

Oral Apremilast in the Treatment of Active Psoriatic Arthritis

Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

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Objective. To evaluate the efficacy and safety of apremilast, a novel, orally available small molecule that specifically targets phosphodiesterase 4, in the treatment of active psoriatic arthritis (PsA).

Methods. This phase II, multicenter, randomized, double-blind, placebo-controlled study included the following: a 12-week treatment phase, with patients receiving

placebo, apremilast 20 mg twice per day, or apremilast 40 mg once per day; a 12-week treatment-extension phase, with patients in the placebo group re-randomized to receive apremilast; and a 4-week observational phase after treatment cessation. The primary end point was the proportion of patients achieving the American College of Rheumatology criteria for 20% improvement (ACR20) at week 12. Safety assessments included adverse events (AEs), physical examinations, vital signs, laboratory parameters, and electrocardiograms.

Results. Of the 204 patients with PsA who were randomized to a treatment group, 165 completed the treatment phase. At the end of the treatment phase (week 12), 43.5% of patients receiving apremilast 20 mg twice per day ($P < 0.001$) and 35.8% of those receiving 40 mg once per day ($P = 0.002$) achieved an ACR20 response, compared with 11.8% of those receiving placebo. At the end of the treatment-extension phase (week 24), >40% of patients in each group (patients receiving apremilast 20 mg twice per day, patients receiving apremilast 40 mg once per day, and patients in the placebo group re-randomized to receive apremilast) achieved the ACR20 level of improvement. Most patients in the treatment phase (84.3%) and treatment-extension phase (68.3%) reported ≥ 1 AE. Diarrhea, headache, nausea, fatigue, and nasopharyngitis were reported most frequently; most events were mild or moderate. No clinically relevant laboratory or electrocardiographic abnormalities were reported.

Conclusion. Treatment with apremilast at a dosage of 20 mg twice per day or 40 mg once per day demonstrated efficacy in comparison with placebo and was generally well tolerated in patients with active PsA. The balance of efficacy, tolerability, and safety supports further study of apremilast in PsA.

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that is present in up to 30% of individuals

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with psoriasis and ~1% of the general population (1,2). Irreversible joint damage begins to occur within the first year of disease onset in some patients and progresses over time, supporting the importance of early intervention (3,4).

PsA differs from rheumatoid arthritis (RA) in that it is characterized by the presence of enthesitis, dactylitis, spondylitis, and lower levels of C-reactive protein (CRP) (5). Approved PsA treatments include 4 biologic disease-modifying antirheumatic drugs (DMARDs): etanercept (6), adalimumab (7), golimumab (8), and infliximab (9). These tumor necrosis factor (TNF) inhibitors offer substantial improvements in efficacy over nonbiologic DMARDs, although concerns regarding their safety and tolerability complicate their use (10). Other biologic DMARDs have not been extensively investigated in patients with PsA (11–13) or have failed to show efficacy (anakinra) (14). Because of the high costs of biologic therapies (10,15), nonbiologic DMARD therapies, such as methotrexate (MTX), cyclosporin A, sulfasalazine, and leflunomide, are used as first-line therapy for PsA (16,17), usually based on their efficacy in psoriasis or RA. However, the efficacy of nonbiologic DMARD therapy in PsA has not been well-established in clinical studies (18). These agents have been associated with substantial safety, tolerability, and drug-interaction issues (16,18–20). With limited evidence-based treatment options, effective and well-tolerated oral PsA therapies, with improved safety profiles, are clearly needed.

The immune system is normally homeostatic, with mechanisms that turn off the immune response and avoid tissue damage from chronic inflammation. Of note, cAMP is one such intrinsic modulator of inflammatory responses. The cAMP level in cells is regulated by phosphodiesterases (PDEs), enzymes that are responsible for its hydrolysis. Phosphodiesterase 4 (PDE4) is a cAMP-specific PDE and the predominant PDE in inflammatory cells (21,22). Inhibition of PDE4 elevates intracellular cAMP levels, which, in turn, down-regulates the inflammatory response by modulating the expression of TNF α , interleukin-23 (IL-23), IL-12, and other inflammatory cytokines (21–24). Elevation of cAMP increases the suppression of antiinflammatory cytokines such as IL-10. Apremilast is a novel, orally available small molecule that specifically targets PDE4, and thus modulates expression of a network of proinflammatory and antiinflammatory mediators implicated in psoriasis and PsA (22). This study evaluated the clinical activity, safety, and tolerability of apremilast in the treatment of active PsA.

PATIENTS AND METHODS

Patients. Patients considered eligible for the study had to be ≥ 18 years of age, to have symptomatic PsA (according to the Moll and Wright criteria [25]) for ≥ 6 months before screening, and to have discontinued treatment with immunosuppressants other than MTX for an adequate washout period (washout duration ≥ 14 days for topical therapy, ≥ 28 days for nonbiologic systemic therapy and phototherapy, ≥ 56 days for etanercept, ≥ 84 days for adalimumab, efalizumab, or infliximab, and ≥ 168 days for alefacept). Participants were also required to have active PsA, defined as ≥ 3 swollen joints and ≥ 3 tender joints, at the time of screening and baseline, and to have tested negative for serum rheumatoid factor. No requirement was specified regarding CRP concentrations.

Patients who had been treated with MTX must have been receiving the therapy for ≥ 24 weeks and to have been receiving MTX at a stable dose for at least 8 weeks before screening and throughout the study. If oral corticosteroids had been prescribed, patients must have been receiving a stable dose of prednisone or equivalent at ≤ 10 mg/day for at least 28 days before screening and throughout the study. Patients who had received nonsteroidal antiinflammatory drugs must have been on a stable regimen for ≥ 14 days before screening and throughout the study.

Patients were not permitted to initiate treatment with a new DMARD during the study, but could remain on stable doses of the above-mentioned therapies. Other permitted treatments were acetaminophen, loratadine, pseudoephedrine, guaifenesin, and calcium. In patients with psoriasis, nonmedicated topical cream and coal tar shampoos were allowed, as were low-to-moderate potency topical corticosteroids for treating palm, face, scalp, plantar, axillae, and groin psoriatic lesions. Topical products were to be discontinued 24 hours before each study visit. Adequate contraception was required for women of childbearing age and men throughout the study. Patients were excluded if they had erythrodermic, guttate, or pustular forms of psoriasis, were at increased risk for opportunistic infections, including active or incompletely treated latent tuberculosis, had risk factors for, or a history of, human immunodeficiency virus, hepatitis B, or hepatitis C infection, had active malignancies within the previous 5 years, or had a history of any clinically significant major disease, such as cardiac, pulmonary, hepatic, or immunologic diseases.

Protocol. This trial (protocol no. PSA-001 from Celgene) was a phase II, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of apremilast in patients with active PsA. Patients were enrolled at 38 sites in Canada, Belgium, Germany, The Netherlands, and the United Kingdom. The study consisted of 4 phases. In the prerandomization phase (≤ 35 days), patients were screened for eligibility as described above. In the treatment phase (0–12 weeks), patients were randomized in a 1:1:1 distribution, in a double-blind manner, to receive placebo, apremilast 20 mg twice per day, or apremilast 40 mg once per day, stratified by baseline MTX use. Because the maximum daily dose at this time was limited to 40 mg, the 20 mg twice per day and 40 mg once per day regimens were evaluated to assess the safety and efficacy of the 2 dosing regimens.

Dose escalation was implemented during the first 7 days of treatment in an attempt to decrease the likelihood of adverse events (AEs) related to treatment initiation. A

one-time dosage reduction to 20 mg daily was allowed for apremilast-treated patients who experienced intolerable AEs. Safety and clinical efficacy assessments were performed at baseline and at weeks 2, 4, 6, 8, 10, and 12 (or early termination).

Upon completion of the 12-week treatment phase, patients could stop treatment and enter into a 4-week observational, treatment-free followup phase or could enroll in a 12-week treatment-extension phase. The initial protocol did not include this treatment-extension phase and was amended after the start of the trial, resulting in a time gap in which a number of patients completed 12 weeks of treatment before the extension phase was open for enrollment.

In the treatment-extension phase, patients originally randomized to receive placebo were re-randomized 1:1 in a double-blind manner (stratified by baseline MTX use) to receive apremilast 20 mg twice per day or 40 mg once per day, using the same dose-titration schedule as that in the placebo-controlled phase. Patients originally randomized to receive apremilast continued the same dosing regimen, including any prior dose reductions.

Safety assessments were performed at weeks 13, 14, 16, 18, 20, 22, and 24 (or early termination). Clinical efficacy assessments were performed at weeks 16 and 20, and at week 24 or early termination.

The observational, treatment-free followup phases, consisting of 2 visits over 4 weeks, were conducted at the end of the treatment phase for patients who did not enter into the

extension phase, at the end of the treatment-extension phase for all patients who entered, or after early termination, to monitor for disease worsening and safety after treatment cessation. Safety assessments and clinical efficacy assessments were performed at the final 4-week followup visit.

All study phases were conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice in the European Community and in accordance with the Declaration of Helsinki. Approval for all phases of the study was provided by the institutional review boards and/or independent ethics committees at each participating investigational center. Written informed consent was obtained from all patients before study entry.

End points. The primary end point was the proportion of patients who achieved the American College of Rheumatology (ACR) modified response criteria for 20% improvement (ACR20) (26,27) at the final treatment phase visit (week 12/early termination) as compared with baseline.

The secondary objectives were to evaluate the safety and tolerability of oral apremilast at dosages of 20 mg twice per day or 40 mg once per day in comparison with placebo in patients with active PsA. Secondary efficacy end points included improvement according to the PsA response criteria (PsARC) and the European League Against Rheumatism (EULAR) response criteria based on the Disease Activity Score in 28 joints (DAS28) (28,29) from baseline to study end, withdrawals due to lack of efficacy and dose reductions,

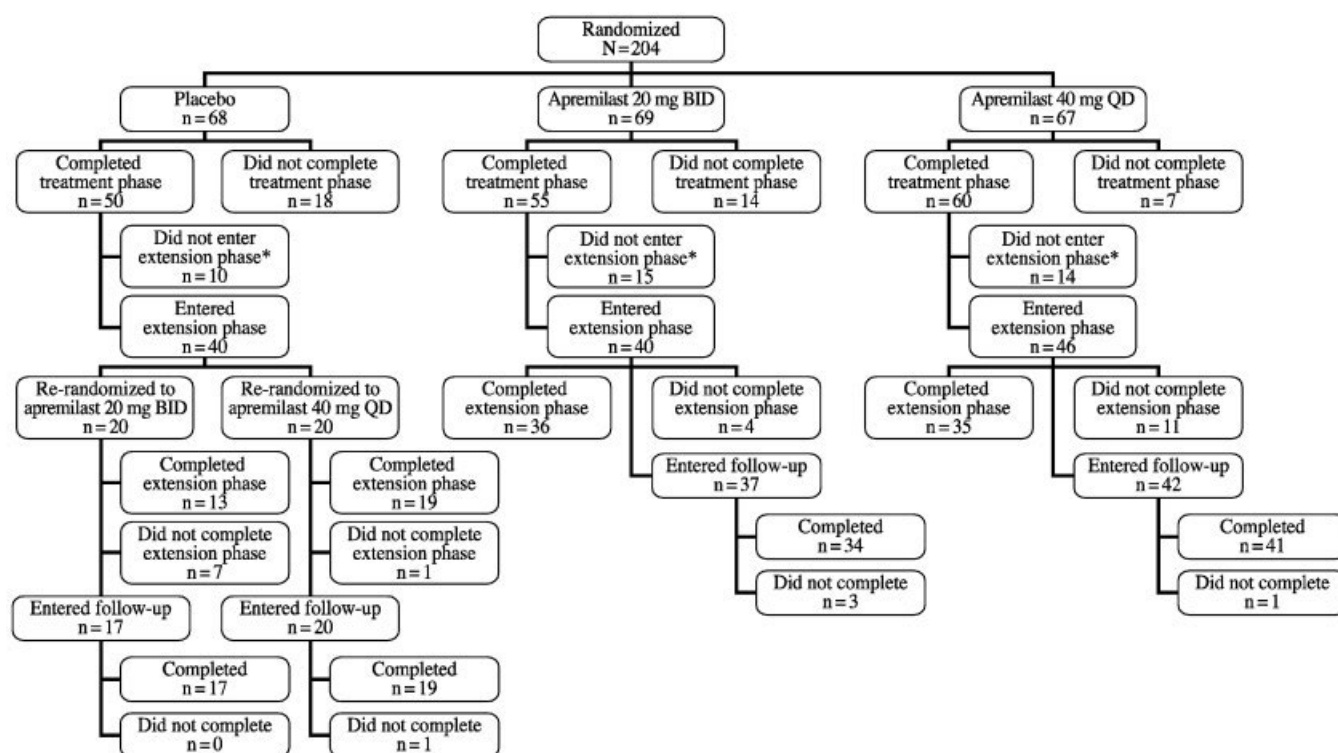


Figure 1. Disposition of patients in the treatment and treatment-extension phases. * = Due to lag time between completion of the treatment and the observational phase and the subsequent addition of the treatment-extension phase, not all patients had the opportunity to participate in the treatment-extension phase; 61 patients entered the observational phase at week 12, with 12 discontinuing prematurely after entry. BID = twice per day; QD = once per day.

Table 1. Demographic and baseline disease characteristics of the patients in the treatment phase (safety population)*

	Placebo (n = 68)	Apremilast 20 mg twice per day (n = 69)	Apremilast 40 mg once per day (n = 67)
Age, mean years	51.1	50.9	49.9
Male sex	32 (47.1)	43 (62.3)	32 (47.8)
Race			
White	68 (100.0)	67 (97.1)	62 (92.5)
Black	0	0	1 (1.5)
Hispanic	0	0	1 (1.5)
Asian/Pacific Islander	0	1 (1.4)	2 (3.0)
Other	0	1 (1.4)	1 (1.5)
Smoker	15 (22.1)	14 (20.3)	13 (19.4)
PsA			
Disease category			
Asymmetric oligoarthritis	20 (29.4)	21 (30.4)	26 (38.8)
Predominant spondylitis	2 (2.9)	3 (4.3)	4 (6.0)
Symmetric polyarthritis	39 (57.4)	36 (52.2)	32 (47.8)
Arthritis mutilans	5 (7.4)	0	2 (3.0)
Predominant DIP involvement	2 (2.9)	9 (13.0)	2 (3.0)
Disease duration, mean years†	7.3	8.4	7.6
Joint counts, mean			
Painful/tender joints	21.3	20.6	23.2
Swollen joints	9.5	10.6	8.4
Psoriasis			
Disease severity			
None	12 (17.6)	7 (10.1)	2 (3.0)
Mild	40 (58.8)	47 (68.1)	41 (61.2)
Moderate	11 (16.2)	15 (21.7)	20 (29.9)
Severe	5 (7.4)	0	4 (6.0)
Disease duration, mean years	15.8	15.5	18.3
MTX use	29 (42.6)	30 (43.5)	30 (44.8)
CRP, mean (range) mg/liter	14.9 (3.0–237.0)	10.4 (3.0–65.4)	10.9 (3.0–95.0)

* Except where indicated otherwise, values are the number (%) of patients. DIP = distal interphalangeal (joint); MTX = methotrexate; CRP = C-reactive protein.

† January was used for a missing month and 01 was used for a missing day to calculate the duration of psoriatic arthritis (PsA).

ACR50 and ACR70 improvement responses, and time to achieve the ACR20 level of improvement. Key secondary efficacy end points in the treatment-extension phase included the ACR20, ACR50, ACR70, and ACR90 improvement responses and the DAS28 from baseline to study end, as well as the number of dose reductions due to AEs and withdrawals due to lack of efficacy.

All abnormal physical examination findings (including vital signs) and electrocardiogram changes were identified as AEs when deemed medically significant by the investigator. The severity of an AE was graded 0–5 (with increasing grades indicating greater severity) based on the patient's symptoms, defined according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0; National Cancer Institute).

Statistical analysis. The safety population consisted of all patients who were randomized to a treatment group and had received ≥ 1 dose of study medication. The intent-to-treat population consisted of all randomized patients for whom at least one of the ACR criteria components had been assessed at baseline. All statistical analyses were performed using SAS software (version 9.1.3), in accordance with the predefined

statistical analysis plan. All efficacy analyses for the treatment phase were performed using the intent-to-treat population; in addition, the per-protocol population was used for the primary efficacy analysis. The last observation carried forward approach was used in these analyses, with the last observation being the last-recorded postbaseline assessment.

The primary efficacy end point was analyzed in a pairwise manner for the 2 apremilast treatment groups compared with placebo, using the continuity-corrected chi-square test. A 95% 2-sided confidence interval for the odds ratio was also presented. As a sensitivity analysis for the ACR20 improvement response, the Cochran-Mantel-Haenszel test, controlled for MTX use, was performed to compare each treatment group with the placebo group.

The Kaplan-Meier procedure was used to characterize the time to achieve clinical response (according to the ACR20, ACR50, and ACR70 response criteria). Data on patients in the treatment-extension phase were summarized using descriptive summary statistics for continuous variables and numeric counts and percentages for discrete variables.

Limited analyses of the ACR20 and the EULAR criteria improvement responses were performed when all

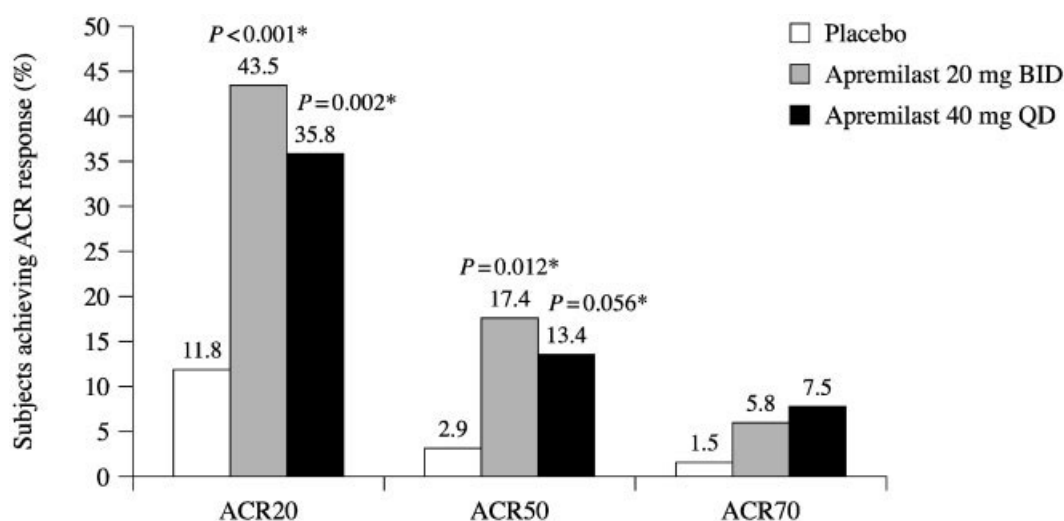


Figure 2. Proportion of patients achieving the American College of Rheumatology 20% improvement response (ACR20), as well as ACR50 and ACR70 responses, at week 12 in the placebo group, apremilast 20 mg twice per day (BID) group, and apremilast 40 mg once per day (QD) group (intent-to-treat population, last observation carried forward). Values over the bars are the percentage of patients. * = *P* values versus placebo.

patients had completed the treatment phase, and the database for the treatment phase was locked. These analyses were performed by an independent statistician to preserve the blinding of the ongoing treatment-extension phase. Final analyses were conducted when the database for the treatment-extension study was locked. No changes were made to efficacy data from the treatment phase.

We performed a literature review to determine sample size. Based on the literature, a clinically relevant level of absolute improvement in the ACR20 would be a difference of 25% in the ACR20 response rate in patients receiving apremilast compared with those receiving placebo. Thus, using a sample size of 51 patients per group and comparing groups by chi-square test with a one-sided level of significance of 0.05, the analysis would have 80% power to detect a difference of

25% between groups. If we allow for a 25% dropout rate, we would therefore need to enroll at least 68 patients in each treatment group, for a total of at least 204 patients.

RESULTS

Of the 270 patients screened, 204 were randomized to a treatment group, and 165 (80.9%) of these patients completed the 12-week treatment phase (Figure 1); 61 patients directly entered the observational followup phase at week 12, with 12 patients discontinuing prematurely after entry. In the treatment-extension phase, 126 patients entered, and 103 (81.7%) completed treatment; 116 patients entered the observational 4-week followup phase at week 24, with 5 discontinuing prematurely.

The demographic and baseline disease characteristics of the patients are shown in Table 1. The mean duration of PsA was 7.8 years, and 89.7% of the patients reported a history of psoriasis. Almost all of the patients (99.0%) reported taking ≥ 1 medication before or at enrollment, including MTX (65.0%), sulfasalazine (24.0%), etanercept (10.8%), cyclosporin A (6.4%), and infliximab (5.9%). Overall, ~44% of the patients were taking MTX at baseline; the most commonly used regimens were 20 mg weekly and 25 mg weekly (range 1.5–30 mg weekly).

Efficacy. A significantly greater proportion of patients achieved the primary end point of an ACR20 response at the end of the treatment phase (week 12) among the group receiving apremilast 20 mg twice per

Table 2. Change from baseline to week 12 for individual components of the American College of Rheumatology improvement response criteria*

	Placebo (n = 68)	Apremilast 20 mg twice per day (n = 69)	Apremilast 40 mg once per day (n = 67)
Tender joint count	−16.7	−39.1	−42.9
Swollen joint count	−40.0	−62.5	−56.5
HAQ DI	0	−21.5	−10.6
VAS pain score	0	−16.7	−14.9
Patient's global health assessment	6.0	−7.3	−21.4
Physician's global health assessment	−23.1	−38.0	−44.2
CRP level	0	0	0

* Values are the median percent change in each end point; a decrease demonstrates improvement. HAQ DI = Health Assessment Questionnaire disability index; VAS = visual analog scale; CRP = C-reactive protein.

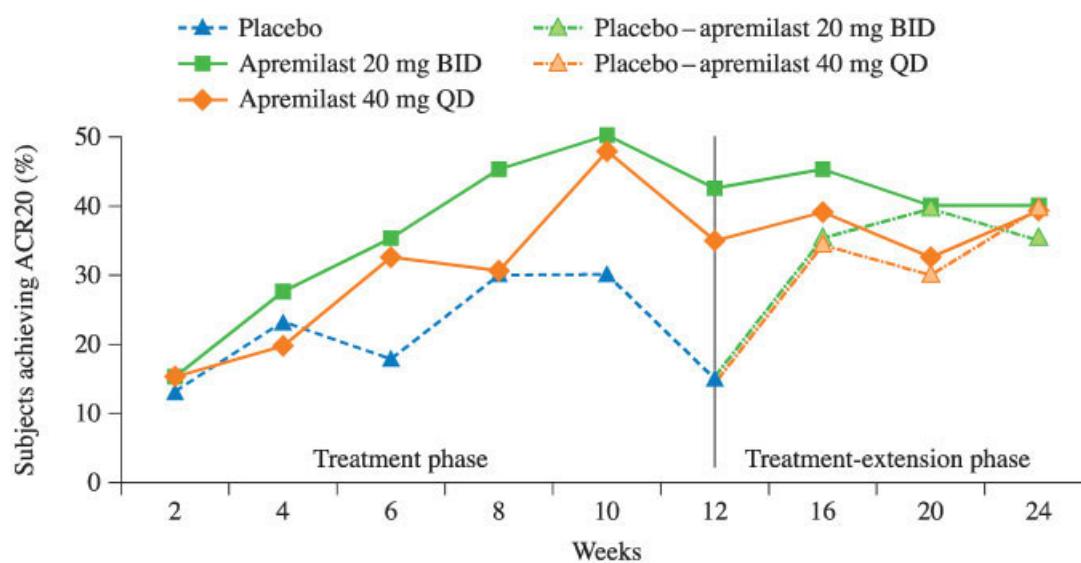


Figure 3. Proportion of patients achieving the American College of Rheumatology 20% improvement response (ACR20) from baseline up to week 12 (treatment phase; horizontal line) and through the treatment-extension phase up to week 24, in the following treatment groups: placebo, apremilast 20 mg twice per day (BID), apremilast 40 mg once per day (QD), placebo re-randomized to apremilast 20 mg twice per day, and placebo re-randomized to apremilast 40 mg once per day (intent-to-treat population in extension phase [$n = 126$]). This analysis does not include last observation carried forward; patients with missing data were considered nonresponders.

day (43.5%) and the group receiving apremilast 40 mg once per day (35.8%), when compared with those receiving placebo (11.8%) ($P < 0.001$ and $P = 0.002$, respectively) (Figure 2). In patients achieving an ACR20 response, the median time to response was 4 weeks.

Changes in scores for the individual components of the ACR response criteria are shown in Table 2. A significantly greater proportion of patients receiving apremilast 20 mg twice per day achieved an ACR50 level of response at week 12 when compared with patients receiving placebo (17.4% versus 2.9%; $P = 0.012$). Differences in the proportion achieving an ACR50 response between patients receiving apremilast 40 mg once per day and those receiving placebo approached, but did not reach, statistical significance (13.4% versus 2.9%; $P = 0.056$). With regard to the proportion of patients achieving an ACR70 response, no significant differences were seen between either apremilast dosing group and the placebo group.

The response in patients randomized to receive apremilast was maintained over the treatment-extension phase (Figure 3). Patients in the placebo group who entered the extension phase and were re-randomized to receive apremilast at week 12 experienced a similar response as that in patients randomized to receive apremilast at baseline during the treatment phase. By week 24 in the extension phase, 42.5%, 43.5%, 40.0%, and 45.0% of patients achieved an ACR20 improvement

response following treatment with apremilast 20 mg twice per day, apremilast 40 mg once per day, placebo/apremilast 20 mg twice per day, and placebo/apremilast 40 mg once per day, respectively. During the treatment-extension phase, among patients receiving apremilast 20 mg twice per day, apremilast 40 mg once per day, placebo/apremilast 20 mg twice per day, and placebo/apremilast 40 mg once per day, 22.5%, 23.9%, 15.0%, and 20.0% of patients, respectively, achieved an ACR50 response, and 17.5%, 13.0%, 5.0%, and 15.0% of patients, respectively, achieved an ACR70 response. The percentage of patients experiencing an improvement response according to the PsARC at week 12 was significantly higher in those receiving apremilast 20 mg twice per day (52.5%, range 40.4–64.0%; $P < 0.001$) and those receiving 40 mg once per day (50.7%, range 38.8–62.7%; $P = 0.001$) compared with those receiving placebo (22.1%, range 12.2–31.9%).

A subgroup analysis of MTX use showed no significant difference in the ACR20 response rates between patients receiving concomitant MTX and those not receiving concomitant MTX (46.7% and 41.0%, respectively, achieving an ACR20 response in the apremilast 20 mg twice per day group; 36.7% and 35.1%, respectively, achieving an ACR20 response in the apremilast 40 mg once per day group). Subanalysis according to PsA subtype revealed slight differences in the efficacy of apremilast between patients with asym-

Table 3. Frequently reported adverse events (AEs) during the treatment, treatment-extension, and observational followup phases (safety population)*

	Placebo	Apremilast 20 mg twice per day	Apremilast 40 mg once per day	Placebo/ apremilast 20 mg twice per day	Placebo/ apremilast 40 mg once per day
Treatment phase					
Patients with ≥ 1 AE	55 (80.9)	59 (85.5)	58 (86.6)	NA	NA
AEs					
Diarrhea	6 (8.8)	14 (20.3)	18 (26.9)	NA	NA
Headache	11 (16.2)	13 (18.8)	15 (22.4)	NA	NA
Nausea	12 (17.6)	12 (17.4)	15 (22.4)	NA	NA
Fatigue	6 (8.8)	5 (7.2)	11 (16.4)	NA	NA
Nasopharyngitis	12 (17.6)	8 (11.6)	8 (11.9)	NA	NA
Dizziness	3 (4.4)	3 (4.3)	7 (10.4)	NA	NA
Pruritus	1 (1.5)	2 (2.9)	5 (7.5)	NA	NA
Upper abdominal pain	3 (4.4)	7 (10.1)	4 (6.0)	NA	NA
Upper respiratory tract infection	0	1 (1.4)	4 (6.0)	NA	NA
Vomiting	4 (5.9)	4 (5.8)	4 (6.0)	NA	NA
Back pain	4 (5.9)	1 (1.4)	2 (3.0)	NA	NA
Migraine	0	6 (8.7)	2 (3.0)	NA	NA
Psoriatic arthropathy	6 (8.8)	3 (4.3)	2 (3.0)	NA	NA
Pharyngolaryngeal pain	4 (5.9)	1 (1.4)	1 (1.5)	NA	NA
Treatment-extension phase					
Patients with ≥ 1 AE		29 (72.5)	30 (65.2)	11 (55.0)	16 (80.0)
AEs					
Nasopharyngitis		7 (17.5)	7 (15.2)	3 (15.0)	6 (30.0)
Nausea		1 (2.5)	4 (8.7)	1 (5.0)	5 (25.0)
Diarrhea		2 (5.0)	3 (6.5)	0	4 (20.0)
Headache		5 (12.5)	2 (4.3)	1 (5.0)	0
Hypertension		0	2 (4.3)	0	1 (5.0)
Psoriatic arthropathy		0	2 (4.3)	1 (5.0)	0
Vomiting		2 (5.0)	1 (2.2)	0	0
Rhinitis		3 (7.5)	0	0	0
Sinusitis		2 (5.0)	0	0	0
Back pain		0	2 (4.3)	0	0
Urinary tract infection		0	0	0	2 (10.0)
Observational followup after treatment phase					
Patients with ≥ 1 AE	8 (40.0)	7 (33.3)	7 (35.0)	NA	NA
AEs					
Psoriatic arthropathy	3 (15.0)	3 (14.3)	3 (15.0)	NA	NA
Psoriasis	0	3 (14.3)	1 (5.0)	NA	NA
Nasopharyngitis	2 (10.0)	0	0	NA	NA
Observational followup after treatment-extension phase					
Patients with ≥ 1 AE		9 (24.3)	11 (26.2)	6 (35.3)	8 (40.0)
AEs					
Nasopharyngitis		1 (2.7)	2 (4.8)	1 (5.9)	2 (10.0)
Psoriatic arthropathy		2 (5.4)	0	3 (17.6)	3 (15.0)
Psoriasis		2 (5.4)	3 (7.1)	2 (11.8)	0

* In the treatment phase (placebo n = 68, apremilast 20 mg twice per day n = 69, apremilast 40 mg once per day n = 67), AEs occurring in $>5\%$ of patients in any treatment group are shown. In the treatment-extension phase (apremilast 20 mg twice per day n = 40, apremilast 40 mg once per day n = 46, placebo/apremilast 20 mg twice per day n = 20, placebo/apremilast 40 mg once per day n = 20), observational followup after the treatment phase (placebo n = 20, apremilast 20 mg twice per day n = 21, apremilast 40 mg once per day n = 20), and observational followup after the treatment-extension phase (apremilast 20 mg twice per day n = 37, apremilast 40 mg once per day n = 42, placebo/apremilast 20 mg twice per day n = 17, placebo/apremilast 40 mg once per day n = 20), AEs occurring in ≥ 2 patients in any treatment group are shown. AEs in the treatment-extension phase are treatment-emergent AEs with onset during weeks 16–24. The placebo/apremilast 20 mg twice per day and placebo/apremilast 40 mg once per day groups represent patients who had received placebo during the treatment phase and who were subsequently re-randomized to receive apremilast 20 mg twice per day or 40 mg once per day in the treatment-extension phase; total apremilast exposure for these patients was up to 12 weeks. Values are the number (%) of patients. NA = not applicable.

metric oligoarthritis and those with symmetric polyarthritis, as indicated by the percentage of patients achieving the ACR20 level of improvement (for those with

asymmetric oligoarthritis achieving an ACR20 response, 11 [52.4%] in the apremilast 20 mg twice per day group and 13 [53.8%] in the apremilast 40 mg once per day

group; for those with symmetric polyarthritis achieving an ACR20 response, 12 [33.3%] in the apremilast 20 mg twice per day group and 6 [18.8%] in the apremilast 40 mg once per day group). The small numbers of patients in each group prevent meaningful clinical inference or statistical testing of these differences.

Overall, apremilast was not associated with a reduction in CRP levels over 12 weeks of treatment. However, in a post hoc analysis of patients with CRP levels >8 mg/liter (representing the upper limit of normal [ULN] of CRP levels obtained on laboratory tests among 77 patients), the median reductions in the CRP level at week 12 were greater with apremilast 20 mg twice per day (change from baseline -49.6% [$n = 25$]) and with apremilast 40 mg once per day (change from baseline -33.8% [$n = 28$]) than with placebo (change from baseline -18.8% [$n = 24$]). A greater percentage of apremilast-treated patients with a baseline CRP level >8 mg/liter achieved the ACR20 response when compared with patients with a baseline CRP level ≤ 8 mg/liter (apremilast 20 mg twice per day, 48.0% versus 41.5%; apremilast 40 mg once per day, 46.4% versus 26.3%; placebo, 8.3% versus 15.8%). The proportion of patients with a baseline CRP level >8 mg/liter who achieved an ACR20 response was significantly greater in the groups receiving apremilast 20 mg twice per day ($P = 0.004$) or 40 mg once per day ($P = 0.005$) compared with those receiving placebo.

Safety. Among all patients, ≥ 1 AE was reported by 84.3% of the patients in the treatment phase and by 68.3% in the treatment-extension phase. The percentage of patients affected by ≥ 1 AE was similar across treatment groups (Table 3). During the treatment phase, the most frequently reported AEs were diarrhea, headache, nausea, fatigue, and nasopharyngitis. Most of these AEs ($>90\%$) were mild to moderate in severity (grades 1 and 2 on the CTCAE version 3.0). During the treatment phase, mild, moderate, and severe AEs were reported by 29.0%, 49.3%, and 5.8% of patients receiving apremilast 20 mg twice per day, respectively, by 31.3%, 47.8%, and 7.5% of patients receiving apremilast 40 mg once per day, respectively, and by 33.8%, 38.2%, and 8.8% of patients receiving placebo, respectively. Over 24 weeks of treatment, 28 patients experienced AEs that led to a reduction or interruption of study medication. During the treatment phase, 6 patients receiving placebo, 9 receiving apremilast 20 mg twice per day, and 12 receiving apremilast 40 mg once per day had treatment interrupted or their dose reduced. During the treatment-extension phase, 2 patients re-randomized to receive apremilast 40 mg once per day had treatment interrupted due to AEs.

Among the patients treated with concomitant MTX, 87.6% experienced ≥ 1 AE (79.3% in the placebo group, 86.7% in the apremilast 20 mg twice per day group, and 96.7% in the apremilast 40 mg once per day group). Among the patients not taking concomitant MTX, ≥ 1 AE was experienced by 81.7% of patients overall (82.1% in the placebo group, 84.6% in the apremilast 20 mg twice per day group, and 78.4% in the apremilast 40 mg once per day group). Gastrointestinal (GI) tract disorders and infections/infestations tended to occur more frequently in patients treated with concomitant MTX when compared with patients not taking concomitant MTX, except in those receiving apremilast 20 mg twice per day (GI tract disorders in MTX versus no MTX, 41.4% versus 30.8%, 43.3% versus 46.2%, and 60.0% versus 40.5% in those receiving placebo, apremilast 20 mg twice per day, and apremilast 40 mg once per day, respectively; infections/infestations in MTX versus no MTX, 34.5% versus 28.2%, 20.0% versus 28.2%, and 46.7% versus 27.0% in those receiving placebo, apremilast 20 mg twice per day, and apremilast 40 mg once per day, respectively).

No grade 4 or grade 5 AEs (life-threatening/disabling or death) were reported during the treatment phase. Grade 3 (severe) AEs were reported by 6 patients receiving placebo (fatigue, balance disorder, anemia, flare of existing psoriasis, guttate psoriasis, and back pain), by 4 receiving apremilast 20 mg twice per day (toothache, decreased blood pressure, asthma, and meniscus lesion), and by 5 receiving apremilast 40 mg once per day (bronchitis, GI tract infection, headache [2 patients], and dizziness). One AE in each group was suspected to be related to the study medication, characterized by dizziness in 1 patient receiving apremilast 40 mg once per day, decreased blood pressure in 1 patient receiving apremilast 20 mg twice per day, and fatigue in 1 patient receiving placebo.

During the treatment-extension phase, no grade 4 or grade 5 AEs were reported. Among patients receiving apremilast 20 mg twice per day, the occurrence of a grade 3 AE (sinusitis) was suspected to be related to the study medication. Among patients receiving apremilast 40 mg once per day, 3 grade 3 AEs (hepatic enzyme increase, headache, and migraine) were suspected to be related to the study medication. Among patients re-randomized from the placebo group to the apremilast 20 mg twice per day group, a grade 3 AE (abdominal abscess, as described below) was suspected to be related to the study medication and classified as a serious AE (SAE).

Fourteen patients experienced ≥ 1 SAE over the 24-week study. In the treatment phase, ≥ 1 SAE

occurred in 4 patients receiving placebo (fall, nausea [2 patients], vomiting, balance disorder, and arthralgias) and in 3 patients receiving apremilast 20 mg twice per day (sinus tachycardia, biliary colic, hyperbilirubinemia, and worsening spinal claudication associated with intervertebral disk degeneration). In the treatment-extension phase, the following SAEs were noted: among those receiving apremilast 20 mg twice per day, 1 patient was diagnosed as having oral neoplasm and prostate neoplasm, 1 experienced worsening osteoarthritis and synovitis, and 1 experienced an exacerbation of hypertensive heart disease; among those receiving apremilast 40 mg once per day, 1 patient was diagnosed as having squamous cell carcinoma of the skin, and 1 patient was diagnosed as having Parkinson's disease; among those who were re-randomized from the placebo group to the apremilast 20 mg twice per day group, 1 patient experienced an abdominal abscess at the site of an appendectomy scar, and subsequently developed a wound infection following excision of the tumor; and among those re-randomized from the placebo group to the apremilast 40 mg once per day group, 1 patient experienced a tibia fracture. Two of these SAEs (nausea, abdominal abscess) were suspected to be related to the study medication. In the patient with the abdominal abscess, the histologic findings revealed the presence of lipofibrotic tissue with granulocytic inflammation (with cultures showing *Anaerococcus prevoti*).

No opportunistic infections were reported, and no deaths occurred. One pregnancy occurred in the partner of a patient receiving apremilast 20 mg twice per day. Twenty-three patients discontinued treatment due to AEs during the treatment phase, and 10 of these AEs were suspected to be caused by the study medication (in 1 patient in the placebo group, 4 patients in the apremilast 20 mg twice per day group [decreased blood bicarbonate, increased blood creatinine, hyperkalemia, upper abdominal pain, PsA flare, vertigo, and fatigue], and 5 patients in the apremilast 40 mg once per day group [hypersensitivity, stomach discomfort, abdominal pain and malaise, diarrhea and nausea, and dizziness and nausea]). During the treatment-extension phase, 8 patients discontinued treatment due to AEs, and in 3 of these patients, the AEs were suspected to be caused by the study medication (1 patient with a lower respiratory tract infection in the apremilast 20 mg twice per day group, 1 patient with migraine in the apremilast 40 mg once per day group, and 1 patient with abdominal abscess [as noted above] in the placebo group re-randomized to receive apremilast 20 mg twice per day).

Eleven patients in the treatment phase reported experiencing worsening psoriatic arthropathy (6 in the

placebo group, 3 in the apremilast 20 mg twice per day group, 2 in the apremilast 40 mg once per day group), while 3 patients in the treatment-extension phase reported this AE (2 in the apremilast 40 mg once per day group, 1 re-randomized from placebo to apremilast 20 mg twice per day). Three of the events were suspected to be related to the study medication. Five patients in the treatment phase (4 in the placebo group, 1 in the apremilast 20 mg twice per day group) and 1 patient in the treatment-extension phase (receiving apremilast 20 mg twice per day) reported experiencing psoriasis flares. One of these events was suspected to be related to the study medication (placebo).

Overall, shifts in liver enzyme levels, total bilirubin levels, or renal panel results were small, with no consistent pattern over time or notable differences between the active-treatment and placebo groups. No patients experienced a shift in aspartate aminotransferase or alanine aminotransferase levels that coincided with an increase in the total bilirubin levels. One patient treated with apremilast 20 mg twice per day had a liver enzyme elevation that was >3 times the ULN, which returned to the normal range following a reduction in the dosage of apremilast to 20 mg once per day. No patient had total bilirubin elevations or a serum creatinine level that was >2 times the ULN. Twenty-three patients experienced creatinine elevations of >0.2 mg/dl (10 patients receiving apremilast 20 mg twice per day, 12 patients receiving apremilast 40 mg once per day, and 1 patient taking placebo during the treatment phase and taking apremilast 40 mg once per day during the treatment-extension phase). In 2 of these patients, the elevations in creatinine were considered treatment-emergent AEs; of these patients, 1 (receiving apremilast 20 mg twice per day) discontinued the study, and 1 (receiving apremilast 40 mg once per day) experienced a return to baseline levels without treatment intervention. The mean and median changes in laboratory parameters were small, and did not show a consistent trend toward liver or renal impairment over time. Electrocardiographic results showed no effect on heart rate, intracardiac conduction, or cardiac repolarization.

DISCUSSION

In this study, patients with active PsA, most of whom had polyarticular disease, who were receiving apremilast 20 mg twice per day or 40 mg once per day for 12 weeks had statistically significantly higher ACR20 response rates than did patients receiving placebo ($P \leq 0.002$). These rates were maintained to the study end at

12 weeks, and were also maintained in those who continued treatment to 24 weeks. Patients in the placebo group who were re-randomized to receive apremilast at week 12 had similar ACR20 response rates at the study end. No difference in efficacy was noted among patients who received concomitant MTX and those who did not receive MTX. Treatment of patients with apremilast 20 mg twice per day or 40 mg once per day achieved a significant response ($P \leq 0.001$) in terms of ameliorating disease activity, as measured by the PsARC, which does not include the CRP level.

An elevated CRP level was not required for study entry, and apremilast did not lower the CRP levels significantly from baseline across all patients, although reductions were greater in patients with baseline CRP levels >8 mg/liter, and a greater percentage of apremilast-treated patients with a baseline CRP level of >8 mg/liter achieved an ACR20 response compared with patients whose baseline CRP level was ≤ 8 mg/liter ($P \leq 0.005$). The modest effect on CRP levels may be a result of the generally low CRP levels at baseline. Alternatively, it could be attributed to the fact that apremilast has an antiinflammatory mechanism that is independent of CRP modulation. Although this suggests that apremilast may possess properties that are generally seen with DMARD therapy, there is no clinical evidence to date to demonstrate an effect of apremilast on radiographic progression.

The observed safety profile of apremilast was consistent with that reported with other PDE4 inhibitors (30–32). AEs reported with other PDE4 inhibitors, including GI tract AEs (nausea, vomiting, and diarrhea), were most frequent in patients treated with apremilast 40 mg once per day. The majority of AEs were of mild or moderate severity. No significant laboratory abnormalities were observed, and no opportunistic infections were reported. Although 2 severe infections occurred with apremilast 40 mg once per day, none resulted in study discontinuation. Concomitant use of MTX did not raise any safety concerns.

Although these findings are encouraging, several limitations should be considered. The study population comprised mostly ($>90\%$) white patients and may not be generalizable to more diverse patient populations. The planned analyses did not examine apremilast efficacy among subgroups stratified according to the type of prior systemic therapy. Extrapolation to other forms of PsA, such as monarticular disease, may not be applicable. The study was relatively short in duration and did not provide data on the long-term efficacy and safety of apremilast for PsA.

This study utilized a randomized, placebo-controlled, double-blind design, with a low dropout rate and low placebo response. It provides strong evidence of the efficacy of apremilast for the treatment of active PsA, with a more balanced profile of efficacy, tolerability, and safety relative to that of other PDE4 inhibitors (21). Based on these findings, a phase III clinical study program, known as the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE), for apremilast in active PsA is under way. The program consists of four 52-week, double-blind, randomized, controlled studies, including a 16-week placebo-controlled phase, followed by long-term open-label extensions (2–5 years). The studies will examine the efficacy and safety of apremilast, including a higher dosage (30 mg twice per day), as was used in a phase II dose-ranging study of patients with psoriasis (33), and will enroll both DMARD-naïve and DMARD-treated subjects in separate trials. These phase III studies will more clearly define the clinical utility of apremilast and its place in PsA therapy. Apremilast is under investigation for the treatment of RA and ankylosing spondylitis, and also for the treatment of psoriasis in phase III clinical trials.

Apremilast 20 mg twice per day and 40 mg once per day showed significantly greater efficacy when compared with placebo in the treatment of active PsA. AEs were largely mild or moderate in severity and did not lead to a significant rate of discontinuation. Overall, the balance of efficacy, tolerability, and safety of apremilast demonstrated in this study supports the ongoing development of phase III clinical trials to address the efficacy and tolerability of apremilast at a higher dose.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Schett had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Schett, Wollenhaupt, Papp, Hu, Stevens, de Vlam.

ROLE OF THE STUDY SPONSOR

Celgene Corporation facilitated the study design. The authors reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Writing and editorial assistance was provided by Peloton Advantage, LLC, and Jennifer Schwinn, RPh, funded by Celgene Corporation. Publication of this article was not contingent upon approval by Celgene Corporation.

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Clinical Images: Digital acrometastasis revealing endometrial cancer relapse

The patient, a 68-year-old woman with a history of localized endometrial adenocarcinoma who had undergone hysterectomy followed by sequential chemotherapy and radiation therapy, was referred for evaluation of a painful mass on the second finger of the right hand (**left**). The mass had been insufficiently controlled by nonsteroidal antiinflammatory drug treatment and had rapidly increased in size during the preceding month. The patient had not experienced any trauma or fever, and acute gouty arthritis was suspected. Routine laboratory tests revealed negative blood cultures, moderate inflammatory syndrome (C-reactive protein 24 mg/liter), and normal levels of plasma uric acid. Plain radiography of the finger revealed osteoarthritis of the distal interphalangeal joint (DIJ) and a large soft tissue mass without calcification and no evidence of erosion of the phalanx (**top right**). Power Doppler ultrasonography of the finger (**bottom right**) (longitudinal view) showed a hypoechoic solid hypervascular mass (blue Doppler signals) (**arrows**) in the soft tissue and surrounding the extensor tendon (**asterisk**), with no demonstrable involvement of the adjacent joints or bones. Histologic examination of a sample obtained by the ultrasound-guided biopsy revealed features of adenocarcinoma, compatible with digital acrometastasis (a rare site of carcinoma metastasis) of the endometrial cancer (1,2). The patient refused palliative amputation of the affected finger to relieve refractory cancer pain. A computed tomography scan showed multimetastatic dissemination to the liver, lung, and lumbar spine, leading to the patient's death 6 months after the presentation described here.

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