



Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial

Kim Papp, Jennifer C Cather, Les Rosoph, Howard Sofen, Richard G Langley, Robert T Matheson, ChiaChi Hu, Robert M Day

Summary

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Probit Medical Research, Waterloo, ON, Canada (K Papp MD); Modern Research Associates, Dallas, TX, USA (J C Cather MD); North Bay Dermatology Centre, North Bay, ON, Canada (L Rosoph MD); Dermatology Research Associates, Los Angeles, CA, USA (H Sofen MD); Dalhousie University, Halifax, NS, Canada (R G Langley MD); Oregon Medical Research Center, Portland, OR, USA (R T Matheson MD); and Celgene Corporation, Summit, NJ, USA (C Hu EdM, R M Day PhD)

Correspondence to:

Dr Kim Papp, Probit Medical Research, Waterloo, ON N2J 1C4, Canada
kapapp@probitmedical.com

Background Apremilast, a small-molecule inhibitor of phosphodiesterase 4, works intracellularly to modulate proinflammatory and anti-inflammatory mediator production, and doses of 20 mg twice daily have shown efficacy in the treatment of moderate to severe plaque psoriasis in a 12-week phase 2 study. We assessed the clinical efficacy and safety of different doses of apremilast in the treatment of patients with moderate to severe plaque psoriasis.

Methods In this phase 2b, multicentre, randomised, placebo-controlled, dose-ranging study, patients (aged ≥ 18 years) with moderate to severe psoriasis were randomly assigned (in a 1:1:1:1 ratio) to receive oral placebo or apremilast 10, 20, or 30 mg twice daily at 35 US and Canadian sites between Sept 24, 2008, and Oct 21, 2009. At week 16, patients in the placebo group were assigned apremilast 20 or 30 mg twice daily until week 24. Randomisation was generated with a permuted-block randomisation list via interactive voice response system. For the first 16 weeks, treatment assignment was concealed from both investigators and participants. During weeks 16–24, investigators and participants all knew that treatment was active, but the dose was concealed. The primary endpoint was the proportion of patients achieving at least 75% reduction from baseline psoriasis area and severity index (PASI-75) at week 16. Analyses were by intention to treat; missing values were imputed by last-observation-carried-forward. This trial is registered with ClinicalTrials.gov, number NCT00773734.

Findings 89 patients were randomly assigned apremilast 10 mg, 87 apremilast 20 mg, and 88 apremilast 30 mg twice daily; 88 were assigned placebo. At week 16, PASI-75 was achieved in five patients (6%) assigned placebo, ten (11%) assigned apremilast 10 mg, 25 (29%) assigned 20 mg, and 36 (41%) assigned 30 mg. Apremilast 10 mg did not differ significantly from placebo in achievement of the endpoint (odds ratio 2.10; 95% CI 0.69–6.42); for both apremilast 20 mg (6.69; 2.43–18.5; $p < 0.0001$) and apremilast 30 mg (11.5; 4.24–31.2; $p < 0.0001$), the differences from placebo were significant. Most adverse events (96%) were mild or moderate; at least 5% of patients had nausea, upper respiratory tract infection, diarrhoea, nasopharyngitis, headache, arthralgia (placebo), gastroenteritis, or dyspepsia. Eight serious adverse events occurred (three each, placebo and apremilast 20 mg; two, apremilast 30 mg); none were judged to be related to apremilast. Apremilast had no apparent effect on the results of haematological, urinalysis, immunological or inflammation, serum chemistry, or electrocardiographic tests.

Interpretation Apremilast, given orally at 20 or 30 mg twice daily, seems to be efficacious, safe, and tolerable for patients with moderate to severe plaque psoriasis. Our results support continuing, longer-term studies.

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Introduction

Long-term treatment of psoriasis with non-biological or biological systemic therapies is often compromised by adverse events, safety and tolerability issues, loss of effect with time, and route of administration (injection vs oral), any of which might contribute to low adherence.^{1–8} An effective, well-tolerated, safe, and easy-to-use treatment for psoriasis is needed.

Drug development for psoriasis has targeted signalling between inflammatory cells, such as T cells and myeloid dendritic cells. Biological therapies target specific pro-inflammatory cytokines, such as tumour necrosis factor α (TNF α), and interleukins 12, 17, and 23.⁹ Phosphodiesterase 4 is an intracellular enzyme that degrades the secondary messenger cAMP, leading to increased production of proinflammatory cytokines.^{10–16} It is the predominant phosphodiesterase expressed in cells of the immune system, including dendritic cells, monocytes,

and neutrophils; it is also expressed in keratinocytes. Phosphodiesterase 4 inhibitors are being investigated because they can modulate cAMP concentrations and the related downstream inflammatory signalling cascade.^{11–15}

Apremilast (CC-10004; Celgene Corporation, Summit, NJ, USA) is a novel, orally available small molecule that specifically inhibits phosphodiesterase 4.¹² In vitro, apremilast decreases production of inflammatory mediators such as TNF α , interleukins 2, 12, and 23, and c-x-c motif chemokine 10 by peripheral blood mononuclear cells, and TNF α by natural killer T cells and keratinocytes. In mice with psoriatic xenografts, apremilast reduced epidermal thickness and proliferation and decreased the severity of psoriasiform features.¹² The pharmacokinetics of apremilast have been characterised (appendix p 1).^{17–21} In a phase 2, randomised, placebo-controlled study, apremilast 20 mg twice daily showed efficacy in patients with moderate to severe plaque

See Online for appendix

psoriasis during 12 weeks of treatment.²² In this dose-ranging study, we assessed the clinical efficacy and safety of apremilast 10, 20, and 30 mg twice daily versus placebo in patients with moderate to severe plaque psoriasis.

Methods

Study design and participants

This phase 2b, randomised, multicentre, placebo-controlled, dose-ranging trial was done at 35 sites in the USA and Canada (appendix p 2) between Sept 24, 2008, and Oct 21, 2009. Patients aged 18 years or older were eligible for enrolment if they had had moderate to severe plaque psoriasis (psoriasis area and severity index [PASI] ≥ 12 ; body surface area $\geq 10\%$) for 6 months or longer and were candidates for phototherapy or systemic therapy. Individuals were excluded if they had a history of, or present, significant disease, including *Mycobacterium tuberculosis* or HIV infection; had a positive screening test for hepatitis B or C; were pregnant or breastfeeding; had used topical therapy within 2 weeks; had used systemic therapy or phototherapy within 4 weeks; had used adalimumab, etanercept, efalizumab, or infliximab within 12 weeks; or had used alefacept within 24 weeks of randomisation.

All patients provided written informed consent before study-related procedures were done, and the protocol and consent were approved by institutional review boards or ethics committees at all investigational sites. Participation of patients in the pharmacokinetic part of the study was optional; patients who participated in this part gave separate written informed consent. An independent data monitoring committee assessed safety data at prespecified points: when 20%, 40%, and 80% of patients had either completed the 24-week treatment period or prematurely discontinued from the study. At each point, the committee decided whether the study should continue or end on the basis of assessments of risk and benefit.

Randomisation and masking

At baseline, eligible patients were randomly assigned in a 1:1:1:1 ratio to oral apremilast 10 mg twice daily, apremilast 20 mg twice daily, apremilast 30 mg twice daily, or placebo, with a permuted-block randomisation list generated by an interactive voice response system (ClinPhone, East Windsor, NJ, USA). Doses were titrated in the first week to mitigate potential dose-dependent adverse events of apremilast; all patients reached the target dose by day 5. Treatment was double-blind for the first 16 weeks of the 24-week treatment phase. During the 8-week active treatment (weeks 16–24), patients and investigators were aware that all treatment was active but were not aware of the apremilast dose.

After a screening period of up to 5 weeks before randomisation, patients began a 24-week treatment phase, comprising 16 weeks of placebo-controlled, double-blind treatment and 8 weeks of dose-blinded

active treatment, in which all patients who had received placebo were randomly assigned (in a 1:1 ratio) to receive apremilast 20 mg or 30 mg twice daily (appendix p 3). Patients who discontinued prematurely or chose not to enrol in the voluntary extension study entered a 4-week post-treatment observational follow-up phase.

The primary efficacy endpoint was the proportion of patients achieving at least 75% improvement from baseline PASI (PASI-75) score at week 16. Secondary efficacy endpoints were the proportion of patients achieving at least PASI-75 at week 24, PASI-50 at week 16, and PASI-90 at week 16; time to achieve PASI-50 or PASI-75 (weeks 0–16); percentage change from baseline PASI after 24 weeks; percentage change from baseline in affected body surface area at week 16; change from baseline in dermatology life quality index (DLQI) and 36-item short-form health survey (SF-36) scores at weeks 16 and 24; and systemic exposure of apremilast at weeks 14 and 24.

Exploratory efficacy analyses examined the proportion of patients achieving the static physician's global assessment score of clear (0) or minimal (1) and percentage change from baseline pruritus visual analogue scale scores at weeks 16 and 24. To obtain the static physician's global assessment score, investigators examined all lesions and assigned a score from 0 (clear, except residual discolouration) to 5 (severe; most plaques have severe thickness, erythema, and scaling) for thickness, erythema, and degree of scaling. The overall score for this measure was the mean of the three scores summed; fractional scores of 0.5 or more were rounded up. Safety was assessed by type, frequency, and severity of adverse events. Pharmacokinetic measures to assess apremilast exposure included area under the plasma concentration-time curve from 0 to 8 h (AUC_{0-8}), peak (maximum) plasma concentration of apremilast (C_{max}), and time to C_{max} of apremilast. Blood samples were collected at some sites in a subset of patients from each treatment group.

Throughout the 24-week treatment phase, concomitant systemic therapy, phototherapy, and biological agents were prohibited. The only topical formulations patients could apply were Eucerin cream (Beiersdorf, Germany) to body lesions and, if needed, low-potency corticosteroids (USA groups VI and VII) to facial, axillary, and groin psoriatic lesions. Patients could use coal-tar shampoo or salicylic-acid scalp preparations for scalp lesions. All background topical treatments had to be discontinued 24 h before study visits. Treatment was discontinued if patients had adverse events that, in the investigator's opinion, posed risk of unacceptable harm or ruled out study continuation, or psoriasis flare, defined as sudden intensification of psoriasis requiring medical intervention or a diagnosis of erythrodermic, pustular, or guttate psoriasis.

Statistical analysis

On the basis of results of a phase 2 study of apremilast,²³ a sample size of 348 patients would yield at least 90% power to detect a 25% difference in the PASI-75 between an active

treatment group and placebo, with a two-group continuity-corrected χ^2 test with a 0.05, two-sided significance level.

Efficacy data were assessed by intention to treat. Missing data were handled with the last-observation-carried-forward method. The primary outcome was analysed with a two-tailed χ^2 ($p < 0.05$) for each of the three active treatments versus placebo. Comparisons were done in a pair-wise, fixed-sequence manner. To examine continuous measures, analysis of covariance, with treatment as factor and baseline as covariate, was applied. For categorical variables, the Mantel-Haenszel procedure, with modified ridit scores, was used; this test is the same as the non-parametric Wilcoxon test and enhances the analysis when the parameter is not normally distributed.^{24,25} The Kaplan-Meier procedure was used to characterise time to achieve PASI-50, PASI-75, and PASI-90. For placebo patients dose-blinded

in the second part of the trial, week 16 assessments were used as baseline for comparison. Pharmacokinetic variables were calculated with non-compartmental analysis and described with summary statistics.

This study is registered with ClinicalTrials.gov, number NCT00773734.

Role of the funding source

The study sponsor designed the study, with input from study investigators. Data were collected by study investigators and analysed by sponsor statisticians. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Results

88 patients were assigned placebo, 89 apremilast 10 mg, 87 apremilast 20 mg, and 88 apremilast 30 mg (figure 1).

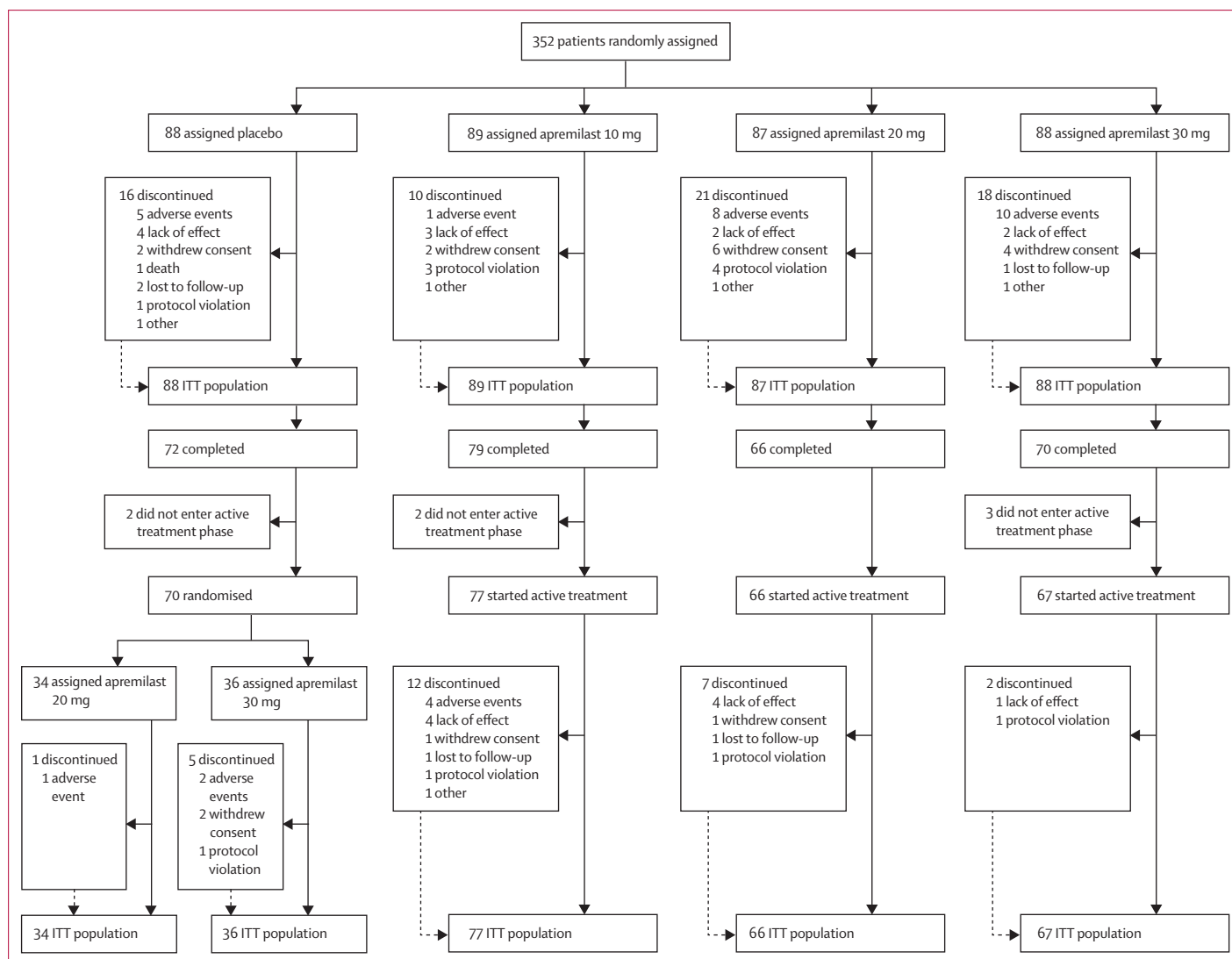


Figure 1: Trial profile

542 patients were screened, 190 were excluded at this stage. ITT=intention-to-treat.

Demographic and baseline characteristics were generally well balanced between treatment groups (table 1). Most patients were male, white, and obese (table 1). Patients had plaque psoriasis for a mean of 19 (SD 12) years and 21% had a history of psoriatic arthritis. The mean baseline PASI score was 18·5 and mean baseline body surface area was 22%.

The primary endpoint of PASI-75 at week 16 was achieved by significantly more patients assigned apremilast 20 mg (odds ratio [OR] 6·69; 95% CI 2·43–18·5; $p<0\cdot0001$) and apremilast 30 mg (11·5; 4·24–31·16; $p<0\cdot0001$) than placebo; apremilast 10 mg did not significantly differ from placebo in achievement of this endpoint (2·10; 0·69–6·42). PASI-75 was achieved in five (6%) of 88 patients assigned placebo, ten (11%) of 89 assigned apremilast 10 mg ($p=0\cdot19$), 25 (29%) of 87 assigned apremilast 20 mg ($p<0\cdot0001$), and 36 (41%) of 88 assigned apremilast 30 mg ($p<0\cdot0001$, appendix p 4).

Much the same pattern of efficacy, with the most favourable results achieved with apremilast 30 mg, was recorded for PASI-50 and PASI-90 scores and mean and median changes in PASI from baseline to week 16 (figure 2, appendix p 4). Figure 3 shows a patient who received apremilast 30 mg and achieved a PASI-100 (completely clear) score at week 16. On the basis of PASI assessments from baseline to week 16, the median number of days to achieve PASI-75 was 57·0 (95% CI 43·0–111) with placebo, 70·0 (45·0–85·0) with apremilast 10 mg, 83·0 (57·0–85·0) with apremilast 20 mg, and 44·0 (43·0–81·0) with apremilast 30 mg. The median number of days to achieve PASI-50 was 45·5 (95% CI 40·0–85·0) with placebo, 41·0 (29·0–44·0) with apremilast 10 mg, 42·0 (34·0–44·0) with apremilast 20 mg, and 30·0 (29·0–43·0) with apremilast 30 mg. The median number of days to achieve PASI-90 was 57·0 (95% CI 43·0–114) with placebo, 50·5 (43·0–113) with apremilast 10 mg, 87·0 (85·0–111) with apremilast 20 mg, and 58·0 (57·0–112) with apremilast 30 mg.

Reductions from baseline PASI scores with apremilast were identified by week 2, with a separation across doses recorded in weeks 2–4, which were maintained for 24 weeks (figure 2). Patients who switched from placebo to apremilast 20 or 30 mg at week 16 also showed rapid improvements. At week 24, the proportion of patients achieving PASI-50 and PASI-75 was generally maintained (appendix p 5).

At week 16, a static physician's global assessment score of 0 or 1 was achieved by 11 (13%) of 88 patients assigned placebo, nine (10%) of 89 assigned apremilast 10 mg, 21 (24%) of 87 assigned apremilast 20 mg ($p=0\cdot0425$ vs placebo), and 29 (33%) of 88 assigned apremilast 30 mg ($p=0\cdot0012$). At week 24, cleared or minimal disease was achieved by 12 (13%) patients assigned apremilast 10 mg, 21 (24%) assigned apremilast 20 mg, and 30 (34%) assigned apremilast 30 mg; in the active treatment phase of 16–24 weeks among patients who had been assigned placebo, cleared or minimal disease was achieved by

	Placebo (n=88)	Apremilast			Total (N=352)
		10 mg (n=89)	20 mg (n=87)	30 mg (n=88)	
Age (years)	44·1 (13·7)	44·4 (13·9)	44·6 (12·6)	44·1 (14·7)	44·3 (13·7)
Male	53 (60%)	63 (71%)	55 (63%)	50 (57%)	221 (63%)
Race					
White	83 (94%)	82 (92%)	82 (94%)	80 (91%)	327 (93%)
Black	1 (1%)	2 (2%)	1 (1%)	2 (2%)	6 (2%)
Asian	4 (5%)	3 (3%)	2 (2%)	4 (5%)	13 (4%)
Other	0	2 (2%)	2 (2%)	2 (2%)	6 (2%)
Hispanic or Latino	7 (8%)	7 (8%)	5 (6%)	4 (5%)	23 (7%)
Height (cm)	171·2 (8·6)	171·5 (10·2)	171·7 (9·6)	171·2 (10·7)	171·5 (9·6)
Weight (kg)	90·4 (21·5)	95·9 (23·2)	89·9 (20·2)	91·4 (23·1)	92·0 (22·0)
Body-mass index (kg/m ²)	30·8 (6·7)	32·5 (7·4)	30·4 (6·1)	31·1 (7·7)	31·2 (7·1)
Total PASI score	18·1 (5·7)	18·1 (6·3)	18·5 (7·3)	19·1 (7·1)	18·5 (6·6)
Body surface area (%)	21·0 (11·2)	21·3 (11·4)	20·7 (12·4)	25·0 (15·3)	22·0 (12·7)
History of psoriatic arthritis	17 (19%)	20 (23%)	16 (18%)	21 (24%)	74 (21%)
Plaque psoriasis history (years)	19·6 (11·6)	18·0 (12·4)	19·2 (12·1)	19·2 (12·0)	19·0 (12·0)
Previous systemic therapy for psoriasis	39 (44%)	47 (53%)	43 (49%)	47 (53%)	176 (50%)

Data are mean (SD) or n (%). PASI=psoriasis area and severity index.

Table 1: Demographic and baseline characteristics

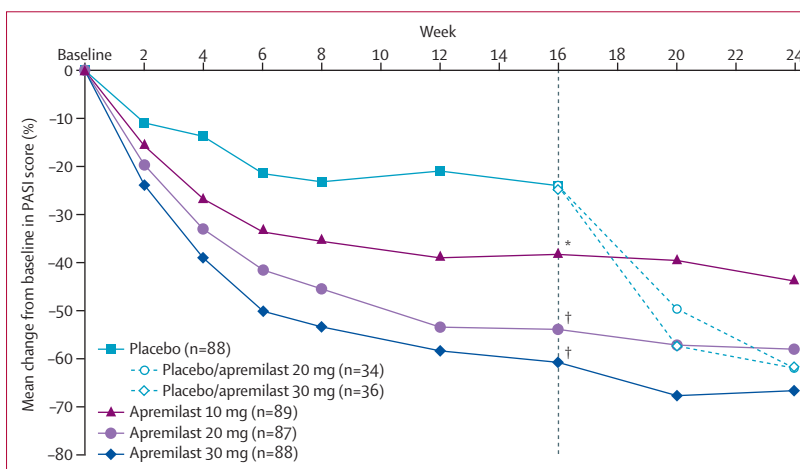


Figure 2: Achievement of and PASI scores during 24 weeks

Placebo/apremilast=placebo patients assigned to apremilast 20 mg or 30 mg twice daily at week 16. PASI=psoriasis area and severity index. * $p=0\cdot016$ vs placebo; † $p<0\cdot0001$.

14 (41%) of 34 assigned apremilast 20 mg, and 18 (50%) of 36 assigned apremilast 30 mg.

At week 16, body surface area scores were significantly lower with all three apremilast doses than with placebo ($p=0\cdot002$ for apremilast 10 mg and $p<0\cdot0001$ for apremilast 20 and 30 mg), and pruritus visual analogue scale scores were significantly lower with apremilast 20 mg ($p=0\cdot0026$) and 30 mg ($p<0\cdot0004$) than with placebo (appendix p 4). Apremilast 20 mg and 30 mg provided rapid relief in pruritus during the first 2 weeks, which was generally maintained for 24 weeks (appendix p 6). Likewise, patients

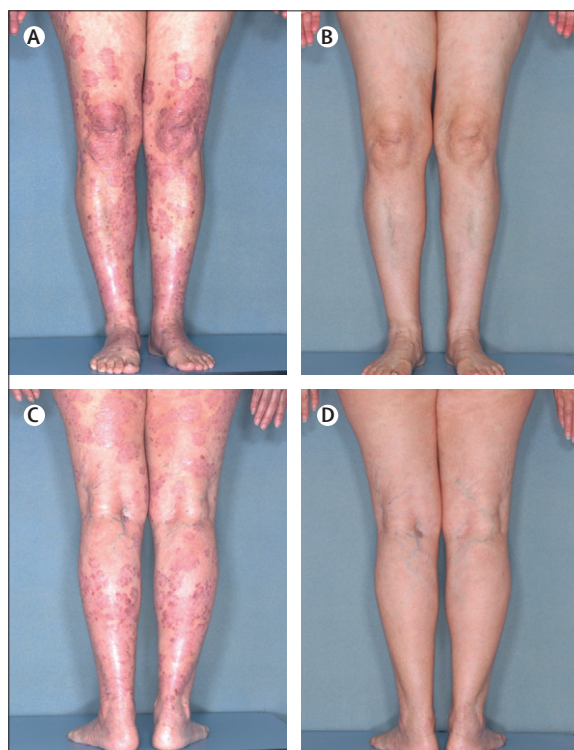


Figure 3: Achievement of PASI-100 in a patient treated with apremilast 30 mg twice daily

assigned to apremilast at week 16 had early, rapid improvement in pruritus during weeks 16–20. At week 24, mean percentage change from baseline pruritus visual analogue scale scores was -14.5 (SD 93.0) for apremilast 10 mg, -36.7 (48.5) for apremilast 20 mg, -41.5 (51.1) for apremilast 30 mg, -41.0 (52.5) for placebo patients assigned apremilast 20 mg at week 16, and -47.9 (64.7) for those assigned apremilast 30 mg at the same time.

Mean improvements from baseline to week 16 in DLQI scores were significantly greater with apremilast 20 mg (mean improvement 11.6 to 5.7; mean difference -5.9 [SD 6.7]; $p < 0.0001$) and apremilast 30 mg (10.6 to 6.0; -4.4 [SD 5.1]; $p = 0.0047$), but not with apremilast 10 mg (10.8 to 7.6; -3.2 [SD 6.0]) compared with placebo (10.7 to 8.6; -1.9 [SD 5.2]). An improvement in DLQI of 5 points or more (minimum clinically important difference)³⁶ was achieved by 22 (25%) of 88 patients assigned placebo, 30 (34%) of 89 assigned apremilast 10 mg, 43 (49%) of 87 assigned apremilast 20 mg ($p = 0.001$ vs placebo), and 39 (44%) of 88 assigned apremilast 30 mg ($p = 0.011$). At week 24, mean change from baseline DLQI score was -3.4 (SD 6.4) for patients assigned apremilast 10 mg, -6.2 (6.5) for patients assigned apremilast 20 mg, -4.9 (5.2) for patients assigned apremilast 30 mg, -4.0 (6.2) for patients assigned apremilast 20 mg in the dose-blinded phase, and -3.5 (5.3) for those assigned apremilast 30 mg. An improvement in DLQI of 5 points or more was achieved by 33 (37%) patients assigned

apremilast 10 mg, 42 (48%) assigned apremilast 20 mg, 40 (45%) assigned apremilast 30 mg, 11 (32%) placebo patients assigned apremilast 20 mg in the active treatment phase, and nine (25%) placebo patients assigned apremilast 30 mg.

At week 16, mean change from baseline in the SF-36 mental component summary score was significantly greater in all three apremilast treatment groups (10 mg $p = 0.0078$, 20 mg $p = 0.0068$, 30 mg $p = 0.0045$) than in the placebo group and mean changes in SF-36 physical component summary scores were numerically greater with apremilast 10 mg, 20 mg, and 30 mg than with placebo, but differences were not statistically significant (appendix p 7). In patients assigned placebo, no significant changes from baseline at week 16 were detected in any SF-36 domain scores. In patients assigned apremilast 10 mg, week 16 mean changes from baseline were significant in three domains: bodily pain ($p = 0.0068$), mental health ($p = 0.0074$), and role-emotional ($p = 0.0068$). In patients assigned apremilast 20 mg, week 16 mean changes from baseline were significant in five domains: bodily pain ($p = 0.0246$), mental health ($p = 0.0116$), physical functioning ($p = 0.0281$), role-emotional ($p = 0.0041$), and social functioning ($p = 0.0465$). In patients assigned apremilast 30 mg, mean changes from baseline were statistically significant in four domains: bodily pain ($p = 0.0234$), mental health ($p = 0.0134$), role-emotional ($p = 0.0055$), and social functioning ($p = 0.0283$, appendix p 7). Responses were generally maintained through week 24 (appendix p 8).

During the 16 week double-blind treatment period, 255 of 352 patients had at least one adverse event: 57 (65%) of 88 assigned placebo, 59 (66%) of 89 assigned apremilast 10 mg, 67 (77%) of 87 assigned apremilast 20 mg, and 72 (82%) of 88 assigned apremilast 30 mg. During the 8 week dose-blinded active treatment period (weeks 16–24), 121 of 280 patients had at least one adverse event: 30 (39%) of 77 assigned apremilast 10 mg; 26 (39%) of 66 assigned apremilast 20 mg; 31 (46%) of 67 assigned apremilast 30 mg; 17 (50%) of 34 placebo patients assigned apremilast 20 mg in the dose-blind phase; and 17 (47%) of 36 placebo patients assigned apremilast 30 mg. Across both treatment periods, most (>96%) adverse events were mild to moderate.

Table 2 and appendix p 9 summarise treatment-emergent adverse events recorded in at least 5% of patients during both treatment periods. Headache, nausea, diarrhoea, and vomiting were generally transient and mild or moderate; most did not prompt treatment adjustment or withdrawal. At least half these events occurred within the first 2 weeks of treatment and resolved within a week. Headache and diarrhoea were reported more frequently with apremilast 30 mg than in the other groups and were mild or moderate, except for one instance of severe headache. Adverse events leading to study discontinuation occurred in five (6%) of

88 patients assigned placebo, two (2%) of 89 assigned apremilast 10 mg, eight (9%) of 87 assigned apremilast 20 mg, and ten (11%) of 88 assigned apremilast 30 mg (appendix p 10). Nausea, vomiting, and headache led to treatment withdrawal in nine patients; no patients discontinued because of diarrhoea.

During double-blind treatment, psoriasis flares occurred in five patients: two patients assigned placebo (one, erythrodermic) and three assigned apremilast 20 mg (one, erythrodermic, which was classified as a serious adverse event). In all cases, treatment was discontinued. No pustular or guttate flares were noted and no psoriasis flare was deemed to be treatment-related. Four of the five patients who had flares were judged as not responding to treatment before study discontinuation (no change or worsening of baseline PASI score); one patient assigned apremilast 20 mg achieved a PASI-50 at week 2 before having the psoriasis flare at week 6. Three patients had psoriasis rebound after treatment cessation: one case occurred during week 24, the day after treatment was stopped, in a patient who received apremilast 30 mg and who was not thought to be responding to treatment (\leq PASI-50); one case arose during week 26 (2 weeks after treatment) in a patient who received apremilast 10 mg and who had achieved PASI-50 at week 16 and last treatment visit; and one case occurred during week 27 (3 weeks after treatment) in a patient who received apremilast 30 mg and who was not thought to be responding to treatment.

During the double-blind treatment period, serious adverse events occurred in two (2%) of 88 patients assigned placebo (one with drug eruption, one with sudden death), none assigned apremilast 10 mg, three (3%) of 87 assigned apremilast 20 mg (one each with erythrodermic psoriasis flare, cellulitis, and nephrolithiasis), and two (2%) of 88 assigned apremilast 30 mg (one with myocardial infarction, one with prostate cancer). During active treatment, one serious event (prostate cancer) was detected in a placebo patient assigned to apremilast 30 mg at week 16. During double-blind treatment, 136 (39%) of 352 patients had at least one infection: 29 (33%) of 88 assigned placebo, 29 (33%) of 89 assigned apremilast 10 mg, 36 (41%) of 87 assigned apremilast 20 mg; and 42 (48%) of 88 assigned apremilast 30 mg. During active treatment, 52 (19%) of 280 patients had at least one infection: 14 (18%) of 77 assigned apremilast 10 mg, 10 (15%) of 66 assigned apremilast 20 mg; 15 (22%) of 67 assigned apremilast 30 mg; seven (21%) of 34 assigned from placebo to apremilast 20 mg; and six (17%) of 36 assigned from placebo to apremilast 30 mg.

During the 24 week study, the most frequently recorded infections were upper respiratory tract infection, nasopharyngitis, and gastroenteritis. No opportunistic infections were identified. All infections were mild to moderate with the exception of two severe infections occurring during double-blind treatment: cellulitis occurred in one patient assigned apremilast

20 mg and severe gastroenteritis occurred in one patient assigned apremilast 20 mg. Two patients assigned apremilast 30 mg became pregnant.

Two patients developed malignant disease (prostate cancer) during the trial: one during the placebo-controlled phase in a patient assigned apremilast 30 mg and one during the active treatment phase in a placebo patient who was assigned apremilast 30 mg. Both these patients were being monitored for increasing prostate-specific antigen concentrations before the study. Two major cardiovascular events occurred during double-blind treatment. One patient in the placebo group, who had a relevant history of chronic obstructive pulmonary disease and moderate alcohol intake, died suddenly of causes unrelated to the study. One patient in the apremilast 30 mg group, who had a relevant history of obesity, hyperlipidaemia, apnoea, chronic obstructive pulmonary disease, smoking, arthritis, and bilateral total knee arthroplasty, had a silent myocardial infarction, diagnosed by abnormal electrocardiographic (ECG) findings at week 8, which prompted discontinuation of study medication. The patient was asymptomatic at the time of the event, but further cardiology investigations confirmed the presence of coronary artery disease and the patient was judged to be at high risk of recurrent cardiovascular events. None of the serious adverse events, severe infections, malignant diseases, or major cardiovascular events was thought to be treatment related. No apparent safety concerns with apremilast were raised on the basis of clinical laboratory assessments of serum chemistry, hepatic laboratories, haematology, urinalysis, immunology or inflammation, or ECG.

Systemic exposure of apremilast was measured in a subset of 15 patients treated with apremilast 10 mg ($n=7$), 20 mg ($n=5$), and 30 mg ($n=3$). At week 14, the respective AUC₀₋₈ were 1008, 1591, and 3467 ng/h per mL with apremilast 10 mg, 20 mg, and 30 mg. The C_{max} and

	Placebo (n=88)	Apremilast		
		10 mg (n=89)	20 mg (n=87)	30 mg (n=88)
Nausea	7 (8%)	10 (11%)	13 (15%)	16 (18%)
Upper respiratory tract infection	5 (6%)	9 (10%)	12 (14%)	14 (16%)
Diarrhoea	4 (5%)	6 (7%)	6 (7%)	12 (14%)
Nasopharyngitis	7 (8%)	9 (10%)	7 (8%)	5 (6%)
Headache*	5 (6%)	5 (6%)	8 (9%)	9 (10%)
Tension headache	6 (7%)	3 (3%)	2 (2%)	14 (16%)
Viral upper respiratory tract infection	7 (8%)	2 (2%)	7 (8%)	7 (8%)
Gastroenteritis	3 (3%)	1 (1%)	4 (5%)	5 (6%)
Dyspepsia	2 (2%)	1 (1%)	5 (6%)	4 (5%)
Arthralgia	6 (7%)	1 (1%)	2 (2%)	2 (2%)
Vomiting	1 (1%)	0	3 (3%)	4 (5%)

Data are n (%). Treatment-emergent adverse events that occurred in at least 5% of patients in any treatment group, from week 0 to week 16. *Per MedDRA preferred term (version 11.0); migraine, sinus, and tension headaches were captured separately.

Table 2: Treatment-emergent adverse events in at least 5% of patients at week 16

Panel: Research in context**Systematic review**

Inhibition of phosphodiesterase 4 increases cellular cAMP, a naturally occurring intracellular secondary messenger that helps maintain immune homeostasis by modulating the production of proinflammatory and anti-inflammatory mediators. Phosphodiesterase 4 inhibitors are, therefore, of interest for the management of inflammatory disease states such as chronic obstructive pulmonary disease, psoriasis, and arthritic disorders. A PubMed search was done to identify relevant published work, with the terms “phosphodiesterase 4” and “psoriasis”, with no limitations or restriction for language, year of publication, or article type, and “phosphodiesterase 4” in human clinical trials or in any article type published between Jan 1, 2009, and Jan 31, 2012.

Interpretation

Apremilast is the first oral phosphodiesterase 4 inhibitor to show consistent efficacy in the management of psoriasis. It is a small molecule that works intracellularly to reduce production of proinflammatory mediators and increase the production of anti-inflammatory mediators. Unlike many treatment options for psoriatic disease that block one component of the inflammatory network, phosphodiesterase 4 inhibition, which increases intracellular cAMP, results in a pattern of partial inhibition of several cytokines and overall modulation of the immune and inflammatory response. Overall, the effects of apremilast on adaptive immunity seem to be minor, especially compared with the reduction of innate immune responses. This study provides evidence of the efficacy and safety of apremilast in the management of patients with moderate to severe psoriasis for 24 weeks during placebo-controlled (16 weeks) and active-treatment (8 weeks) phases. So far, the toxic effects and safety risks reported with commonly used systemic therapies for psoriasis have not been reported in clinical studies of apremilast; however, longer-term data are needed to confirm the positive results of this study and the potential place for apremilast as a new option in psoriasis treatment. On the basis of the results of this study, apremilast 30 mg twice daily has been selected for further investigation in phase 3 clinical trials.

median T_{max} were 208 ng/mL and 2.0 h with apremilast 10 mg, 298 ng/mL and 2.0 h with apremilast 20 mg, and 637 ng/mL and 1.0 h with apremilast 30 mg. At week 24, the respective AUC_{0-8} were 1200, 1257, and 3477 ng/h per mL with apremilast 10 mg, 20 mg, and 30 mg. The C_{max} and median T_{max} , respectively, were 238 ng/mL and 1.0 h with apremilast 10 mg, 236 ng/mL and 1.5 h with apremilast 20 mg, and 670 ng/mL and 1.0 h with apremilast 30 mg.

Discussion

Apremilast, given orally at 20 or 30 mg twice daily, seems to be efficacious, safe, and tolerable for patients with moderate to severe plaque psoriasis. The primary endpoint of PASI-75 at week 16 was achieved by significantly more patients assigned apremilast 20 mg or apremilast 30 mg than placebo, but apremilast 10 mg did not significantly differ from placebo in efficacy. Although no statistical comparisons between apremilast doses were done, apremilast 30 mg had the most favourable outcome and this dose is being investigated for patients with moderate to severe plaque psoriasis in phase 3 trials. Significantly more patients achieved PASI-75, PASI-50, and PASI-90 and had greater improvements in body surface area with apremilast 20 mg or 30 mg than with placebo. Patients had

a rapid improvement in pruritus, an important symptom in psoriasis,²⁷ which was sustained throughout treatment, and up to a third of patients achieved a static physician's global assessment score of 0 or 1. Additionally, apremilast 20 mg and 30 mg were associated with significant improvements in quality of life. All apremilast doses were generally well tolerated, with more than 96% of adverse events rated mild to moderate. Although the rate of overall reported adverse events was generally related to dose, this pattern was not consistent across individual adverse events. Headache, nausea, and diarrhoea were the most frequently reported with apremilast 30 mg; at least half of these events occurred within 2 weeks of treatment initiation and resolved within a week. Adverse and serious adverse event rates leading to study discontinuation were generally low and much the same in all treatment groups. No serious adverse events, malignancies, major cardiovascular events, or serious infections were deemed to be related to apremilast treatment.

Our study had several limitations. The trial enrolled a small number of mainly obese, white men with moderate to severe plaque psoriasis, much the same as in other psoriasis studies. Therefore, the results which show response in the study population might not generalise to more diverse populations, such as individuals of other races or ethnicities, those with non-plaque forms of psoriasis, or those with comorbidities or medical histories who were excluded from this study. The effect of apremilast on signs and symptoms of psoriatic arthritis was not explored; however, in a phase 2 trial of active psoriatic arthritis, apremilast showed efficacy and tolerability.²⁸ The present trial was short (24 weeks) and did not examine safety and efficacy with long-term treatment. Data from a 32 week, open-label extension trial, which enrolled patients who completed this study, and a 48 month, long-term safety study of these patients are awaited. The present analysis handled missing data with the last-observation-carried-forward method, which limits within-patient variability, potentially heightening the effect of bias attributable to attrition.

Two phase 3, double-blind, placebo-controlled, multi-centre trials of apremilast for psoriasis (ESTEEM 1 [NCT01194219] and 2 [NCT01232283]) are underway. Both studies will assess the long-term efficacy and safety of apremilast 30 mg twice daily in adults with moderate to severe plaque psoriasis. These trials include a 52 week masked portion (with a 16 week primary endpoint) and a 4 year extension phase. Subsequent to demonstration of efficacy and an acceptable safety and tolerability profile in patients with psoriatic arthritis in a phase 2 trial,²⁸ apremilast is being studied in four independent phase 3 studies in patients with psoriatic arthritis, including patients who have received disease-modifying antirheumatic drugs and those who have not (PALACE 1 [NCT01172938], PALACE 2 [NCT01212757], PALACE 3 [NCT01212770], and PALACE 4 [NCT01307423]).

Our results support continuing, longer-term studies (panel). Efficacy was recorded rapidly within 2 to 4 weeks and was maintained for 24 weeks of treatment in patients with a long-standing history of severe disease and high baseline body surface area and PASI scores. Although this was not a comparator study, efficacy results seem to be much the same as those recorded for the biological agents etanercept and efalizumab. Importantly, no opportunistic infections occurred and adverse events commonly associated with phosphodiesterase 4 inhibition (headache, diarrhoea, nausea, vomiting) were generally mild to moderate and transient. These findings, along with oral dosing and apparent lack of need for monitoring of liver and kidney function, suggest that apremilast offers an efficacious treatment option with an acceptable safety and tolerability profile and improved convenience compared with present options and could help to fill a gap in the management of psoriasis.

Contributors

KP contributed to the study design, study logistics, collection of data, interpretation of data, review, and final approval of the report; JCC, LR, HS, RGL, and RTM contributed to collection of data, interpretation of data, review, and final approval of the report; CH contributed to study design, study logistics, interpretation of data, and review of the report; and RMD contributed to study design, study logistics, interpretation of data, and review of the report.

PSOR-005 primary investigators

D R Baker, F Behringer, J C Cather, D Fiorentino, S A Fretzin, B S Goffe, T K Hamilton, R Hamlin, M P Heffernan, S E Kempers, C L Leonardi, K H Loven, M Magliocco, R T Matheson, K Gordon, E Monroe, P Rich, M Saruk, S Smith, H Sofen, L Albrecht, C Maari, D Gratton, L Guenther, R A Kunyetz, R Langley, K Papp, Y Poulin, M Robern, L Rosoph, D Toth, R Vender, N R Wasel, Z Tomi.

Conflicts of interest

KP has served as an investigator for Abbott, Amgen, Celgene, Centocor, Galderma, Incyte, Isotechnika, Janssen, Lilly, Medimmune, Merck, Novartis, and Pfizer; an adviser for Abbott, Amgen, Astellas, BMS, Celgene, Centocor, Galderma, Incyte, Isotechnika, Janssen, Johnson & Johnson, Lilly, Medimmune, Merck, Novartis, Pfizer, and UCB; and a speaker for Abbott, Amgen, Astellas, Celgene, Centocor, Isotechnika, Janssen, Novartis, and Pfizer. JCC has served as an investigator for Celgene, Centocor, Novartis, and Pfizer; as a speaker for Centocor and Abbott; and as an adviser for Pfizer, Abbott, and Novartis. LR has been a paid investigator for doing clinical trials for Amgen, Genentech, Abbott, Centocor, Basilea, Leo, Isotechnika, Stiefel, GSK, Galderma, 3-M, Serono, Novartis, Astellas, UCB, Celgene, Johnson & Johnson, and Pfizer. HS has served as an investigator for Abbott, Centocor, Celgene, Amgen, and Pfizer; as a speaker for Abbott and Centocor; and as an adviser for Centocor. RGL has served as an investigator for Abbott, Centocor, Celgene, Amgen, Pfizer, Johnson & Johnson/Ortho Biotech, and Novartis; as a speaker for Abbott, Centocor, Amgen, Pfizer, Johnson & Johnson/Ortho Biotech, and Novartis; and as an adviser for Abbott, Centocor, Celgene, Amgen, Pfizer, Johnson & Johnson/Ortho Biotech, and Novartis. RTM has served as an investigator for Abbott, Centocor, Celgene, Amgen, Novartis, Lilly, Pfizer, Allergan, and Galderma; as a speaker for Centocor and Amgen; and as an adviser for Centocor. CH and RMD are employees of Celgene Corporation.

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