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Original article

Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial

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Abstract

Objectives. The PALACE 4 trial evaluated apremilast monotherapy in patients with active PsA who were DMARD-naive.

Methods. Eligible patients were randomized (1:1:1) to placebo, apremilast 20 mg twice a day or apremilast 30 mg twice a day. At week 16 or 24, placebo patients were rerandomized to apremilast. Double-blind apremilast treatment continued to week 52, with extension up to 4 years. The primary endpoint was the proportion of patients achieving $\geqslant$20% improvement in ACR response criteria (ACR20) at week 16; secondary endpoints included the mean change in the HAQ Disability Index (HAQ-DI) score at week 16.

Results. A total of 527 patients with mean disease duration of 3.4 years and high disease activity were randomized and received treatment. More apremilast patients achieved ACR20 response at week 16 [placebo, 15.9%; 20 mg, 28.0% ($P = 0.0062$); 30 mg, 30.7% ($P = 0.0010$)]. The mean HAQ-DI improvements were -0.17 (20 mg; $P = 0.0008$) and -0.21 (30 mg; $P < 0.0001$) *vs* 0.03 (placebo). Both apremilast doses showed significant ACR50 responses *vs* placebo at week 16 and improvements in secondary efficacy measures (swollen/tender joint counts) and psoriasis assessments, with sustained improvements through week 52. Common adverse events (AEs) over 52 weeks were diarrhoea, nausea, headache and upper respiratory tract infection; most events were mild or moderate. Serious AEs and AEs leading to discontinuation were comparable between groups. Laboratory abnormalities were infrequent and transient.

Conclusions. In DMARD-naive patients, apremilast monotherapy improved PsA signs/symptoms over 52 weeks and was generally well tolerated.

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

Key words: apremilast, monotherapy, phase III clinical trial, phosphodiesterase 4 inhibitor, psoriatic arthritis

CLINICAL SCIENCE

Rheumatology key messages

- PALACE 4 findings demonstrate the efficacy and safety of apremilast monotherapy in DMARD-naive PsA patients.
- Apremilast monotherapy demonstrated sustained response and improvement in PsA signs and symptoms over 52 weeks.
- Long-term treatment with apremilast demonstrated an acceptable safety profile and apremilast was generally well tolerated.

Introduction

PsA often involves skin and joints and leads to poor quality of life and sometimes joint damage [1–3]. Treatment recommendations emphasize addressing the spectrum of PsA clinical manifestations and associated comorbidities while minimizing complications associated with untreated disease or therapy [4]. Although numerous

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NSAIDs, conventional synthetic DMARDs (csDMARDs) such as MTX and biologic DMARDs (bDMARDs) are available, efficacy varies among agents and many are associated with safety issues and limitations that can impact a patient's comfort level when initiating or continuing therapy [4–7]. The importance of effective, earlier PsA treatment was highlighted in the TIght COntrol in Psoriatic Arthritis study, which demonstrated the benefits associated with tight control of early PsA [8].

The fourth Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE 4) study in the phase III clinical trial programme is evaluating the efficacy, safety and tolerability of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with active PsA. PALACE 1, 2 and 3 evaluated apremilast in patients with active PsA who were considered inadequate responders to csDMARDs or bDMARDs [9–12], with benefits observed up to 156 weeks [13]. PALACE 4 assessed apremilast use earlier in the treatment algorithm in patients with active PsA who were csDMARD naive and biologic naive. This report describes the results of the first 52 weeks of PALACE 4.

Methods

Patients

Adults ($\geqslant$18 years of age) were eligible to enrol if they had a documented PsA diagnosis for $\geqslant$3 months, had three or more swollen and three or more tender joints and met the Classification Criteria for Psoriatic Arthritis [14]. No prior treatment with csDMARDs or biologics was allowed.

Patients were excluded if they had erythrodermic, guttate or generalized pustular psoriasis; inflammatory joint disease or rheumatic disease other than PsA; ACR Classification of Functional Status in Rheumatoid Arthritis class IV status; other clinically significant disease (as determined by the investigator) or other major uncontrolled disease; active tuberculosis, a history of incompletely treated tuberculosis (no purified protein derivative or QuantiFERON screening for latent tuberculosis was required) or significant infection within 4 weeks of screening; or malignancy (except treated basal cell or squamous cell skin carcinoma or early forms of cervical carcinoma with no recurrence in 5 years).

Concomitant medication

Stable doses of oral corticosteroids (prednisone $\leqslant$10 mg/day or equivalent for $\geqslant$1 month) and NSAIDs ($\geqslant$2 weeks) before study entry were permitted. Background therapy with low-potency topical corticosteroids for face, axillae and groin psoriatic lesions, coal tar shampoo and/or salicylic acid scalp preparations for scalp lesions and non-medicated emollient for body lesions was permitted, except within 24 h before each study visit.

During the study, patients could not receive treatment with csDMARDs or biologics, topical therapy for psoriasis (except those permitted for background therapy), immunosuppressive systemic therapies or phototherapy (i.e. ultraviolet B, psoralen + ultraviolet A).

Study design

The parallel-group study has an overall duration of up to 5 years. Patients were randomized (1:1:1) to placebo, apremilast 20 mg twice a day (BID) or apremilast 30 mg BID. Apremilast was dose-titrated over the first week of treatment (10 mg on the first day, with increases of 10 mg/day up to the target dose). At week 16, patients not achieving $\geqslant$20% improvement in swollen and tender joint counts (SJC and TJC) were considered non-responders and were required to enter early escape; patients initially randomized to placebo were rerandomized (1:1) to apremilast 20 mg BID or 30 mg BID; apremilast patients continued with their initial apremilast dose. At week 24, the remaining placebo patients were rerandomized to blinded treatment with apremilast 20 mg BID or 30 mg BID. At week 52, patients could enter a long-term, open-label extension phase for up to 4 additional years.

Assessments

The primary efficacy endpoint was the proportion of patients achieving $\geqslant$20% improvement in ACR response criteria (ACR20) at week 16. Response criteria were modified for PsA by inclusion of the DIP joints of the toes and CMC joints to the total joint counts [15, 16].

The key secondary efficacy endpoint was a change in the HAQ Disability Index (HAQ-DI) score at week 16. Additional efficacy endpoints included ACR50 and ACR70 responses; changes from baseline in SJC, TJC, CRP, patient's and physician's global assessment of disease activity (visual analogue scale) scores, patient's assessment of pain, 28-joint DAS using CRP (DAS28-CRP), Clinical Disease Activity Index and 36-item Short-Form Health Survey (SF-36) version 2; proportions of patients achieving minimal clinically important differences in the HAQ-DI score [using prespecified thresholds based on the literature at the time of protocol development (improvement $\geqslant$0.13 [17] or $\geqslant$0.30 [18])] and EULAR good or moderate response; mean change in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and proportions of patients with enthesitis at baseline achieving a MASES of 0 [19]; mean change in dactylitis count and proportions of patients with dactylitis at baseline achieving a dactylitis count of 0; and proportions of patients achieving modified Psoriatic Arthritis Response Criteria response and $\geqslant$50 and $\geqslant$75% improvements from baseline Psoriasis Area and Severity Index scores (PASI-50 and PASI-75) in patients with baseline psoriasis involving $\geqslant$3% of the body surface area (BSA) [9]. Efficacy assessments were conducted at weeks 16, 24 and 52, and ACR20 response and HAQ-DI scores were evaluated at week 40.

Safety assessments included collection of adverse events (AEs), clinical laboratory evaluation, physical examination and vital signs at each visit and 12-lead electrocardiogram at baseline and weeks 16, 24 and 52 and in the event of early termination/withdrawal.

Statistical analysis

Based on phase II apremilast study results [20], an estimated sample of 165 patients per treatment group was needed to achieve 95% power to detect a 20% difference in modified ACR20 response between apremilast treatment and placebo using a two-group chi-square test with a two-sided significance level of 0.025.

Efficacy during the placebo-controlled period was evaluated based on the modified intent-to-treat population, in which patients who were randomized in error and did not receive any study medication were excluded. All data handling rules were determined before unblinding the database.

The ACR20 response at week 16 (primary endpoint) was analysed using a chi-square test; missing values were handled using the non-responder imputation rule. Pairwise comparisons for each apremilast group *vs* placebo were performed using the Hochberg procedure [21] to maintain type 1 error at 0.05. Results were considered statistically significant if both apremilast-*vs*-placebo comparisons achieved a P-value <0.05 or if one of the comparisons achieved a P-value <0.025.

Change from the baseline HAQ-DI score at week 16 (key secondary endpoint) was analysed using an analysis of covariance model, with treatment as a factor and baseline value as a covariate; missing values were imputed using the last-observation-carried-forward methodology.

Other binary and continuous parameters were analysed using the same methodology as for ACR20 response and HAQ-DI score, respectively. Patients who early escaped at week 16 were considered as having missing values at week 24. Other summaries with no comparisons to placebo, including those at week 52, were described using observed data.

Safety outcomes were analysed using data from the safety population, which comprised all patients who received one or more doses of study medication. AEs were classified using the Medical Dictionary for Regulatory Activities (https://www.meddra.org). Events occurring after the first dose of study medication and $\leqslant$28 days after the last dose were summarized descriptively.

Safety data were assessed by actual exposure to placebo, apremilast 20 mg and apremilast 30 mg. Placebo exposure includes data through 16 weeks for placebo patients who escaped and through 24 weeks for patients who continued placebo until 24 weeks. Apremilast exposure includes all available treatment data through 52 weeks for all patients who received one or more doses of apremilast.

Ethics and informed consent

PALACE 4 (NCT01307423) was conducted in accordance with the Declaration of Helsinki's general ethical principles and received approval from institutional review boards/independent ethics committees. Informed written consent was obtained from each patient prior to any study-related procedure.

Results

Patient disposition is summarized in supplementary Fig. S1, available at *Rheumatology* online. Of the 658 screened patients, 528 were randomized; 1 patient was randomized in error and did not receive any study medication. The modified intent-to-treat population, which excluded this patient, comprised 527 patients, 471 (89.4%) of whom completed week 24, with similar completion rates across treatment groups (88.1–91.4%). Baseline patient demographics, disease characteristics and prior and concurrent PsA-related therapy were balanced among treatment groups (Table 1). These DMARD-naive patients had active disease, with a mean baseline SJC of 11.2 and TJC of 20.1. Many patients had disease activity in other domains at baseline (58% had psoriasis affecting $\geqslant$3% of their BSA, 65% had enthesitis and 50% had dactylitis).

ACR20 response

At week 16, significantly more apremilast-treated patients achieved an ACR20 response *vs* placebo [placebo, 15.9%; apremilast 20 mg, 28.0% ($P=0.0062$); apremilast 30 mg, 30.7% ($P=0.0010$)] (Fig. 1A). An analysis of ACR20 response in the completer population revealed similar results [placebo, 17.2%; apremilast 20 mg, 30.2% ($P=0.0056$); apremilast 30 mg, 32.9% ($P=0.0010$)]. ACR20 response was sustained through the placebo-controlled period at 24 weeks [placebo, 13.1%; apremilast 20 mg, 29.1% ($P=0.0002$); apremilast 30 mg, 24.4% ($P=0.0063$)] and over 52 weeks with apremilast treatment (Fig. 2A).

HAQ-DI scores

Apremilast-treated patients demonstrated significant improvements in functionality *vs* placebo, as measured by changes in the HAQ-DI score at week 16 [placebo, 0.03; apremilast 20 mg, −0.17 ($P=0.0008$); apremilast 30 mg, −0.21 ($P<0.0001$)] (Fig. 1B). At week 16, significantly more apremilast-treated patients achieved a minimal clinically important difference in HAQ-DI improvement of $\geqslant$0.13 and $\geqslant$0.30 *vs* placebo patients (Table 2). The HAQ-DI improvement was sustained over 52 weeks with continued apremilast treatment (Table 3 and Fig. 2B).

Other efficacy measures

Apremilast improved a broad range of efficacy parameters at week 16 (Table 2). Notably, significantly more patients achieved an ACR50 response (but not an ACR70 response) with apremilast *vs* placebo. In addition to ACR responses, the efficacy of apremilast was significant *vs* placebo in other composite measures of disease activity, including mean change in DAS28-CRP, mean change in Clinical Disease Activity Index and proportions of patients meeting the modified Psoriatic Arthritis Response Criteria or achieving a EULAR good or moderate response (Table 2). Changes in ACR components (SJC, TJC, patient's and physician's global assessments of disease activity, patient's assessment of pain) were significantly greater for both doses of apremilast *vs* placebo except for CRP. These improvements were maintained through

Table 1 Baseline demographic and clinical characteristics: modified intent-to-treat population ($N = 527$)

Characteristics	Placebo ($n = 176$)	Apremilast 20 mg BID ($n = 175$)	Apremilast 30 mg BID ($n = 176$)
Age, mean (S.D.), years	50.5 (11.6)	49.2 (12.0)	48.4 (12.5)
Female, *n* (%)	86 (48.9)	95 (54.3)	96 (54.5)
Race, *n* (%)			
White	174 (98.9)	174 (99.4)	172 (97.7)
Asian	0 (0.0)	1 (0.6)	2 (1.1)
Black	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (1.1)	0 (0.0)	2 (1.1)
Region, *n* (%)			
North America	51 (29.0)	51 (29.1)	53 (30.1)
Europe	83 (47.2)	73 (41.7)	82 (46.6)
Rest of world	42 (23.9)	51 (29.1)	41 (23.3)
Weight, mean (S.D.), kg	82.4 (18.24)	84.5 (22.09)	85.7 (20.60)
BMI, mean (S.D.), kg/m^2	28.7 (5.6)	29.8 (7.2)	29.7 (6.4)
Duration, mean (S.D.), years			
PsA	3.4 (5.1)	3.2 (4.7)	3.6 (5.0)
Psoriasis	16.8 (13.7)	15.3 (12.7)	15.4 (13.3)
PASI score (0–72),[a] mean (S.D.)	6.6 (6.14)	8.3 (7.95)	6.6 (5.11)
Psoriasis BSA $\geqslant$3%, *n* (%)	93 (52.8)	104 (59.4)	109 (61.9)
SJC (0–76), mean (S.D.)	11.3 (7.6)	11.3 (7.8)	10.9 (8.6)
TJC (0–78), mean (S.D.)	19.6 (13.7)	21.1 (15.1)	19.5 (14.4)
HAQ-DI (0–3), mean (S.D.)	1.0 (0.61)	1.1 (0.59)	1.1 (0.58)
CRP (normal range 0–0.5), mean (S.D.), mg/dl	1.1 (2.7)	0.9 (1.1)	0.8 (1.1)
Pain VAS (0–100), mean (S.D.)	52.8 (21.0)	54.5 (21.6)	52.6 (21.4)
Patient's global assessment of disease activity (0–100 mm VAS), mean (S.D.)	54.0 (21.9)	52.3 (21.1)	53.6 (20.1)
Physician's global assessment of disease activity (0–100 mm VAS), mean (S.D.)	54.3 (18.5)	54.1 (18.8)	51.7 (17.5)
DAS28-CRP, mean (S.D.)	4.6 (1.1)	4.7 (1.1)	4.5 (1.0)
CDAI (0–76), mean (S.D.)	26.5 (11.8)	26.8 (11.7)	25.7 (12.0)
SF-36v2 physical functioning (norm-based), mean (S.D.)	36.1 (10.8)	35.2 (9.9)	35.7 (10.5)
Presence of enthesitis, *n* (%)	115 (65.3)	117 (66.9)	111 (63.1)
Presence of dactylitis, *n* (%)	90 (51.1)	89 (50.9)	84 (47.7)
Baseline use of NSAIDs, *n* (%)	129 (73.3)	123 (70.3)	133 (75.6)
Baseline corticosteroids (mean dose[b] 6.71 mg/day), *n* (%)	12 (6.8)	13 (7.4)	13 (7.4)
Baseline use of opiate analgesic, *n* (%)	8 (4.5)	17 (9.7)	10 (5.7)

n reflects the number of modified intent-to-treat patients; the actual number of patients available for each parameter may vary. [a]Examined among patients with psoriasis involving $\geqslant$3% of BSA at baseline and having a PASI score at baseline (placebo, $n = 93$; apremilast 20 mg BID, $n = 104$; apremilast 30 mg BID, $n = 107$). [b]All converted to oral prednisone dose. CDAI: Clinical Disease Activity Index; SF-36v2: 36-item Short-Form Health Survey version 2; VAS: visual analogue scale.

week 52 with continued apremilast treatment (Table 3; supplementary Fig. S2A and S2B, available at *Rheumatology* online).

Functionality improvements, similar to those seen with the HAQ-DI, were observed at week 16 using the physical functioning subscale and physical component summary scores of the SF-36 version 2 (Table 2).

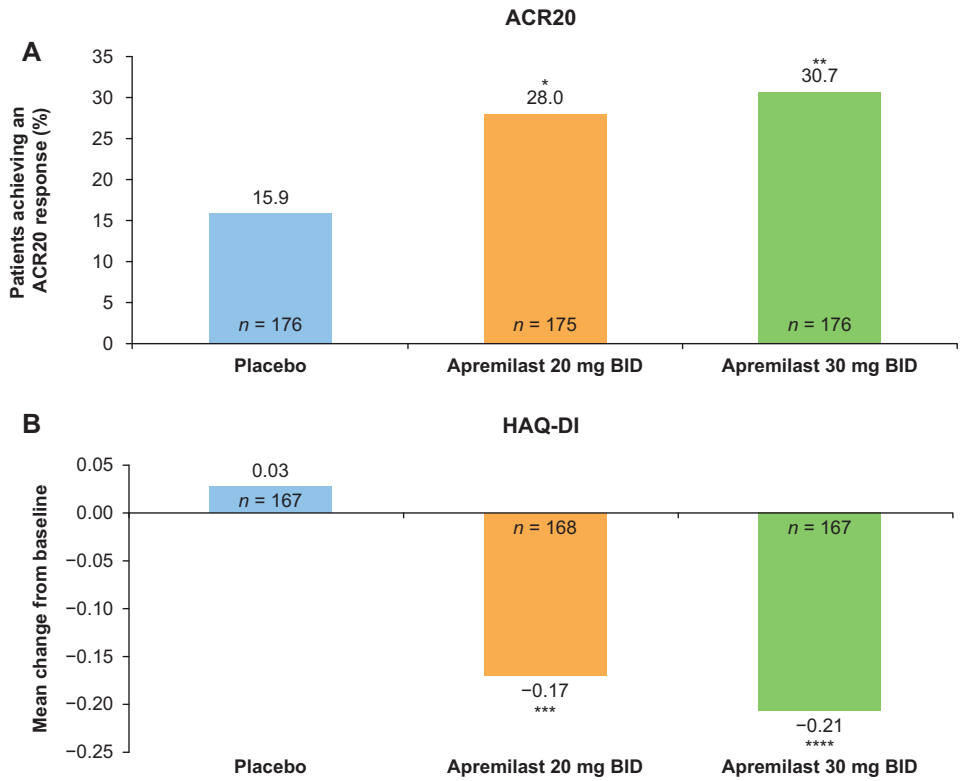
Clinical responses in other PsA domains were observed in apremilast-treated patients. In the subsets of patients with enthesitis and dactylitis at baseline, MASES and dactylitis counts were significantly reduced with apremilast treatment at week 16 (Table 2). Additionally, for patients in these subsets who were initially randomized to apremilast, resolution of clinically active enthesitis (enthesitis count = 0) and clinically active dactylitis (dactylitis count = 0) was observed at week 52 (Table 3; supplementary Fig. S3A and S3B, available at *Rheumatology* online).

Patients with psoriasis involvement $\geqslant$3% of BSA at baseline experienced significant improvements in psoriasis at week 16, except for PASI-75 response with apremilast 20 mg (Table 2); PASI-50 and PASI-75 responses were sustained over 52 weeks with apremilast (Table 3 and Fig. 2C).

Safety and tolerability

The nature, incidence and severity of AEs were comparable during 0–24 weeks and 0–52 weeks (Table 4). Most

FIG. 1 ACR20 response rates and HAQ-DI scores at week 16 (modified intent-to-treat population)



(**A**) Proportion of patients achieving ACR20 response at week 16 (NRI, non-responder imputation): modified intent-to-treat population. *P = 0.0062, **P = 0.0010 *vs* placebo. (**B**) Mean change from baseline in HAQ-DI at week 16 (last-observation-carried-forward methodology): modified intent-to-treat population. ***P = 0.0008, ****$P < 0.0001$ *vs* placebo.

AEs were mild or moderate in severity. Serious AE (SAE) rates were not higher in the apremilast arms (1.1%) *vs* placebo (2.8%) during 0–24 weeks. Discontinuations due to AEs during 0–24 weeks were low and similar across all treatment arms (2.3–3.4%); overall, during 0–52 weeks of apremilast exposure, cumulative proportions of patients who discontinued due to AEs were low with apremilast 20 mg (5.6%) and 30 mg (4.8%).

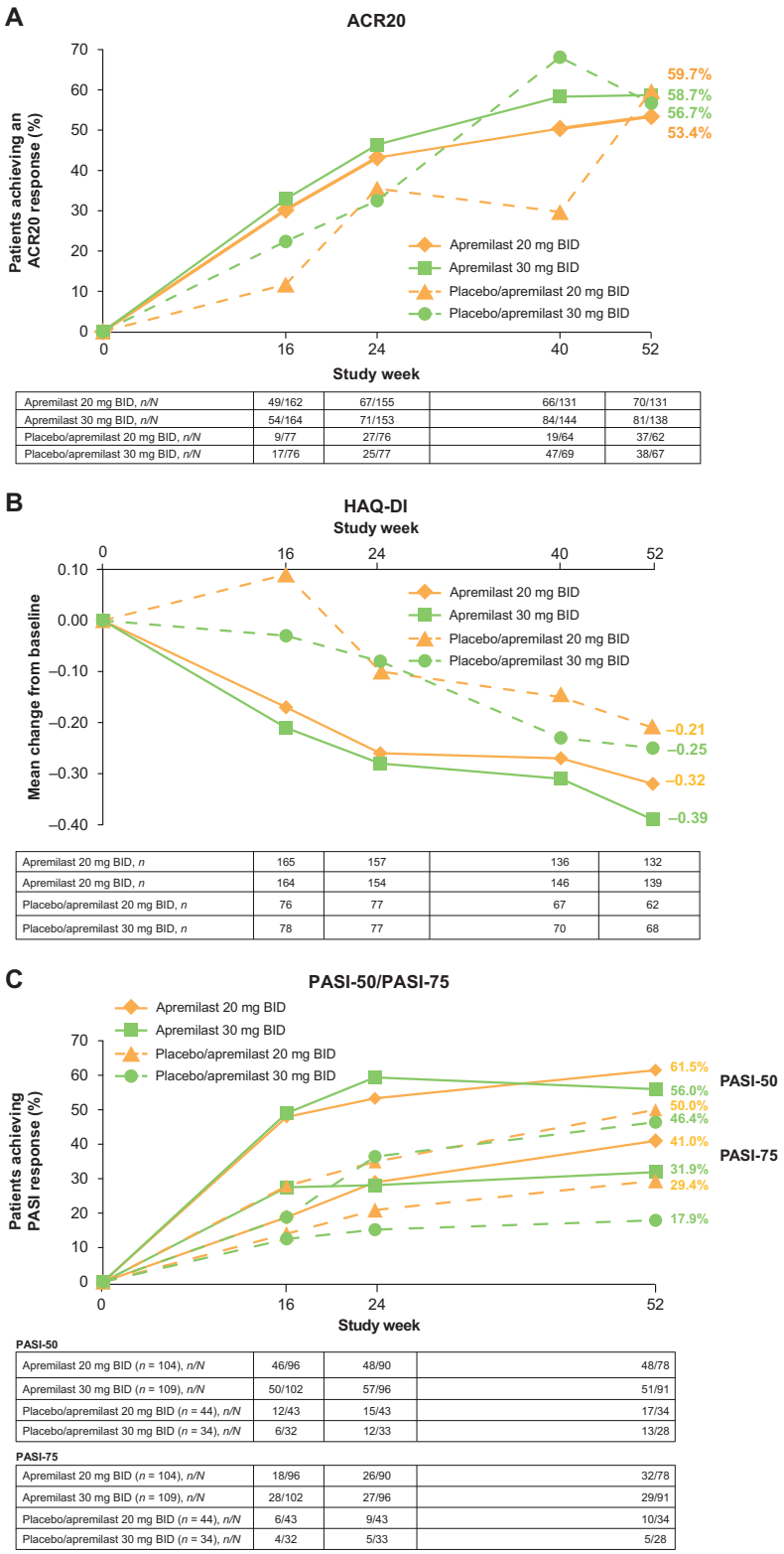
The most common AEs, occurring in $\geqslant$5% of any treatment group during 0–24 weeks, were diarrhoea, nausea and headache. Diarrhoea and nausea were generally reported within the first 2 weeks of treatment and usually resolved within 4 weeks in the vast majority of cases without medical intervention. During 0–52 weeks of apremilast exposure, no diarrhoea or nausea AEs were reported as serious; 2.0 and 1.0% of patients treated with apremilast discontinued due to diarrhoea and nausea, respectively.

Over 0–52 weeks of apremilast exposure, 22 patients experienced an SAE. Back pain (apremilast 20 mg, n = 2) was the only SAE reported by more than one patient in any treatment group. Among the SAEs were three serious infections: one chronic tonsillitis (apremilast 20 mg), one gallbladder empyema (apremilast 30 mg) and one acute pyelonephritis (apremilast 30 mg); none were opportunistic.

One patient randomized to apremilast 20 mg tested positive for latent tuberculosis at screening and received isoniazid for tuberculosis prophylaxis during the study. No cases of reactivation or *de novo* tuberculosis were reported. Two cases of basal cell carcinoma (placebo, n = 1; apremilast 30 mg, n = 1) and one case of squamous cell carcinoma (apremilast 30 mg) were reported. One case of prostate cancer was reported (apremilast 20 mg) and did not lead to treatment interruption or withdrawal. One case of cutaneous vasculitis was reported (apremilast 30 mg) after 1 year of treatment; this was not serious, no treatment was required and study treatment was unchanged. One acute myocardial infarction (apremilast 20 mg) occurred during the study in a 65-year-old patient with pre-existing hypertensive heart disease, hypercholesterolaemia and a BMI of 32.6 kg/m^2. No relationship to the study drug was suspected and treatment was not interrupted or discontinued. No deaths occurred during the 52-week study.

Marked laboratory abnormalities were infrequent (Table 4) and returned to baseline with continued treatment or were associated with a concurrent medical condition.

Fig. 2 ACR20, HAQ-DI and PASI-50/PASI-75 response rates over 52 weeks (data as observed)



Apremilast 20 mg BID, *n/N*	49/162	67/155	66/131	70/131
Apremilast 30 mg BID, *n/N*	54/164	71/153	84/144	81/138
Placebo/apremilast 20 mg BID, *n/N*	9/77	27/76	19/64	37/62
Placebo/apremilast 30 mg BID, *n/N*	17/76	25/77	47/69	38/67

Apremilast 20 mg BID, *n*	165	157	136	132
Apremilast 20 mg BID, *n*	164	154	146	139
Placebo/apremilast 20 mg BID, *n*	76	77	67	62
Placebo/apremilast 30 mg BID, *n*	78	77	70	68

PASI-50

Apremilast 20 mg BID (*n* = 104), *n/N*	46/96	48/90	48/78
Apremilast 30 mg BID (*n* = 109), *n/N*	50/102	57/96	51/91
Placebo/apremilast 20 mg BID (*n* = 44), *n/N*	12/43	15/43	17/34
Placebo/apremilast 30 mg BID (*n* = 34), *n/N*	6/32	12/33	13/28

PASI-75

Apremilast 20 mg BID (*n* = 104), *n/N*	18/96	26/90	32/78
Apremilast 30 mg BID (*n* = 109), *n/N*	28/102	27/96	29/91
Placebo/apremilast 20 mg BID (*n* = 44), *n/N*	6/43	9/43	10/34
Placebo/apremilast 30 mg BID (*n* = 34), *n/N*	4/32	5/33	5/28

(**A**) ACR20, (**B**) HAQ-DI and (**C**) PASI-50/PASI-75. Based on patients randomized to apremilast; the placebo/apremilast 20 mg BID and placebo/apremilast 30 mg BID groups include patients who were randomized to placebo at baseline and rerandomized to apremilast 20 mg BID and apremilast 30 mg BID, respectively, at week 16 or 24; the apremilast 20 mg BID and apremilast 30 mg BID groups include patients randomized to the respective regimen at baseline. Patients with baseline psoriasis involvement ⩾3% of BSA were included.

Table 2 Secondary efficacy endpoints at week 16: modified intent-to-treat population

Endpoints	Placebo ($n = 176$)	Apremilast 20 mg BID ($n = 175$)	Apremilast 30 mg BID ($n = 176$)
ACR50, *n* (%)[a]	8 (4.5)	20 (11.4)*	20 (11.4)*
ACR70, *n* (%)[a]	2 (1.1)	7 (4.0)	7 (4.0)
Change in HAQ-DI (0–3), mean (S.D.)	0.03 (0.47)	−0.17 (0.46)**	−0.21 (0.51)***
HAQ-DI (0–3) MCID ⩾0.13, *n* (%)[a]	48 (27.3)	74 (42.3)**	75 (42.6)**
HAQ-DI (0–3) MCID ⩾0.30, *n* (%)[a]	34 (19.3)	62 (35.4)**	59 (33.5)**
Change in SF-36v2 physical functioning, mean (S.D.)[b]	−0.03 (7.9)	2.4 (7.9)**	3.2 (8.0)**
Change in SF-36v2 physical component summary, mean (S.D.)[b]	1.0 (7.2)	3.2 (7.1)**	4.1 (7.4)***
EULAR good/moderate response, *n* (%)[a]	44 (25.0)	72 (41.1)**	78 (44.3)***
mPsARC response, *n* (%)[a]	43 (24.4)	68 (38.9)**	80 (45.5)***
Change in DAS28-CRP, mean (S.D.)	−0.16 (1.0)	−0.62 (1.1)***	−0.67 (1.0)***
DAS28-CRP <2.6, *n* (%)[a]	15 (8.5)	23 (13.1)	17 (9.7)
Change in CDAI (0–76), mean (S.D.)	−2.0 (10.2)	−7.0 (11.6)***	−7.5 (10.1)***
Percent change in SJC (0–76), mean (S.D.)	−12.7 (63.5)	−35.6 (61.5)**	−36.4 (58.2)**
Percent change in TJC (0–78), mean (S.D.)	1.3 (65.0)	−18.1 (66.4)**	−26.1 (46.7)***
Change in CRP (normal range: 0–0.5), mean (S.D.), mg/dl	−0.03 (3.0)	−0.02 (1.1)	−0.11 (0.8)
Change in patient's global assessment of disease activity (0–100 mm VAS), mean (S.D.)	0.8 (26.4)	−2.9 (27.1)*	−7.0 (29.9)**
Change in physician's global assessment of disease activity (0–100 mm VAS), mean (S.D.)	−6.4 (21.7)	−14.3 (25.1)**	−16.9 (23.0)***
Change in patient's assessment of pain (0–100 mm VAS), mean (S.D.)	−2.7 (25.3)	−8.2 (25.5)*	−9.8 (29.0)**
PASI-50, *n/N* (%)[a,c]	18/93 (19.4)	46/104 (44.2)**	50/109 (45.9)***
PASI-75, *n/N* (%)[a,c]	10/93 (10.8)	18/104 (17.3)	28/109 (25.7)*
Change in MASES (0–13), mean (S.D.)[d]	−0.4 (2.6)	−0.6 (2.6)	−1.4 (2.8)**
MASES = 0, *n/N* (%)[a,d]	22/115 (19.1)	25/117 (21.4)	39/111 (35.1)*
Change in dactylitis count (0–20), mean (S.D.)[e]	−0.9 (3.0)	−1.8 (2.9)*	−1.9 (3.3)*
Dactylitis count = 0, *n/N* (%)[a,e]	28/90 (31.1)	36/89 (40.4)	34/84 (40.5)

n reflects modified intent-to-treat patients; the actual number of patients available for each endpoint may vary. $^{*}P < 0.05$; $^{**}P \leqslant 0.005$; $^{***}P \leqslant 0.0001$ *vs* placebo, based on analysis of covariance model for continuous endpoints and chi-square test for binary endpoints. [a]Patients who discontinued or did not have sufficient data were counted as non-responders. [b]Increase indicates improvement. [c]Examined among patients with BSA ⩾3% at baseline (placebo, $n = 93$; apremilast 20 mg BID, $n = 104$; apremilast 30 mg BID, $n = 109$). [d]Examined among patients with enthesitis at baseline (placebo, $n = 115$; apremilast 20 mg BID, $n = 117$; apremilast 30 mg BID, $n = 111$). [e]Examined among patients with dactylitis at baseline (placebo, $n = 90$; apremilast 20 mg BID, $n = 89$; apremilast 30 mg BID, $n = 84$). MCID: minimal clinically important difference; mPsARC: modified Psoriatic Arthritis Response Criteria; SF-36v2: 36-item Short-Form Health Survey version 2; VAS: visual analogue scale.

A history of depression was reported in 10.8% of patients at baseline. Rates of depression reported during 0–24 weeks were 0.9% with apremilast and 0.6% with placebo. The exposure-adjusted incidence of depression was 2.0/100 patient-years for apremilast in the 0- to 24-week period and 2.1/100 patient-years for apremilast in the 0- to 52-week period and thus did not indicate an increase with longer-term exposure to apremilast.

Weight decrease was reported as an AE in two patients receiving apremilast 30 mg during the 52-week apremilast exposure period. Additional analyses, using prospectively collected weight measurements, showed the majority of apremilast patients maintained their weight within 5% at their last weight measure at or before week 52 (apremilast 20 mg, 86.7%; apremilast 30 mg, 80.1%); 59 of 494 (11.9%) patients showed weight loss of >5% and the mean change in weight from baseline at their last weight measure at or before week 52 was −0.77 kg with apremilast 20 mg and −0.80 kg with apremilast 30 mg.

Discussion

The PALACE clinical trial programme, comprising four phase III studies, is one of the largest development programmes for PsA to date. PALACE 1, 2 and 3 assessed the efficacy and safety of apremilast in patients with active PsA and prior use of csDMARD and/or biologic therapy [9, 10]. PALACE 4, described here, evaluated apremilast monotherapy as the first systemic treatment for DMARD-naive and biologic-naive patients with active PsA.

PALACE 4 demonstrated therapeutic effects of apremilast monotherapy in DMARD-naive patients with active PsA, establishing statistically significant advantages of apremilast over placebo across various manifestations of PsA. Improvements in signs and symptoms, physical function and psoriasis were sustained over 52 weeks of continued apremilast treatment. The safety profile for apremilast was similar to that observed in previous investigations [9, 20, 22]. Importantly, PALACE 4 is one of the

Table 3 Efficacy results at week 52 (data as observed[a])

Efficacy parameters	Placebo/ apremilast 20 mg BID (*n* = 61)	Placebo/ apremilast 30 mg BID (*n* = 68)	Apremilast 20 mg BID (*n* = 132)	Apremilast 30 mg BID (*n* = 141)
ACR20, *n/N* (%)	37/62 (59.7)	38/67 (56.7)	70/131 (53.4)	81/138 (58.7)
ACR50, *n/N* (%)	19/62 (30.6)	17/67 (25.4)	35/129 (27.1)	44/138 (31.9)
ACR70, *n/N* (%)	5/61 (8.2)	7/68 (10.3)	18/131 (13.7)	25/138 (18.1)
Change in HAQ-DI (0–3), mean (S.D.)	−0.21 (0.45)	−0.25 (0.53)	−0.32 (0.56)	−0.39 (0.57)
HAQ-DI (0–3) MCID ⩾0.13, *n/N* (%)	33/62 (53.2)	38/68 (55.9)	75/132 (56.8)	82/139 (59.0)
HAQ-DI (0–3) MCID ⩾0.30, *n/N* (%)	25/62 (40.3)	30/68 (44.1)	64/132 (48.5)	68/139 (48.9)
Change in SF-36v2 physical functioning, mean (S.D.)[b]	4.8 (8.5)	6.1 (10.1)	4.6 (8.8)	6.4 (9.5)
Change in SF-36v2 physical component summary, mean (S.D.)[b]	5.2 (7.8)	6.9 (8.4)	5.6 (8.2)	6.7 (8.3)
EULAR good/moderate response, *n/N* (%)	40/62 (64.5)	50/68 (73.5)	98/130 (75.4)	109/138 (79.0)
mPsARC response, *n/N* (%)	45/61 (73.8)	53/67 (79.1)	99/131 (75.6)	104/137 (75.9)
Change in DAS28-CRP, mean (S.D.)	−1.1 (1.1)	−1.3 (1.0)	−1.4 (1.1)	−1.4 (1.0)
DAS28-CRP <2.6, *n/N* (%)	19/62 (30.6)	20/68 (29.4)	41/130 (31.5)	54/138 (39.1)
Change in CDAI (0–76), mean (S.D.)	−11.0 (10.3)	−14.7 (11.9)	−14.3 (11.1)	−14.0 (10.5)
Percent change in SJC (0–76), mean (S.D.)	−65.3 (48.2)	−75.8 (33.5)	−72.9 (42.8)	−76.1 (38.6)
Percent change in TJC (0–78), mean (S.D.)	−51.8 (45.1)	−58.3 (42.0)	−52.7 (48.2)	−60.0 (43.0)
Change in CRP (normal range 0–0.5), mean (S.D.), mg/dl	−0.56 (3.2)	−0.01 (1.1)	−0.26 (1.2)	−0.03 (1.2)
Change in patient's global assessment (0–100 mm VAS), mean (S.D.)	−14.2 (28.8)	−15.0 (24.7)	−9.4 (27.8)	−12.4 (29.8)
Change in physician's global assessment (0–100 mm VAS), mean (S.D.)	−28.6 (23.0)	−33.2 (21.3)	−31.6 (22.3)	−29.1 (20.8)
Change in patient's assessment of pain (0–100 mm VAS), mean (S.D.)	−13.1 (25.6)	−18.9 (24.3)	−15.6 (27.3)	−14.2 (28.1)
PASI-50, *n/N* (%)[c]	17/34 (50.0)	13/28 (46.4)	48/78 (61.5)	51/91 (56.0)
PASI-75, *n/N* (%)[c]	10/34 (29.4)	5/28 (17.9)	32/78 (41.0)	29/91 (31.9)
Change in MASES (0–13), mean (S.D.)[d]	−1.7 (2.4)	−1.8 (2.3)	−1.5 (2.6)	−1.8 (3.0)
MASES = 0, *n/N* (%)[d]	16/41 (39.0)	26/42 (61.9)	36/91 (39.6)	39/85 (45.9)
Change in dactylitis count (0–20), mean (S.D.)[e]	−2.2 (1.9)	−2.9 (2.5)	−2.2 (4.1)	−2.9 (3.6)
Dactylitis count = 0, *n/N* (%)[e]	24/32 (75.0)	30/38 (78.9)	48/70 (68.6)	44/64 (68.8)

[a]Based on patients randomized to apremilast; the placebo/apremilast 20 mg BID and placebo/apremilast 30 mg BID groups include patients who were randomized to placebo at baseline and rerandomized to apremilast 20 mg BID and apremilast 30 mg BID, respectively, at week 16 or 24; the apremilast 20 mg BID and apremilast 30 mg BID groups include patients randomized to the respective regimen at baseline. *n* reflects the number of patents who completed 52 weeks; the actual number of patients may vary for each endpoint, depending on the availability of data. [b]Increase indicates improvement. [c]Examined among patients with psoriasis involvement ⩾3% of BSA at baseline who had data at week 52 (placebo/apremilast 20 mg BID, *n* = 34; placebo/apremilast 30 mg BID, *n* = 28; apremilast 20 mg BID, *n* = 78; apremilast 30 mg BID, *n* = 91). [d]Examined among patients with enthesitis at baseline who had data at week 52 (placebo/apremilast 20 mg BID, *n* = 41; placebo/apremilast 30 mg BID, *n* = 42; apremilast 20 mg BID, *n* = 91; apremilast 30 mg BID, *n* = 85). [e]Examined among patients with dactylitis at baseline who had data at week 52 (placebo/apremilast 20 mg BID, *n* = 32; placebo/apremilast 30 mg BID, *n* = 38; apremilast 20 mg BID, *n* = 70; apremilast 30 mg BID, *n* = 64). MCID: minimal clinically important difference; mPsARC: modified Psoriatic Arthritis Response Criteria; SF-36v2: 36-item Short-Form Health Survey version 2; VAS: visual analogue scale.

first studies to demonstrate the efficacy and safety of a novel agent in solely DMARD-naive PsA patients.

Patients in this study were DMARD naive and biologic naive, but not all had early PsA; the mean PsA duration at baseline was 3.4 years (range 0–31.4). With disease recognition and management challenges, it is not surprising that many patients with longer disease duration are also DMARD naive.

Both apremilast doses demonstrated an advantage over placebo in ACR20 responses, reduction in SJC and TJC and improvements in physical disability as measured by the HAQ-DI score at week 16. Among patients with psoriasis involvement of ⩾3% of BSA at baseline, psoriasis symptoms improved with apremilast treatment. Other efficacy assessments showed statistically significant therapeutic effects of one or both doses of apremilast *vs* placebo at week 16, except for ACR70 response, DAS28-CRP <2.6 response and serum CRP levels. Improvements observed at week 16 were sustained among those continuing treatment up to 52 weeks. These results supplement the PALACE 1, 2 and 3 studies of DMARD-experienced patients by providing apremilast efficacy and safety information in PsA patients who were DMARD naive [9, 10].

The two most common AEs were diarrhoea and nausea, which generally occurred early (within the first 2 weeks of

Table 4 AEs and laboratory abnormalities during the placebo-controlled period (weeks 0–24) and apremilast exposure period (weeks 0–52)

Events and Laboratory Assessments	Weeks 0–24[a]			Weeks 0–52[b]	
		Apremilast		Apremilast	
	Placebo ($n = 176$)	20 mg BID ($n = 175$)	30 mg BID ($n = 175$)	20 mg BID ($n = 252$)	30 mg BID ($n = 252$)
Overview of AEs, *n* (%)					
Any AE	73 (41.5)	87 (49.7)	99 (56.6)	146 (57.9)	157 (62.3)
Any SAE	5 (2.8)	3 (1.7)	1 (0.6)	16 (6.3)	6 (2.4)
Any AE leading to drug withdrawal	4 (2.3)	4 (2.3)	6 (3.4)	14 (5.6)	12 (4.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs reported by ⩾5% of patients in any treatment group, *n* (%)					
Nausea	4 (2.3)	16 (9.1)	28 (16.0)	20 (7.9)	34 (13.5)
Diarrhoea	3 (1.7)	12 (6.9)	21 (12.0)	23 (9.1)	28 (11.1)
Headache	4 (2.3)	6 (3.4)	15 (8.6)	8 (3.2)	23 (9.1)
Upper respiratory tract infection	4 (2.3)	6 (3.4)	7 (4.0)	10 (4.0)	15 (6.0)
Select laboratory assessments, *n/m* (%)[c]					
Alanine aminotransferase >150 U/l	2/174 (1.1)	0/173 (0.0)	0/171 (0.0)	1/250 (0.4)	2/246 (0.8)
Creatinine (male >156 μmol/l; female >126 μmol/l)	0/174 (0.0)	1/173 (0.6)	0/171 (0.0)	1/250 (0.4)	1/246 (0.4)
Haemoglobin (male: decrease >2.0 and value <10.5 g/dl; female: decrease >2.0 and value <10.0 g/dl)	0/174 (0.0)	0/173 (0.0)	0/170 (0.0)	1/250 (0.4)	5/245 (2.0)
Leucocytes <2.0, 10^9/l	1/174 (0.6)	0/173 (0.0)	0/171 (0.0)	0/250 (0.0)	1/246 (0.4)
Neutrophils <0.75, 10^9/l	1/174 (0.6)	1/173 (0.6)	1/170 (0.6)	2/250 (0.8)	1/245 (0.4)
Platelets <75, 10^9/l	0/174 (0.0)	0/173 (0.0)	0/170 (0.0)	0/250 (0.0)	0/246 (0.0)

[a]Placebo-controlled period includes data through week 16 for patients who initially received placebo who escaped and data through week 24 for all other patients. [b]Includes all patients who received one or more doses of apremilast, regardless of when treatment started. [c]Represents patients with at least one occurrence of the abnormality (*n*)/patients with a baseline value and at least one post-baseline value for criteria requiring baseline or patients with at least one post-baseline value for criteria not requiring baseline (*m*).

treatment) and usually resolved within 4 weeks in the vast majority of cases without the need for treatment or intervention. Although many conventional PsA agents require ongoing laboratory monitoring for safety concerns [23, 24], no clinically meaningful effects on laboratory measurements were observed with apremilast up to week 52. The safety profile observed here is similar to that in previous investigations of apremilast in PsA and psoriasis [9, 20, 22].

PsA is a chronic immune disease typically emerging after psoriasis onset and often requiring long-term treatment [25, 26]. For patients with polyarticular disease or with refractory oligoarthritis, early institution of DMARDs has become the standard of care [27, 28]. However, these agents have demonstrated marginal efficacy in PsA and are associated with potential long-term toxicities requiring ongoing laboratory monitoring [23, 24]. In the TIght COntrol in Psoriatic Arthritis study, when MTX (alone or with concomitant csDMARDs or biologics) was given as part of a tight control regimen in DMARD-naive patients, patients had higher clinical outcomes; however, they also experienced a higher frequency of AEs such as respiratory tract infection, nausea, fatigue and gastrointestinal upset compared with standard therapy [8]. SAEs were also more frequently reported in the tight control group [8]. While efficacious in PsA, biologic therapy is not broadly prescribed in DMARD-naive patients and requires ongoing safety monitoring; these injectable therapies also may be burdensome for some patients [7, 29]. Access to effective treatment for PsA may be limited due to a lack of experienced specialists concerned with the somewhat burdensome monitoring required for agents such as MTX and biologics. The new warnings put forth by the Food and Drug Administration on the use of NSAIDs limit the use of these agents in PsA patients, especially those with underlying cardiovascular risk factors or those with a history of gastrointestinal and renal complications.

Patient concerns with safety and the need for laboratory monitoring can further hinder the initiation and continuation of needed treatment, underscoring the importance of effective as well as safe treatment options. According to the Multinational Assessment of Psoriasis and Psoriatic Arthritis survey, 35% of patients who had ever used biologics and 57% of patients who had taken conventional therapies found them burdensome, in part because of AEs, required laboratory monitoring and inconvenience [7]. A quarter of the biologic patients and about two-fifths of the oral therapy patients who discontinued therapy did so because of safety and tolerability issues [7]. In addition, about 50% of patients noted concerns about long-term health risks with chronic biologic or oral therapy [7].

The lack of monitoring requirements and the overall long-term benefit–risk profile with oral apremilast make it a therapeutic option for patients with active PsA whose systemic treatment choices may be limited by efficacy, frequent laboratory safety requirements and tolerability.

Limitations

PALACE 4 required patients to be DMARD naive and biologic naive; nevertheless, many patients had long-standing disease. As such, findings may not be fully extrapolated to an early PsA and DMARD-naive population. A subgroup analysis of individuals with PsA diagnosis <2 years showed greater treatment effect for apremilast *vs* placebo (week 16 ACR20, 31.1% *vs* 12.3%). PALACE 4 did not allow for combination therapies and thus cannot address whether apremilast with another DMARD would have additive efficacy in a DMARD-naive population. However, the PALACE 1–3 studies describe apremilast efficacy in patients with prior use of csDMARD and/or biologics [9, 30, 31].

Longer-term findings at week 52 are not placebo controlled and may reflect non-random patient dropout over time due to AEs or lack of efficacy. No imputations were made for missing values for week 52 data. While this limits the ability to assess whether symptoms may have improved without active treatment, it is not uncommon in long-term clinical studies and may be representative of what can be expected in real-world clinical practice.

Conclusion

This report represents the first phase III data supporting the efficacy and safety of apremilast monotherapy in DMARD-naive patients with active PsA. Apremilast led to clinically meaningful improvements in the signs and symptoms of PsA, physical function and psoriasis up to 52 weeks. Apremilast demonstrated an acceptable safety profile and was generally well tolerated up to 52 weeks. Given the favourable benefit–risk profile, apremilast may be a treatment option for DMARD-naive patients with active PsA.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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