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EXTENDED REPORT

Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor

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ABSTRACT

Objectives Apremilast, an oral phosphodiesterase 4 inhibitor, regulates inflammatory mediators. Psoriatic Arthritis Long-term Assessment of Clinical Efficacy 1 (PALACE 1) compared apremilast with placebo in patients with active psoriatic arthritis despite prior traditional disease-modifying antirheumatic drug (DMARD) and/or biologic therapy.

Methods In the 24-week, placebo-controlled phase of PALACE 1, patients (N=504) were randomised (1:1:1) to placebo, apremilast 20 mg twice a day (BID) or apremilast 30 mg BID. At week 16, patients without ≥20% reduction in swollen and tender joint counts were required to be re-randomised equally to either apremilast dose if initially randomised to placebo or remained on their initial apremilast dose. Patients on background concurrent DMARDs continued stable doses (methotrexate, leflunomide and/or sulfasalazine). Primary outcome was the proportion of patients achieving 20% improvement in modified American College of Rheumatology response criteria (ACR20) at week 16.

Results At week 16, significantly more apremilast 20 mg BID (31%) and 30 mg BID (40%) patients achieved ACR20 versus placebo (19%) (p<0.001). Significant improvements in key secondary measures (physical function, psoriasis) were evident with both apremilast doses versus placebo. Across outcome measures, the 30-mg group generally had higher and more consistent response rates, although statistical comparison was not conducted. The most common adverse events were gastrointestinal and generally occurred early, were self-limiting and infrequently led to discontinuation. No imbalance in major adverse cardiac events, serious or opportunistic infections, malignancies or laboratory abnormalities was observed.

Conclusions Apremilast was effective in the treatment of psoriatic arthritis, improving signs and symptoms and physical function. Apremilast demonstrated an acceptable safety profile and was generally well tolerated.

Clinical trial registration number NCT01172938.

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INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthritis present in up to 30% of patients with psoriasis, with an estimated prevalence of 0.3–1.0% of the general population.[1] While there are therapeutic options for PsA, not all patients respond to or tolerate currently available treatments.[2–5] Thus, a need exists for additional oral treatment options with a novel mechanism of action.

Apremilast is an oral phosphodiesterase 4 inhibitor that has been shown to regulate inflammatory mediators.[6] Phosphodiesterase 4, the dominant phosphodiesterase expressed in immune cells, degrades cyclic AMP (cAMP) into AMP. Phosphodiesterase 4 inhibition thereby elevates intracellular cAMP, which can down-regulate the inflammatory responses through mechanisms such as partially inhibiting expression of inflammatory cytokines and increasing expression of anti-inflammatory mediators such as interleukin-10.[6 7]

The phase 3 Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) clinical trial programme assessed the efficacy, tolerability and safety of apremilast in patients with active PsA across four placebo-controlled trials. This report describes results from the first trial (PALACE 1) that enrolled patients with active PsA despite prior traditional disease-modifying antirheumatic drugs (DMARDs) and/or biologics.

METHODS

Patients

Patients were eligible for enrolment if they were ≥18 years of age and were diagnosed with active PsA. The institutional review boards at each participating medical centre approved the protocol and all patients provided written informed consent before study entry. Patients were required to meet the Classification Criteria for Psoriatic Arthritis (CASPAR)[8] at screening and have a minimum of both three swollen and three tender joints, despite prior treatment with traditional DMARDs and/or biologic treatment or concurrent treatment with traditional DMARDs. Prior tumour necrosis factor blocker efficacy failures were limited to ≤10% of enrolled patients. Patients taking methotrexate, leflunomide or sulfasalazine must have been treated for at least 16 weeks and on a stable dose (oral or parenteral methotrexate ≤25 mg/week; leflunomide ≤20 mg/day; sulfasalazine ≤2 g/day; or a combination) for at least 4 weeks before the screening visit. Stable doses of oral corticosteroids (prednisone ≤10 mg/day or equivalent for at least 1 month) and non-steroidal anti-inflammatory drugs (≥2 weeks) were permitted.

Key exclusion criteria were failure of more than three agents for PsA (DMARDs or biologics) or more

than one tumour necrosis factor blocker. Patients were also excluded if they had a history of or current (1) inflammatory, rheumatic or autoimmune joint disease other than PsA; (2) erythrodermic, guttate or generalised pustular psoriasis; (3) were functional class IV, defined by the American College of Rheumatology (ACR) Classification of Functional Status in Rheumatoid Arthritis; (4) had used phototherapy or DMARDs other than methotrexate, leflunomide or sulfasalazine within 4 weeks of randomisation; (5) had used adalimumab, etanercept, golimumab, infliximab, certolizumab pegol or tocilizumab within 12 weeks of randomisation or alefacept or ustekinumab within 24 weeks of randomisation; or (6) had prior treatment with apremilast. Topical therapy for psoriasis within 2 weeks of randomisation was not permitted. Patients with active tuberculosis or a history of incompletely treated tuberculosis could not participate.

Study design

PALACE 1, a phase 3, randomised, placebo-controlled study, was conducted at 83 sites in 13 countries beginning 2 June 2010 (clinical trial registration NCT01172938, ClinicalTrials.gov). Patients were randomised (1:1:1) to placebo, apremilast 20 mg twice a day (BID) or apremilast 30 mg BID stratified by baseline DMARD use (yes/no). Apremilast was dose-titrated over the first week of treatment (10 mg on the first day, with increases of 10 mg/day until the target dose was reached). Study visits were conducted at weeks 4, 16 and 24 for safety and weeks 16 and 24 for efficacy assessments. Patients whose swollen and tender joint counts had not improved by ≥20% were considered non-responders at week 16 and were required to enter the protocol-defined early escape. Patients receiving placebo were re-randomised (1:1) to apremilast 20 mg BID or 30 mg BID, while those on apremilast remained on their initial apremilast dose. Treatment was continued through week 24, at which time all remaining placebo patients were re-randomised (1:1) to apremilast 20 mg BID or 30 mg BID. Subsequently, all patients entered the 28-week randomised, double-blind, active-treatment phase until week 52. Individual patient treatment assignments remained blinded to the investigators until final data analyses were completed after week 52. The active-treatment, long-term safety phase started at week 52, and patients are continuing their assigned treatment up to a total of 5 years. This report describes outcomes from the 24-week placebo-controlled phase.

Efficacy assessments

The primary efficacy endpoint was the proportion of patients meeting 20% improvement in modified ACR response criteria (ACR20)[9] at week 16. The key secondary endpoint was change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) at week 16. Additional efficacy outcome measures at week 24 included improvements in the signs and symptoms of PsA, physical function, enthesitis, dactylitis and psoriasis (see online supplementary table S1).

Safety assessments

Safety was evaluated at all scheduled clinic visits based on adverse events (AEs), vital signs, weight, physical examination and clinical laboratory investigations; a 12-lead electrocardiogram was obtained at screening, baseline and weeks 16 and 24. Safety assessments were also conducted in the event of early termination. There was no protocol requirement to stop study medication for an infection, no exclusions for vaccinations (including live virus) and no screening required for latent tuberculosis. AEs occurring after randomisation were classified using the Medical Dictionary for Drug Regulatory Activities Classification System.

Statistical analysis

Sample size estimations were based on the results of a phase 2 study of apremilast[10]; thus, it was estimated that 165 patients would be needed to provide 95% power to detect a 20% absolute difference in the ACR20 response between apremilast treatment and placebo using a two-group χ^2 test with a 0.025 two-sided significance level. Efficacy was evaluated for the per-protocol population, which included all patients in the safety population (ie, randomised patients receiving at least one dose of study medication) who had at least one post-treatment ACR evaluation and no critical protocol violations. Protocol violations excluding patients from the per-protocol population were determined before unblinding of the 24-week database. The primary analysis of ACR20 response at week 16 was compared between apremilast treatment groups and placebo using a Cochran-Mantel-Haenszel test adjusted for concomitant DMARD use at baseline. Patients who terminated the study early, before week 16, or did not have sufficient data for assessment at week 16 were considered non-responders (non-responder imputation approach); last-observation-carried-forward methodology was used for the sensitivity analysis. Pairwise comparisons of each apremilast group versus placebo were performed. The Hochberg procedure was used to maintain type 1 error at the 0.05 significance level. Results were considered statistically significant if both the apremilast 20 mg BID and 30 mg BID versus placebo comparisons achieved $p<0.05$, or one of the apremilast versus placebo comparisons achieved $p<0.025$.

Analysis of covariance was used to compare the change in HAQ-DI score from baseline to week 16, with treatment and DMARD use as factors and baseline HAQ-DI score as a covariate. Categorical variables were analysed using the Cochran-Mantel-Haenszel test, and continuous variables were analysed using the analysis of covariance model. Safety data were summarised descriptively for the safety population.

RESULTS

Patients

A total of 615 patients were screened and 504 were randomised and received at least one dose of study medication (figure 1). The pre-specified per-protocol efficacy population included 489 patients; 15 (3.0%) were excluded for critical protocol violations, which included not having at least one post-baseline efficacy assessment that allowed for ACR20 calculation; one patient also had very low treatment compliance (41%). In all, 444 (88.1%) patients completed week 24.

Baseline demographics, disease characteristics and prior or concurrent therapy were comparable across treatment groups (table 1). In addition, these were generally consistent in the subgroup of biologic-experienced patients. As would be expected, relative to the overall population, patients with biologic experience tended to have a longer duration of both PsA and psoriasis, a greater proportion had baseline psoriasis body surface area ≥3%, and a lower proportion were taking concomitant DMARDs at baseline. At baseline, 327 (64.9%) patients were taking DMARDs, of whom 273 (83.5%) were taking methotrexate; 119 (23.6%) had prior biologic exposure, and 47 (9.3%) were considered biologic therapeutic failures.

Efficacy

At week 16, significantly more patients receiving apremilast 20 mg BID (51/163 (31.3%); p=0.0140) and 30 mg BID (64/161 (39.8%); p=0.0001) achieved an ACR20 response versus placebo (32/165 (19.4%); figure 2A). The intent-to-treat

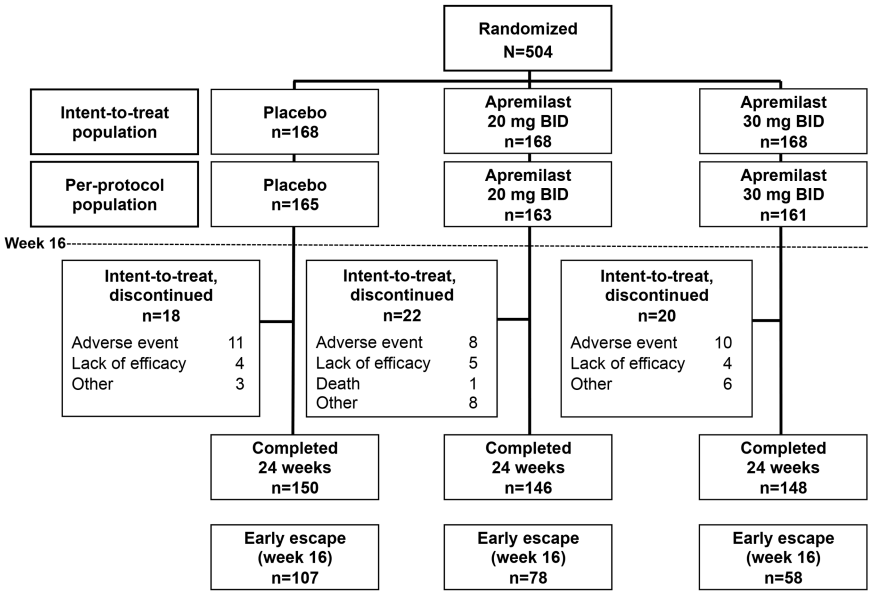

Figure 1 Patient disposition through week 24.

analysis, which included all patients who were randomised as specified in the protocol, demonstrated consistent results (placebo, 32/168 (19.0%); apremilast 20 mg BID, 51/168 (30.4%), p=0.0166; apremilast 30 mg BID, 64/168 (38.1%), p=0.0001). Efficacy was demonstrated across patients with varying treatment experience. Biologic-naïve patients generally experienced higher absolute ACR20 response rates compared with biologic-experienced patients and patients with a history of biologic failure (figure 2B). In general, a dose-related effect was observed with higher ACR20 response rates achieved in those receiving apremilast 30 mg BID versus 20 mg BID, although statistical comparison was not conducted.

Secondary efficacy measures

Week 16 values for baseline clinical characteristics are presented in online supplementary table S2. At week 16, apremilast was associated with significantly greater reductions (improvements) in HAQ-DI compared with placebo (key secondary endpoint). The mean (SE) changes from baseline were −0.09 (0.04) (placebo), −0.20 (0.04) (apremilast 20 mg BID; p=0.0252 vs placebo), and −0.25 (0.04) (apremilast 30 mg BID; p=0.0015 vs placebo). The intent-to-treat analysis demonstrated consistent results (placebo: −0.09 (0.04); apremilast 20 mg BID: −0.20 (0.04) (p=0.0252); apremilast 30 mg BID: −0.24 (0.04) (p=0.0017)). At week 16, a significantly greater proportion of patients receiving apremilast 30 mg BID achieved minimal clinically important differences (MCID) of ≥0.13 and ≥0.30 on the HAQ-DI compared with placebo; differences between apremilast 20 mg BID and placebo did not reach statistical significance. MCID≥0.13 was achieved by 38.8% (placebo), 44.8% (apremilast 20 mg BID), and 50.3% (apremilast 30 mg BID; p=0.0334 vs placebo) of patients. MCID≥0.30 was achieved by 27.3% (placebo), 33.7% (apremilast 20 mg BID) and 39.8% (apremilast 30 mg BID, p=0.0149 vs placebo) of patients.

Table 2 summarises the effects of apremilast on additional efficacy measures at week 24. A significantly greater proportion of patients receiving apremilast 20 mg BID and 30 mg BID achieved ACR20, ACR50 and ACR70 versus placebo; these response rates were maintained in the active treatment groups. An ACR20 response of 45.3% was observed at week 24 in patients treated with apremilast 30 mg BID independent of their response at week 16. A statistically significant improvement in physical function was observed with apremilast, as measured by changes from baseline in HAQ-DI score and the 36-Item Short-Form Health Survey v2 Physical Functioning domain score. Significant improvements in most ACR component scores, particularly swollen and tender joint counts and patient assessment of pain, were also observed (table 2).

In patients with baseline enthesitis, the mean change from baseline in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was significantly higher for apremilast 30 mg BID versus placebo (p=0.0334) (table 2), and significantly greater proportions of patients receiving apremilast 20 mg BID (32/100 (32.0%); p=0.0037) and 30 mg BID (36/107 (33.6%); p=0.0013) achieved a MASES score of 0 at week 24 versus placebo (14/97 (14.4%)). In patients with baseline dactylitis, mean change from baseline in dactylitis severity score was higher with apremilast versus placebo and resulted in greater proportions of patients with dactylitis scores achieving 0 at week 24 (apremilast 20 mg BID: 29/57 (50.9%); apremilast 30 mg BID: 31/65 (47.7%)) versus placebo (27/66 (40.9%)). However, these differences did not reach statistical significance at week 24.

In patients with baseline psoriasis affecting ≥3% of the body surface area, significantly greater proportions of patients receiving either dose of apremilast achieved at least 50% reduction from baseline Psoriasis Area and Severity Index[11] (PASI-50) score (apremilast 20 mg BID: 25/74 (33.8%), p=0.0439; apremilast 30 mg BID: 41/81 (50.6%), p=0.0001) and PASI-75 score (13/74 (17.6%), p=0.0180; 17/81 (21.0%), p=0.0040) versus placebo (PASI-50: 12/65 (18.5%); PASI-75: 3/65 (4.6%)).

Safety

During the 24-week placebo-controlled phase, AEs occurring in ≥5% of any treatment group included diarrhoea, nausea, headache and upper respiratory tract infection (table 3). Most AEs were mild to moderate in severity, and discontinuations due to AEs were comparable across groups (placebo: 8/168 (4.8%); apremilast 20 mg BID: 10/168 (6.0%); apremilast 30 mg BID: 12/168 (7.1%)). Gastrointestinal AEs were predominantly mild or moderate in severity, presented early, were self-limited and did not recur. Antidiarrhoeal use was low; 16 patients took antidiarrhoeal medication during the study, with 11 of these

Table 1 Baseline demographics and clinical characteristics: intent-to-treat population (N=504*)

		Apremilast	
	Placebo n=168	20 mg BID n=168	30 mg BID n=168
Age, mean (SD), years	51.1 (12.1)	48.7 (11.0)	51.4 (11.7)
Age ≥65 years, n	19 (11.3%)	11 (6.5%)	22 (13.1%)
Female, n	80 (47.6%)	83 (49.4%)	92 (54.8%)
Race, n			
White	153 (91.1%)	150 (89.3%)	152 (90.5%)
Asian	8 (4.8%)	8 (4.8%)	8 (4.8%)
Black	0 (0.0%)	2 (1.2%)	0 (0.0%)
Other	7 (4.2%)	8 (4.8%)	8 (4.8%)
Region, n			
North America	81 (48.2%)	73 (43.5%)	69 (41.1%)
Europe	39 (23.2%)	41 (24.4%)	42 (25.0%)
Rest of world	48 (28.6%)	54 (32.1%)	57 (33.9%)
Weight, mean (SD), kg	89.8 (22.4)	88.8 (21.1)	87.1 (19.6)
Body mass index, mean (SD), kg/m^2	31.1 (6.6)	30.9 (7.3)	30.6 (5.9)
Duration of psoriatic arthritis, mean (SD), years	7.3 (7.1)	7.2 (6.8)	8.1 (8.1)
Swollen joint count (0–76), mean (SD)	12.8 (8.8)	12.5 (9.5)	12.8 (7.8)
Tender joint count (0–78), mean (SD)	23.3 (15.2)	22.2 (15.9)	23.1 (14.5)
HAQ-DI (0–3), mean (SD)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)
Patient Global Assessment (0–100 mm VAS), mean (SD)	58.8 (22.3)	55.3 (23.7)	55.9 (21.5)
Physician Global Assessment (0–100 mm VAS), mean (SD)	55.2 (20.3)	54.1 (21.8)	55.7 (19.2)
CRP (mg/dL, normal range <0.5), mean (SD)	1.1 (1.436)	0.90 (1.409)	0.84 (1.024)
Patient assessment of pain (0–100 mm VAS), mean (SD)	61.2 (20.2)	54.9 (22.9)	57.9 (20.2)
SF-36v2 PF score, mean (SD)	33.8 (10.6)	35.1 (10.7)	33.0 (10.2)
DAS-28 (CRP), mean (SD)	4.9 (1.0)	4.8 (1.1)	4.9 (1.0)
CDAI (0–76), mean (SD)	29.7 (12.0)	28.4 (13.1)	29.4 (11.5)
Duration of psoriasis, mean (SD), years	15.7 (13.0)	15.5 (11.9)	16.5 (12.3)
Psoriasis involvement of body surface area ≥3%, n	68 (40.5%)	77 (45.8%)	82 (48.8%)
PASI score (0–72),† mean (SD)	9.1 (9.5)	7.4 (8.7)	9.2 (9.7)
Presence of enthesitis, n	98 (58.3%)	103 (61.3%)	114 (67.9%)
MASES (0–13),‡ mean (SD)	5.4 (3.5)	5.0 (3.3)	4.4 (3.1)
Presence of dactylitis, n	68 (40.5%)	59 (35.1%)	68 (40.5%)
Dactylitis severity score (0–20),§ mean (SD)	3.3 (3.3)	4.1 (4.2)	2.9 (2.4)
Prior use of DMARDs (biologic-naïve), n	120 (71.4%)	129 (76.8%)	124 (73.8%)
Prior use of biologics, n	41 (24.4%)	37 (22.0%)	41 (24.4%)
Prior biologic failures, n	19 (11.3%)	14 (8.3%)	14 (8.3%)
Baseline DMARD use, n	110 (65.5%)	111 (66.1%)	106 (63.1%)
Methotrexate (mean dose, 16.6 mg/week)	90 (53.6%)	95 (56.5%)	88 (52.4%)
Leflunomide (mean dose, 17.2 mg/day)	11 (6.5%)	10 (6.0%)	9 (5.4%)
Sulfasalazine (mean dose, 2.3 g/day)	18 (10.7%)	16 (9.5%)	20 (11.9%)
Baseline corticosteroids,¶ n (mean dose, 6.1 mg/day)	12 (7.1%)	25 (14.9%)	16 (9.5%)
Baseline use of NSAIDs, n	118 (70.2%)	123 (73.2%)	120 (71.4%)

*The n reflects the number of randomised patients; actual number of patients available for each endpoint may vary.
†Examined among patients who had body surface area ≥3% affected at baseline.
‡Examined among patients who had enthesitis at baseline.
§Examined among patients who had dactylitis at baseline.
¶Prednisone ≤10 mg/day (or equivalent).
CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS-28, 28-joint Disease Activity Score; DMARDs, disease-modifying antirheumatic drugs; HAQ-DI, Health Assessment Questionnaire–Disability Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; NSAIDs, non-steroidal anti-inflammatory drugs; PASI, Psoriasis Area and Severity Index; SF-36v2 PF, 36-Item Short-Form Health Survey v2 Physical Functioning domain; VAS, visual analogue scale.

patients taking medication while experiencing diarrhoea as an AE. Hence, a low rate of discontinuation was associated with gastrointestinal AEs (placebo: 4/168 (2.4%); apremilast 20 mg BID: 3/168 (1.8%); apremilast 30 mg BID: 7/168 (4.2%)). Severe nausea was reported by one patient in each apremilast group, and severe diarrhoea was reported by one patient each in the placebo and apremilast 20 mg BID groups. In patients receiving apremilast, median onset of diarrhoea (56 events in 51 patients) and nausea (59 events in 47 patients) was 9 and 10 days, respectively, and the median duration was 29.5 and 17 days. Of note, the first study visit occurred at week 4.

Serious AEs were low and comparable across treatment groups. Among these were four serious infections, two of which occurred with placebo (cellulitis and bacterial wound infection) and two of which occurred with apremilast 30 mg BID (gastrointestinal clostridial infection and pneumonia). All patients with

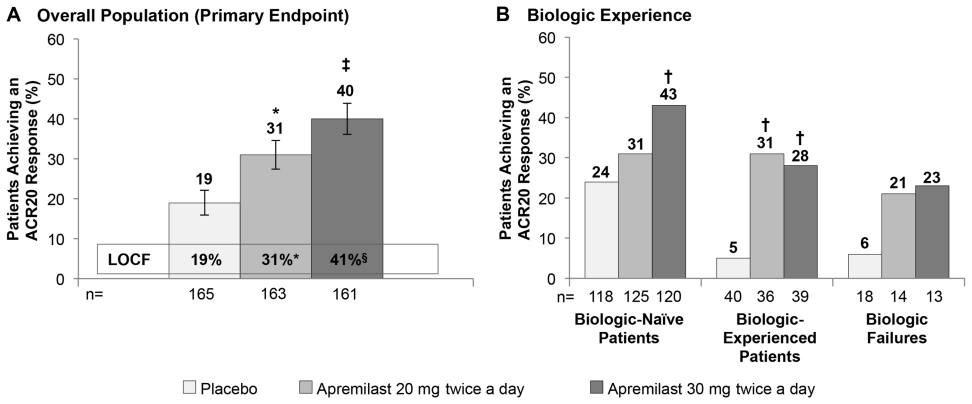

Figure 2 Proportion of patients achieving 20% improvement in modified American College of Rheumatology (ACR20) response criteria at week 16. (A) The proportion of patients achieving an ACR20 response at week 16 (primary efficacy endpoint). (B) The proportion of patients achieving an ACR20 response by biologic experience. The per-protocol population (n=489) was analysed using non-responder imputation for missing data; last-observation-carried-forward (LOCF) methodology was used for sensitivity analyses. Error bars represent SE. *p<0.02; †p<0.007; ‡p<0.001.

serious infections recovered after standard courses of antibiotic treatment and continued the study. Other serious events included two myocardial infarctions (placebo and apremilast 20 mg BID) and two solid tumour malignancies (placebo: prostate cancer; apremilast 30 mg BID: breast cancer). One death occurred on day 73 in a 52-year-old woman receiving apremilast 20 mg BID plus methotrexate; the primary cause of death was multiorgan failure secondary to pre-existing vitamin B12 deficiency and was considered unrelated to study medication by the investigator. No cases of active tuberculosis (new or reactivation, despite no latent tuberculosis screening requirements), lymphoma or vasculitis were reported.

Table 2 Secondary outcomes at week 24: per-protocol population (n=489*)

		Apremilast			
	Placebo n=165	20 mg BID n=163	p Value vs placebo	30 mg BID n=161	p Value vs placebo
ACR20, n†	22 (13.3%)	43 (26.4%)	0.0032	59 (36.6%)	<0.0001
ACR50, n†	7 (4.2%)	24 (14.7%)	0.0013	32 (19.9%)	<0.0001
ACR70, n†	1 (0.6%)	9 (5.5%)	0.0102	17 (10.6%)	0.0001
HAQ-DI (0–3), LS mean change (SE)	−0.08 (0.04)	−0.21 (0.04)	0.0092	−0.26 (0.04)	0.0004
SF-36v2 PF score, LS mean change (SE)‡	1.5 (0.67)	3.5 (0.68)	0.0295	5.1 (0.67)	0.0001
EULAR good/moderate response, n	27 (16.4%)	51 (31.3%)	0.0016	71 (44.1%)	<0.0001
DAS-28 (CRP), LS mean change (SE)	−0.20 (0.09)	−0.66 (0.09)	0.0002	−0.91 (0.09)	<0.0001
DAS-28 (CRP) <2.6, n	4 (2.4%)	19 (11.7%)	0.0011	30 (18.6%)	<0.0001
CDAI (0–76), LS mean change (SE)	−3.1 (0.97)	−7.6 (0.96)	0.0010	−9.6 (0.95)	<0.0001
Patient assessment of pain (0–100 mm VAS), LS mean change (SE)	−4.1 (1.8)	−11.3 (1.8)	0.0045	−14.8 (1.8)	<0.0001
Swollen joint count (0–76), LS mean change (SE)	−1.4 (0.63)	−4.1 (0.63)	0.0023	−5.1 (0.63)	<0.0001
Tender joint count (0–78), LS mean change (SE)	−0.91 (1.01)	−5.0 (1.0)	0.0035	−7.8 (1.0)	<0.0001
Patient Global Assessment (0–100 mm VAS), LS mean change (SE)	−2.1 (1.9)	−8.0 (1.9)	0.0285	−12.1 (1.9)	0.0002
Physician Global Assessment (0–100 mm VAS), LS mean change (SE)	−6.7 (1.9)	−14.4 (1.9)	0.0040	−19.1 (1.9)	<0.0001
CRP (mg/dL, normal range <0.5), LS mean change (SE)	0.17 (0.09)	−0.02 (0.09)	0.1321	−0.05 (0.09)	0.0713
MASES (0–13),§ LS mean change (SE)	−0.8 (0.31)	−1.6 (0.30)	0.0678	−1.7 (0.29)	0.0334
Dactylitis severity score (0–20),¶ LS mean change (SE)	−1.3 (0.27)	−2.0 (0.30)	0.0710	−1.8 (0.27)	0.1753
PASI-50, n**	12 (18.5%)	25 (33.8%)	0.0439	41 (50.6%)	0.0001
PASI-75, n**	3 (4.6%)	13 (17.6%)	0.0180	17 (21.0%)	0.0040

Imputation methods included non-responder imputation for categorical endpoints that involve joint counts and last observation carried forward for all continuous endpoints and categorical endpoints that do not involve joint counts.
*The n reflects the number of randomised patients in the per-protocol population; actual number of patients available for each endpoint may vary.
†Patients who escaped early, discontinued early or did not have sufficient data for ACR response determination were counted as non-responders.
‡Increase in score from baseline indicates improvement.
§Examined among patients who had enthesitis at baseline and ≥1 post-baseline value at or prior to week 24 (placebo: n=96; apremilast 20 mg BID: n=100; apremilast 30 mg BID: n=107).
¶Examined among patients who had dactylitis at baseline and ≥1 post-baseline value at or prior to week 24; each digit on the patient's hand and feet was assessed for presence (score=1) or absence (score=0) of dactylitis. The dactylitis score was the sum of the individual assessments for all 20 digits (placebo: n=64; apremilast 20 mg BID: n=56; apremilast 30 mg BID: n=65).
**Examined among patients who had body surface area ≥3% at baseline (placebo: n=65; apremilast 20 mg BID: n=74; apremilast 30 mg BID: n=81).
ACR20/50/70, 20%/50%/70% improvement in modified American College of Rheumatology response criteria; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS-28 (CRP), 28-joint Disease Activity Score (using CRP as acute-phase reactant); EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire–Disability Index; LS, least-squares; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; PASI-50/75, 50%/75% reduction from baseline Psoriasis Area and Severity Index score; SF-36v2 PF, 36-Item Short-Form Health Survey Physical Functioning domain; VAS, visual analogue scale.

Table 3 Adverse events and laboratory abnormalities during the placebo-controlled phase (weeks 0–24)*

Patients	Placebo n=168	Apremilast 20 mg BID n=168	Apremilast 30 mg BID n=168
Overview of adverse events, n			
Any adverse event	81 (48.2%)	101 (60.1%)	103 (61.3%)
Any severe adverse event	6 (3.6%)	8 (4.8%)	11 (6.5%)
Any serious adverse event	7 (4.2%)	8 (4.8%)	9 (5.4%)
Any adverse event leading to drug withdrawal	8 (4.8%)	10 (6.0%)	12 (7.1%)
Adverse events reported by ≥5% of patients in any treatment group, n			
Diarrhoea	4 (2.4%)	19 (11.3%)	32 (19.0%)
Nausea	11 (6.5%)	16 (9.5%)	31 (18.5%)
Headache	8 (4.8%)	17 (10.1%)	18 (10.7%)
Upper respiratory tract infection	6 (3.6%)	10 (6.0%)	7 (4.2%)
Adverse events leading to discontinuation in >1 patient in any treatment group, n			
Diarrhoea	3 (1.8%)	0 (0.0%)	4 (2.4%)
Nausea	2 (1.2%)	2 (1.2%)	3 (1.8%)
Migraine	0 (0.0%)	1 (0.6%)	2 (1.2%)
Patients with select laboratory value shifts from normal to > the upper limit of normal, n†			
Alanine transaminase, U/L	20/150 (13.3%)	12/146 (8.2%)	12/155 (7.7%)
Creatinine, μmol/L	3/159 (1.9%)	7/151 (4.6%)	10/158 (6.3%)
Patients with select laboratory value shifts from normal to < the lower limit of normal, n†			
Leukocytes, 10^9/L	1/155 (0.6%)	4/155 (2.6%)	2/159 (1.3%)
Neutrophils, 10^9/L	2/146 (1.4%)	2/145 (1.4%)	5/151 (3.3%)
Platelets, 10^9/L	0/146 (0.0%)	0/142 (0.0%)	1/151 (0.7%)
Haemoglobin, g/dL	8/148 (5.4%)	7/149 (4.7%)	14/153 (9.2%)

*The safety population in the placebo-controlled phase includes all data through week 16 for patients initially assigned to placebo who escaped, and data through week 24 for all other patients.
†Represents the number of patients with at least one occurrence of the abnormality/the number of patients with a baseline value of normal and at least one post-baseline. Individual abnormalities were infrequent and returned to baseline values with continuation of apremilast administration or were associated with a concurrent medical condition or medication. There were no cases of liver function test elevations meeting Hy's Law.

Clinically meaningful laboratory abnormalities were infrequent, self-limited, and comparable between apremilast treatment arms and placebo. Observed weight loss was treatment-related, with <2% of patients with weight-related AEs. Mean (SD) weight change from baseline up to week 24 was 0.19 (2.6) kg with placebo (n=167), −1.29 (3.4) kg with apremilast 20 mg BID (n=166) and −0.97 (2.8) kg with apremilast 30 mg BID (n=168).

DISCUSSION

PsA is a chronic immune disease associated with significant morbidity. Traditional DMARDs remain the mainstay of PsA treatment. However, currently available DMARDs have demonstrated variable efficacy in treating all of the rheumatologic and dermatologic manifestations of PsA. The biologic agents, particularly tumour necrosis factor blockers, have demonstrated substantial responses for many, but not all, patients. All available agents have some potential safety concerns. Thus, there is an unmet medical need for novel therapeutic agents that address the varied clinical manifestations of PsA and offer a favourable benefit/risk profile.

This study presents the first phase 3 data demonstrating the efficacy of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with PsA and prior experience with traditional DMARDs and/or biologic therapies, including treatment failures. The majority of patients (>74.0%) had received prior treatment with one or more traditional DMARDs; 64.9% were on at least one DMARD at baseline, most commonly methotrexate. Of note, 23.6% of the patients had previous biologic exposure and 9.3% were considered biologic therapeutic failures. The enrolled patients were representative of a population with active, long-standing disease and a history of treatment experience. C-reactive protein (CRP) levels at baseline were lower than other PsA studies that, unlike the current study, had enrolment requirement criteria for CRP,[12 13] and, as expected, may be lower than patient populations with rheumatoid arthritis, as PsA is generally associated with lower CRP levels compared with rheumatoid arthritis.[14]

Both doses of apremilast significantly improved the signs and symptoms of PsA at week 16. Efficacy was observed with apremilast regardless of prior biologic experience or concomitant DMARD use, with a higher absolute rate of ACR20 response in biologic-naïve patients. Apremilast demonstrated statistically significant improvements in physical function, as measured by the HAQ-DI score at week 16. Continued dosing through week 24 maintained or further improved the signs and symptoms of PsA and physical function. Results based on additional efficacy measures, including ACR50, ACR70, swollen and tender joint counts, 36-item Short-Form Health Survey v2 Physical Functioning domain and PASI-75 score, were consistent with the positive ACR20 response rates and change in HAQ-DI score. A significantly greater proportion of patients receiving apremilast 20 mg BID and 30 mg BID achieved DAS-28 (CRP) remission (<2.6) compared with placebo. Across most efficacy measures, response rates and improvements were greater with apremilast 30 mg BID versus apremilast 20 mg BID, although the study was not designed to make formal efficacy comparisons.

Apremilast at doses of 20 mg BID and 30 mg BID was generally well tolerated over 24 weeks. The most common AEs were largely gastrointestinal, including diarrhoea and nausea; most of these occurred in the first month of treatment, were

predominantly mild or moderate in severity, and did not lead to discontinuation. Two serious infections (gastrointestinal clostridial infection, pneumonia) occurred in the apremilast treatment groups; each resolved with appropriate antibiotic treatment, and patients continued apremilast without interruption. No imbalance was observed between placebo and apremilast in terms of major adverse cardiac events, serious infections including systemic opportunistic infections or malignancies, including lymphoma. No cases of active tuberculosis or vasculitis were reported. Apremilast use did not result in clinically meaningful laboratory abnormalities, suggesting that routine laboratory monitoring may not be required when using apremilast.

The study was limited in duration, and results from the ongoing long-term phase are anticipated. This is the first study in the PALACE apremilast clinical trial programme, which comprises four phase 3 randomised, placebo-controlled trials with long-term, open-label extensions for up to 5 years. The programme is one of the largest to date in PsA patients who have prior DMARD and/or biologic experience. The significant efficacy observed in PALACE 1, across multiple domains of PsA, along with the safety and tolerability profile, and potential lack of requirement for laboratory monitoring, suggest apremilast may become an important addition to the current PsA treatment armamentarium.

CONCLUSION

These findings demonstrate that apremilast is effective for the treatment of active PsA across a diverse group of patients with prior treatment experience, alone or in combination with traditional DMARDs. Furthermore, apremilast was well tolerated in the majority of patients and demonstrated an acceptable safety profile. These results confirm the therapeutic potential of apremilast BID for treatment of patients with PsA.

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REFERENCES

1 Gladman DD, Antoni C, Mease P, *et al*. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005;64(Suppl 2):ii14–17.
2 Ash Z, Gaujoux-Viala C, Gossec L, *et al*. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2012;71:319–26.
3 Gossec L, Smolen JS, Gaujoux-Viala C, *et al*. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 2012;71:4–12.
4 Kingsley GH, Kowalczyk A, Taylor H, *et al*. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology (Oxford)* 2012;51:1368–77.
5 Menter A, Korman NJ, Elmets CA, *et al*. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol* 2009;61:451–85.
6 Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol* 2012;83:1583–90.
7 Schafer PH, Parton A, Gandhi AK, *et al*. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *Br J Pharmacol* 2010;159:842–55.
8 Taylor W, Gladman D, Helliwell P, *et al*. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
9 Felson DT, Anderson JJ, Boers M, *et al*. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727–35.
10 Schett G, Wollenhaupt J, Papp K, *et al*. Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2012;64:3156–67.
11 Mease PJ. Measures of psoriatic arthritis: tender and swollen joint assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). *Arthritis Care Res (Hoboken)* 2011;63(Suppl 11):S64–85.
12 McInnes IB, Kavanaugh A, Gottlieb AB, *et al*. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013;382:780–9.
13 Kavanaugh A, McInnes I, Mease P, *et al*. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009;60:976–86.
14 Lindqvist UR, Alenius GM, Husmark T, *et al*. The Swedish early psoriatic arthritis register—2-year followup: a comparison with early rheumatoid arthritis. *J Rheumatol* 2008;35:668–73.

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Notes