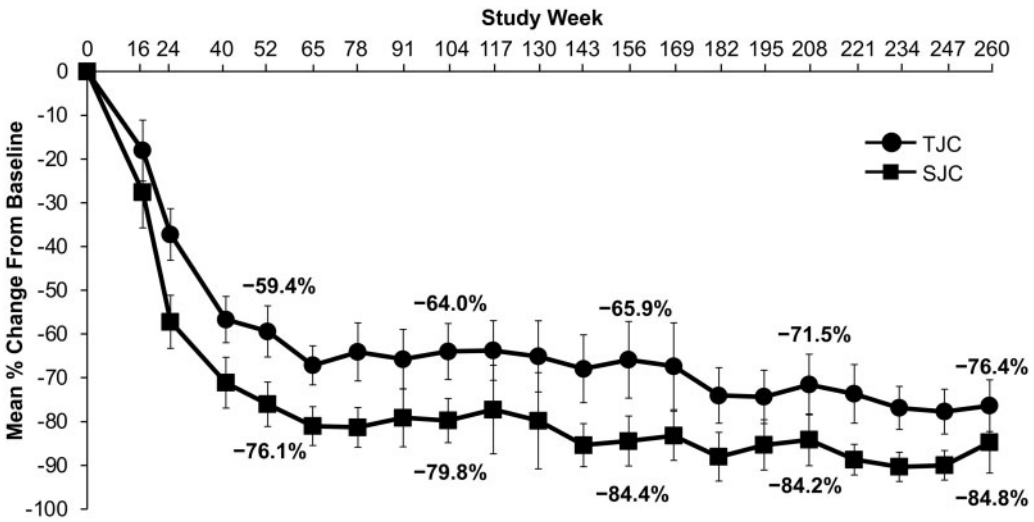
Fig. 1 ACR responses in PsA patients receiving apremilast 30 mg BID up to 260 weeks



ACR20, n	205	194	188	178	171	160	156	142	142	139	133	132	132	127	126	123	117
ACR50, n	205	194	188	178	172	163	156	144	141	139	133	130	129	128	127	122	118
ACR70, n	206	196	188	178	172	164	157	143	143	137	134	131	130	129	127	124	118

Data as observed. Analysis includes all patient data, including the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16 or week 24). The proportions of PsA patients achieving ACR20, ACR50 or ACR70 responses at study visits up to week 260 are shown. Error bars represent 95% CI. The *n* represents the number of patients with evaluable data at the time point; it may vary slightly for each outcome. BID: twice a day.

Fig. 2 SJC/TJC improvements in PsA patients receiving apremilast 30 mg BID up to 260 weeks



Apremilast 30 mg BID, n	206	197	187	179	172	164	158	144	142	140	134	134	132	130	128	124	118

Data as observed. Analysis includes all patient data, including the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16 or week 24). The mean percentage changes in swollen joint count (SJC) and tender joint count (TJC) for PsA patients at study visits up to week 260 are shown. Error bars represent 95% CI. The *n* represents the number of patients with data available at that time point. BID: twice a day.

(0.2%) and other reasons (3.4%). At the end of the study, 9.6% of patients remaining in the trial reported concomitant use of csDMARD (9.1% specifically for PsA), 17.8% reported concomitant steroid use (8.3% specifically for PsA), and 24.8% used a csDMARD or steroid (14.8% specifically for PsA) for any reason.

Efficacy outcomes

Of the patients receiving apremilast 30 mg twice a day, 58.0% achieved an ACR20 response at week 52; among patients who continued apremilast treatment, 65.8% achieved an ACR20 response at week 260. Similarly, ACR50 and ACR70 responses increased from baseline and were sustained over 260 weeks with continued treatment (Fig. 1). Mean SJC and TJC improved 76.1% and 59.4%, respectively, at week 52 with apremilast 30 mg; further reductions from baseline of 84.8% and 76.4%, respectively, were observed at week 260 with continued treatment (Fig. 2).

Among the patients receiving apremilast 30 mg who had enthesitis at baseline, the mean change in MASES at week 260 was −2.4; the proportions of those achieving a MASES of 0 increased over 52 weeks and suggested maintenance of improvements through week 260 with continued apremilast treatment (Fig. 3). Likewise, among patients receiving apremilast 30 mg who had dactylitis at baseline, the mean change in dactylitis count at week 260 was −3.2; the proportions of those achieving a dactylitis count of 0 increased over 52 weeks and indicated maintenance of improvements through week 260 with continued apremilast treatment (Fig. 3).

Improvements in physical function were maintained through week 260 in patients who continued receiving apremilast 30 mg, including mean change from baseline in HAQ-DI (−0.15, −0.35 and −0.38 at weeks 16, 52 and 260, respectively) and the proportion achieving a HAQ-DI minimal clinically important difference was ≥0.35 (Fig. 4).

Among patients with plaque psoriasis involving ≥3% of the body surface area at baseline, the proportions of patients achieving PASI-50 or PASI-75 responses were generally maintained through week 260 with continued treatment (Fig. 5).

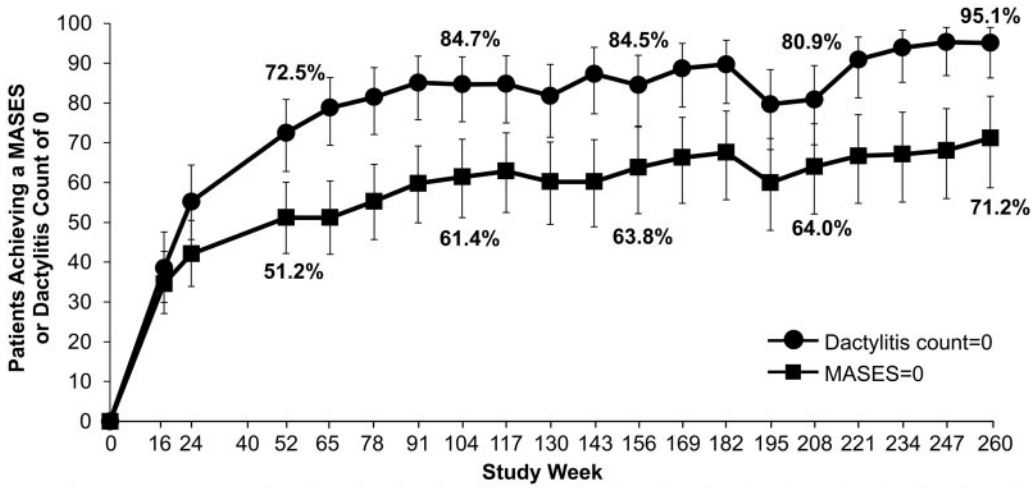
Efficacy outcomes were similar among patients receiving apremilast 20 mg and are presented along with apremilast 30 mg results in supplementary Table S1, available at *Rheumatology* online.

Safety outcomes

During weeks 0 to ≤52, most AEs were mild or moderate in severity with both apremilast doses. Common AEs (e.g. those occurring in ≥5% of apremilast-exposed patients) included diarrhoea and nausea (both apremilast doses), and headache and upper respiratory tract infection (apremilast 30 mg; Table 1). Most diarrhoea and nausea AEs were reported within the first 2 weeks of treatment and usually resolved within 4 weeks.

With apremilast exposure up to 260 weeks, no new safety concerns or increases in the incidence or severity of AEs were seen and similar safety profiles between

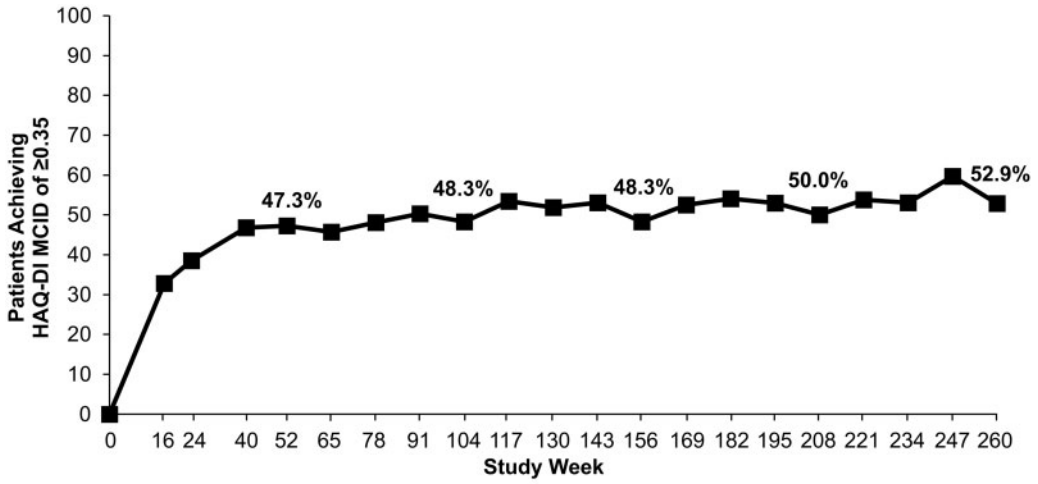
Fig. 3 Enthesitis/dactylitis improvements in PsA patients receiving apremilast 30 mg BID up to 260 weeks



MASES=0, n	127	121	114	107	101	97	93	83	80	80	74	75	75	75	73	72	66
Dactylitis count=0, n	102	99	92	87	85	79	77	71	71	71	68	69	68	66	66	64	61

Data as observed. Analysis includes all patient data, including the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16 or week 24). The proportions of patients achieving a Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) of 0 (indicating enthesitis) or a dactylitis count of 0 at study visits up to week 260 are shown. Error bars represent 95% CI. The *n* represents the number of patients with either MASES >0 or dactylitis count >0 at baseline and data available at that time point. BID: twice a day.

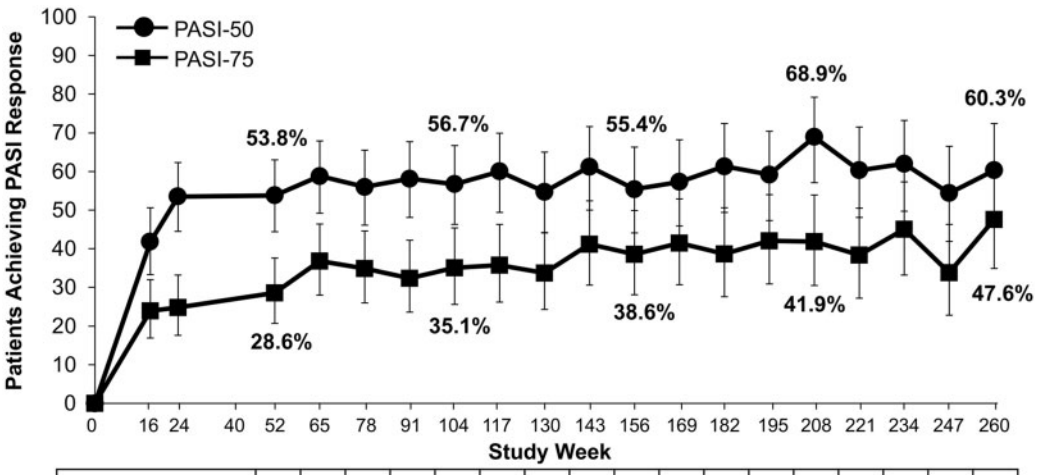
Fig. 4 Improvements in disability among PsA patients receiving apremilast 30 mg BID up to 260 weeks



Apremilast 30 mg BID, n	207	197	189	179	174	163	158	145	143	139	135	134	132	130	128	124	119

Data as observed. Analysis includes all patient data, including the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16 or week 24). The proportions of patients achieving a HAQ Disability Index (HAQ-DI) minimal clinically important difference (MCID) of ≥0.35 at study visits up to week 260 are shown. The *n* represents the number of patients with data available at that time point. BID: twice a day.

Fig. 5 PASI responses in PsA patients receiving apremilast 30 mg BID up to 260 weeks



PASI-50, n	119	114	109	105	97	95	95	85	83	82	75	76	74	73	71	68	63
PASI-75, n	119	114	109	105	97	95	95	85	83	82	75	76	74	73	71	68	63

Data as observed. Analysis includes all patient data, including the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16 or week 24). The proportions of patients achieving a ≥50% or ≥75% improvement from baseline in Psoriasis Area and Severity Index (PASI) score at study visits up to week 260 are shown. Error bars represent 95% CI. The *n* represents the number of patients with psoriasis body surface area involvement ≥3% at baseline and data available at that time point. BID: twice a day.

the apremilast 20 mg and 30 mg doses were observed (Table 1). The frequency of gastrointestinal AEs decreased with longer apremilast exposure and the frequency of other common AEs decreased or remained stable with prolonged exposure. Discontinuations due to AEs during weeks 0 to ≤52 occurred in 5.2% of apremilast 30 mg patients and 5.6% of apremilast 20 mg patients. During treatment periods beyond 52 weeks, ≤3.5% and ≤2.3% of patients treated with apremilast 30 mg and 20 mg, respectively, discontinued because of

Table 1 Summary of safety in PsA patients through 260 weeks of apremilast treatment by treatment period

Patients, *n* (%)	Apremilast treatment period[a]									
	Weeks 0 to ≤52		Weeks >52 to ≤104		Weeks >104 to ≤156		Weeks >156 to ≤208		Weeks >208	
	30 mg BID (*n* = 252)	20 mg BID (*n* = 252)	30 mg BID (*n* = 201)	20 mg BID (*n* = 177)	30 mg BID (*n* = 163)	20 mg BID (*n* = 146)	30 mg BID (*n* = 138)	20 mg BID (*n* = 132)	30 mg BID (*n* = 130)	20 mg BID (*n* = 118)
Patients with										
≥1 AE	165 (65.5)	155 (61.5)	108 (53.7)	91 (51.4)	69 (42.3)	66 (45.2)	61 (44.2)	55 (41.7)	61 (46.9)	48 (40.7)
≥1 serious AE	8 (3.2)	18 (7.1)	10 (5.0)	11 (6.2)	12 (7.4)	5 (3.4)	8 (5.8)	7 (5.3)	5 (3.8)	2 (1.7)
AE leading to study withdrawal	13 (5.2)	14 (5.6)	7 (3.5)	4 (2.3)	5 (3.1)	3 (2.1)	0 (0.0)	3 (2.3)	2 (1.5)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs occurring in ≥5% of any treatment group/ period										
Diarrhoea	28 (11.1)	24 (9.5)	4 (2.0)	7 (4.0)	4 (2.5)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.8)	2 (1.7)
Nausea	35 (13.9)	20 (7.9)	4 (2.0)	3 (1.7)	4 (2.5)	2 (1.4)	1 (0.7)	1 (0.8)	0 (0.0)	1 (0.8)
Headache	24 (9.5)	8 (3.2)	2 (1.0)	2 (1.1)	1 (0.6)	2 (1.4)	1 (0.7)	3 (2.3)	1 (0.8)	0 (0.0)
URT infection	15 (6.0)	10 (4.0)	9 (4.5)	9 (5.1)	4 (2.5)	6 (4.1)	6 (4.3)	5 (3.8)	5 (3.8)	4 (3.4)
Nasopharyngitis	9 (3.6)	9 (3.6)	7 (3.5)	5 (2.8)	7 (4.3)	5 (3.4)	9 (6.5)	4 (3.0)	9 (6.9)	5 (4.2)
Select laboratory assessments, *n*/ *m* (%)										
ALT >150 U/l	2/246 (0.8)	1/250 (0.4)	2/200 (1.0)	2/175 (1.1)	3/161 (1.9)	1/146 (0.7)	2/137 (1.5)	0/130 (0.0)	0/130 (0.0)	0/118 (0.0)
Creatinine, >156 μmol/l (male) or	1/246 (0.4)	1/250 (0.4)	2/200 (1.0)	1/175 (0.6)	3/161 (1.9)	1/146 (0.7)	3/137 (2.2)	0/130 (0.0)	2/130 (1.5)	2/118 (1.7)

(continued)

Table 1 Continued

Patients, *n* (%)	Apremilast treatment period[a]									
	Weeks 0 to ≤ 52		Weeks >52 to ≤ 104		Weeks >104 to ≤ 156		Weeks >156 to ≤ 208		Weeks >208	
	30 mg BID (*n* = 252)	20 mg BID (*n* = 252)	30 mg BID (*n* = 201)	20 mg BID (*n* = 177)	30 mg BID (*n* = 163)	20 mg BID (*n* = 146)	30 mg BID (*n* = 138)	20 mg BID (*n* = 132)	30 mg BID (*n* = 130)	20 mg BID (*n* = 118)
>126 μmol/l (female)										
Haemoglobin <10.5 g/dl (male) or <8.5 g/dl (female) and >2 g/dl decrease	4/245 (1.6)	1/250 (0.4)	3/199 (1.5)	1/176 (0.6)	1/160 (0.6)	2/146 (1.4)	4/136 (2.9)	1/130 (0.8)	6/129 (4.7)	2/117 (1.7)
Leukocytes $<2 \times 10^9$/l	1/245 (0.4)	0/250 (0.0)	0/199 (0.0)	0/176 (0.0)	0/160 (0.0)	0/146 (0.0)	0/136 (0.0)	0/130 (0.0)	0/129 (0.0)	0/117 (0.0)
Neutrophils $<0.75 \times 10^9$/l	1/244 (0.4)	2/250 (0.8)	0/199 (0.0)	0/176 (0.0)	0/160 (0.0)	0/146 (0.0)	0/136 (0.0)	0/130 (0.0)	1/129 (0.8)	0/117 (0.0)
Platelets $<75 \times 10^9$/l	0/244 (0.0)	0/250 (0.0)	0/198 (0.0)	0/176 (0.0)	0/160 (0.0)	0/146 (0.0)	0/136 (0.0)	0/130 (0.0)	0/129 (0.0)	0/117 (0.0)

[a]Includes all patients who received apremilast during the time interval relative to the start of apremilast treatment (*n*/*m* is the number of patients with the specific event/number of patients with sufficient data for evaluation). AE: adverse event; ALT: alanine aminotransferase; BID: twice a day; URT: upper respiratory tract.

AEs. AEs leading to discontinuation of ≥1% of all apremilast-treated patients were diarrhoea, nausea and headache; these AEs led to discontinuation in ≤2.4%, ≤1.6% and ≤1.2% of patients, respectively, in either dose group across all five treatment periods.

Serious AEs occurred in ≤7.4% and ≤7.1% of patients treated with apremilast 30 mg and 20 mg, respectively, across all five treatment periods. Serious AEs affecting >0.5% of the total apremilast-treated patients ($n = 504$) were transient ischaemic attack ($n = 3$; 0.6%), angina pectoris ($n = 3$; 0.6%), coronary artery disease ($n = 3$; 0.6%), cholelithiasis ($n = 3$; 0.6%) and inguinal hernia ($n = 5$; 1.0%). Serious infections were rare, affecting ≤1.5% of patients in either dose group across all five treatment periods.

During the study there were no reports of lymphoma; SIR was 0. Overall, apremilast combined treatment was not associated with an increased risk of basal or squamous skin carcinoma when compared with expected rates reported for the general population. SIR of basal cell carcinoma was 1.03 (95% CI 0.213, 3.015); SIR was 1.59 (95% CI 0.040, 8.840) for squamous cell carcinoma of skin (supplementary Fig. S1, available at *Rheumatology* online). The SIRs for basal cell carcinoma and squamous cell carcinoma of skin relative to the general population with high sun exposure (reference, New Mexico: basal cell carcinoma rate, 0.2688; squamous cell carcinoma of skin rate, 0.0678) or low sun exposure (reference, Seattle: basal cell carcinoma rate, 0.1606; squamous cell carcinoma of skin rate, 0.0281) are shown in supplementary Fig. S1, available at *Rheumatology* online.

In the placebo-controlled phase (weeks 0–24), reports of depression were rare but greater with apremilast 30 mg compared with placebo (1.1%, 0.6%); the rate for apremilast 20 mg was 0.6%. Rates of depression during the long-term study were consistent over time and were low, with 2.0% and 1.6%, 2.5% and 0.6%, 2.5% and 0.0%, 0.0% and 0.8%, and 0.0% and 0.8% for apremilast 30 mg and 20 mg across weeks 0 to ≤52, weeks >52 to ≤104, weeks >104 to ≤156, weeks >156 to ≤208, and weeks >208, respectively. Mean weight changes ranged from −1.59 to −0.74 kg with apremilast 30 mg and from −0.98 to −0.66 kg with apremilast 20 mg across treatment periods, with the majority of patients maintaining their weight within 5% of baseline during the study. At the last measure of patients' treatment, weight loss >5% was observed in 22.0% (54/246) of apremilast 30 mg patients and 18.1% (45/248) of 20 mg patients. Marked laboratory abnormalities were generally infrequent, transient and of similar incidence during all periods (Table 1).

Discussion

The phase III PALACE 4 study evaluated the long-term efficacy and safety of apremilast treatment for up to 5 years in patients with active PsA who were DMARD naïve. A total of 43% of patients continued apremilast treatment through 260 weeks. At the end of the study, 24.8% of patients remaining in the trial reported using a csDMARD or steroid for any reason, suggesting that ∼75% of patients responded sufficiently with apremilast alone whereas concomitant csDMARD or steroid could have contributed to treatment response in the remaining 25%. Patients who continued apremilast treatment for 5 years maintained improvements in PsA signs and symptoms, including SJC, TJC and physical function. Enthesitis, dactylitis and psoriasis also showed improvements in patients with these manifestations at baseline. Apremilast continued to demonstrate a favourable safety profile in patients with active PsA who were DMARD naïve.

Treatment guidelines acknowledge the importance of early treatment for patients with PsA to help optimize long-term outcomes [1, 2, 11]. Prior studies suggest that delays in receiving rheumatology care and treatment for PsA may be associated with less favourable outcomes over time [12–16]. In PALACE 4, DMARD-naïve patients with active PsA who continued on apremilast treatment for up to 5 years achieved sustained improvements in PsA. These findings suggest that apremilast may offer long-term benefits to DMARD-naïve patients with active PsA who initiate apremilast early in the course of their treatment paradigm. Furthermore, the PALACE 4 data supplement the long-term efficacy and safety with apremilast demonstrated in DMARD-experienced patients in the PALACE 1–3 studies [17].

Limitations

A limitation of controlled clinical studies is the enrolment of highly selected patients with restricted eligibility criteria, which may not be representative of patients with PsA seen in the clinic setting. Additionally, long-term efficacy results may be biased by non-random discontinuation of patients due to lack or loss of response, AEs and absence of a control arm. Open-label extensions do, however, offer insight into the efficacy and safety of therapies in those patients who remain on longer term therapy.

There is a need for long-term treatment options that are efficacious, safe and convenient for patients with PsA. The findings from the open-label extension phase of the PALACE 4 study demonstrate that apremilast offers sustained efficacy in DMARD-naïve PsA patients continuing treatment, as well as a favourable safety profile.

Conclusions

In this 5-year analysis of the PALACE 4 study, apremilast demonstrated clinically meaningful, sustained, improvements in PsA signs and symptoms as well as physical function following continued treatment. Safety was maintained with apremilast, with no new safety concerns identified for up to 5 years with treatment.

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Data availability statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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