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Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2)

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Conflicts of interest
Conflicts of interest statements are listed in the Appendix.

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Summary

Background Apremilast, an oral phosphodiesterase 4 inhibitor, regulates immune responses associated with psoriasis.
Objectives ESTEEM 2 evaluated the efficacy and safety of apremilast 30 mg twice daily for moderate-to-severe plaque psoriasis.
Methods This phase III, double-blind, placebo-controlled trial randomized adults to apremilast or placebo (2 : 1). At week 16, placebo patients switched to apremilast. At week 32, apremilast patients achieving ≥ 50% reduction in Psoriasis Area and Severity Index (PASI 50) were rerandomized (1 : 1) to continue apremilast or receive placebo. Upon loss of 50% of PASI improvement obtained at week 32, patients rerandomized to placebo resumed apremilast.
Results The modified intention-to-treat population (full analysis set) included 137 placebo and 274 apremilast patients. At week 16, significantly more apremilast patients achieved PASI 75 (28·8%), PASI 50 (55·5%) and static Physician's Global Assessment score of 0 or 1 (20·4%) vs. placebo (5·8%, 19·7%, 4·4%, respectively; $P < 0·001$). Most patients rerandomized to apremilast at week 32 had a PASI 50 response at week 52 (80%). Patients treated with apremilast showed significant improvements in quality of life (as assessed by the Dermatology Life Quality Index) and pruritus at week 16 compared with placebo ($P < 0·001$). The exposure-adjusted incidence of adverse events did not increase with continued apremilast treatment for up to 52 weeks. The most common adverse events were nausea, diarrhoea, nasopharyngitis and upper respiratory tract infection.
Conclusions Apremilast was effective in the treatment of moderate-to-severe plaque psoriasis over 52 weeks.

What's already known about this topic?

- Psoriasis is a chronic inflammatory disease of the skin resulting from an uncontrolled immune response, which leads to a chronic imbalance in the production of pro- and anti-inflammatory cytokines.
- Recent surveys show that many patients with psoriasis report discontinuing treatment with conventional systemic agents or biologics due to lack of tolerability, safety issues, lack or loss of effectiveness, burden of monitoring or injections.

What does this study add?

- In ESTEEM 2, apremilast, an oral phosphodiesterase 4 inhibitor, significantly reduced the severity of moderate-to-severe plaque psoriasis over 16 weeks, with response generally maintained in patients continuing apremilast for 52 weeks.
- Apremilast was effective in difficult-to-treat nail, scalp and palmoplantar psoriasis and in improving pruritus and skin discomfort/pain.
- Apremilast demonstrated an acceptable safety profile; no new significant adverse events emerged with continued apremilast exposure for up to 52 weeks.

Psoriasis is a systemic inflammatory disease that can affect the skin and joints and has multiple associated comorbidities.[1] Psoriasis prevalence varies worldwide, from < 1% in Asia to 8·5% in Norway.[2] In patients with psoriasis, exaggerated innate and adaptive immune responses to stimuli result in a chronic imbalance in the production of pro- and anti-inflammatory cytokines.[3–9] Apremilast is a phosphodiesterase 4 inhibitor that regulates the immune response associated with psoriasis.[10–12] In 2014, oral apremilast was approved by the U.S. Food and Drug Administration for the treatment of adult patients with active psoriatic arthritis and for patients with moderate-to-severe plaque psoriasis. Apremilast has since been approved in multiple countries, including Canada and some countries in the European Union.[13,14]

The Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) is a global, multicentre, phase III clinical trial programme comprising two randomized, placebo-controlled studies evaluating the efficacy, safety and tolerability of apremilast 30 mg twice daily (referred to hereafter as apremilast) in the treatment of patients with moderate-to-severe plaque psoriasis. This article provides 52-week efficacy and safety data from ESTEEM 2.

Materials and methods

The ESTEEM 2 study, conducted at 40 sites in Austria, Canada, Denmark, France, Germany, Italy, Spain, Switzerland and the U.S.A. (NCT01232283), enrolled the first patient in November 2010. The last patient completed the first 52 weeks of the study in December 2012. All patients provided written informed consent. The protocol and consent were approved by the institutional review boards/ethics committees at all investigational sites. The study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki.

Study population

Adults aged ≥ 18 years were eligible if they had a diagnosis of chronic plaque psoriasis for ≥ 12 months. The patients had moderate-to-severe plaque psoriasis, defined as Psoriasis Area and Severity Index (PASI) score ≥ 12, body surface area involvement ≥ 10% and static Physician's Global Assessment (sPGA) score ≥ 3 (moderate to severe), and were candidates for phototherapy or systemic therapy. Patients previously treated with phototherapy or systemic therapy (conventional or biologic), including treatment failures, were permitted to enrol. The main exclusion criteria were clinically significant cardiac, endocrinological, pulmonary, neurological, psychiatric, hepatic, renal, haematological or immunological disease; other major uncontrolled disease; significant infection; active tuberculosis or history of incompletely treated tuberculosis (testing for latent tuberculosis was not required); prolonged sun or ultraviolet exposure; or use of biologics within 12–24 weeks, conventional systemic treatments within 4 weeks or active topical treatments for psoriasis within 2 weeks of randomization. There was no protocol requirement to stop study medication for an infection.

Permitted concomitant medications

Low-potency topical corticosteroids were allowed as background therapy for face, axilla and groin psoriasis lesions only; coal tar shampoo and/or salicylic acid preparations for scalp lesions and nonmedicated emollients for body lesions were also permitted, except within 24 h before each study visit. Patients were not precluded from receiving live vaccinations during the study.

Study design

ESTEEM 2 consisted of three treatment periods (periods A, B and C; Fig. 1). In period A (placebo-controlled phase; weeks 0–16), eligible patients were randomized (2 : 1) via an interactive

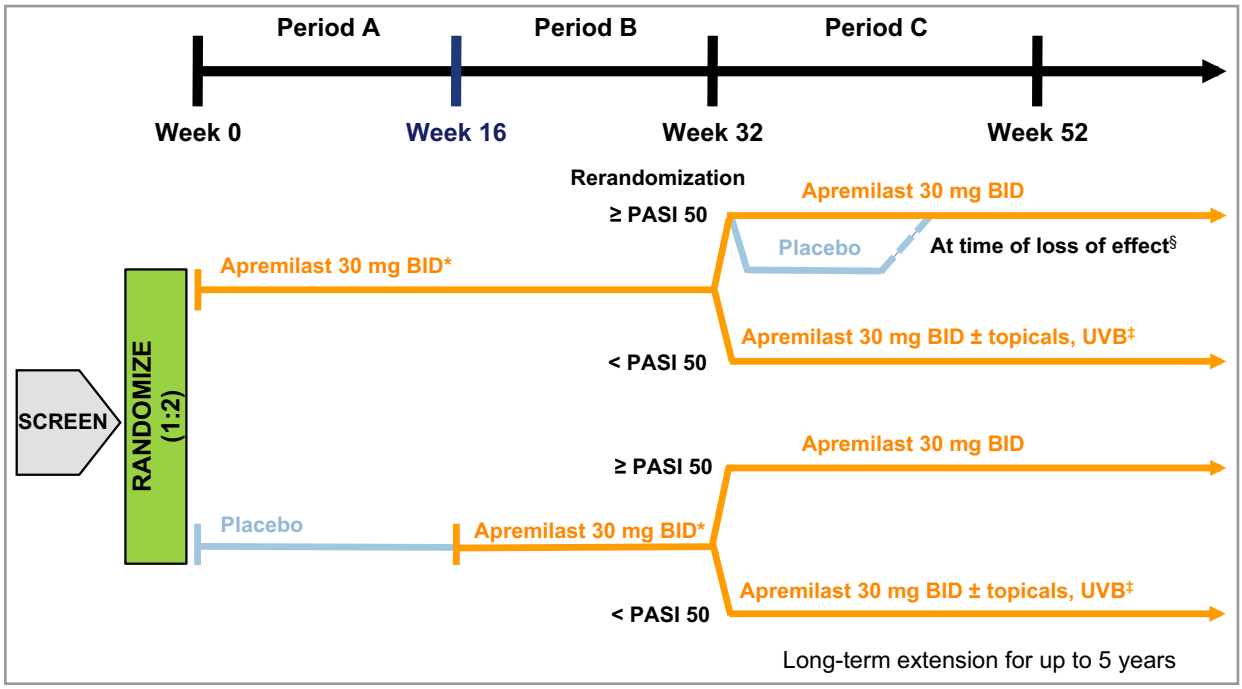


Fig 1. ESTEEM 2 study design. *Doses of apremilast were titrated during the first week of administration and at week 16, when placebo patients were switched to apremilast 30 mg twice daily (BID). §Patients restarted apremilast 30 mg BID at the time of loss of effect, defined as the time of loss of 50% of the Psoriasis Area and Severity Index (PASI) improvement obtained at week 32 compared with baseline, but no later than week 52. ‡Patients initially randomized to placebo or apremilast 30 mg BID who did not attain PASI 50 were able to add topicals and/or ultraviolet (UV)B phototherapy at week 32 at the discretion of the investigator.

voice response system to apremilast or placebo, respectively. Apremilast was dose titrated in 10-mg daily increments (beginning with 10 mg daily) over the first week. All patients received apremilast during period B (maintenance phase; weeks 16–32), with placebo patients being titrated to apremilast 30 mg twice daily over the first week. In period C (weeks 32–52), patients initially randomized to apremilast at baseline who achieved ≥ 50% reduction from baseline in PASI (PASI 50) at week 32 were rerandomized (1 : 1, blinded) to continue apremilast or switch to placebo (treatment withdrawal). Patients rerandomized to placebo resumed apremilast without dose titration when they lost 50% of the PASI improvement obtained at week 32 compared with baseline (loss of response; no later than week 52). All patients initially randomized to placebo in period A and switched to apremilast at week 16 continued apremilast through week 52. At week 32, patients with less than PASI 50 response, regardless of initial treatment, could add topical treatment and/or ultraviolet B phototherapy, based on investigator discretion (results for these patients are not reported in this paper). Blinding was maintained until all patients discontinued or completed the week 52 visit. Upon completing the week 52 visit, patients could enter a long-term extension phase and receive apremilast for an additional 4 years.

Efficacy assessments

The primary end point was the proportion of patients who achieved PASI 75 response at week 16. The major secondary end point was the proportion of patients who achieved sPGA response at week 16, defined as an sPGA score of 0 (clear) or 1 (almost clear) with ≥ 2-point reduction from baseline. All changes in PASI, including PASI 50, PASI 75 and PASI 90, were calculated compared with the baseline PASI scores at week 0.

Safety assessments

Safety assessments included adverse events (AEs), vital signs, laboratory testing, physical examinations, chest radiograph and 12-lead electrocardiogram.

Statistical analysis

Efficacy assessments were conducted for the modified intention-to-treat (mITT) population or the full analysis set (FAS), which included all patients who were randomized as specified in the protocol; patients randomized in error and not dispensed study medication were excluded from the mITT population. The safety population comprised all randomized patients who received at least one dose of study drug.

Approximately 405 patients were planned to be randomized into the study. This proposed sample size was to provide a sufficient database for safety evaluations. This sample size provided > 90% power to detect a 20% difference between apremilast and placebo in PASI 75 response. Multiplicity con-

trol of statistical testing was conducted in a hierarchical manner for secondary end points to control the overall type I error rate.

An ANCOVA model with treatment as a factor and baseline value as a covariate was used for analysis of continuous variables. The last-observation-carried-forward methodology was used to

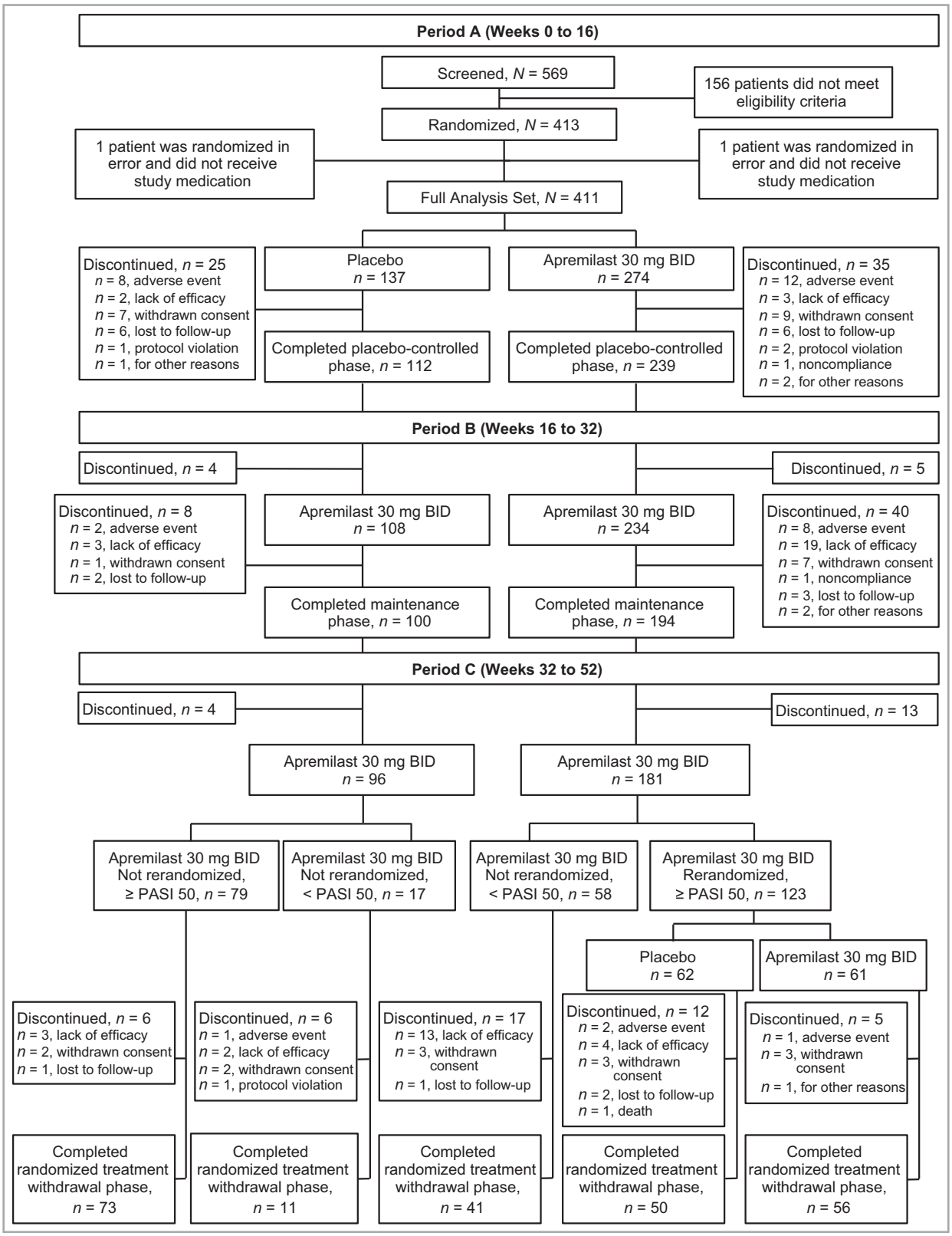


Fig 2. Patient disposition. BID, twice daily; PASI 50, ≥ 50% reduction from baseline in Psoriasis Area and Severity Index.

impute missing efficacy measurements. Multiple sensitivity analyses (including nonresponder imputation) were conducted. AEs were summarized using descriptive statistics for period A and for the apremilast exposure period, which included all patients receiving apremilast regardless of when treatment started for weeks 0–52. All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, U.S.A.).

Results

Patients

In total 413 patients were randomized; 411 comprised the mITT (and FAS) population (placebo, n = 137; apremilast, n = 274), as two patients were randomized in error and did not have study medication dispensed, and thus were excluded from the mITT population (period A; Fig. 2). The baseline demographic and disease characteristics were well balanced between groups (Table 1). At baseline, the mean duration of psoriasis was 18·2 years and the mean PASI score was 19·3.

Efficacy

Period A: weeks 0–16

At week 16, significantly more patients receiving apremilast achieved a PASI 75 response (primary end point) vs. placebo (28·8% vs. 5·8%; $P < 0·001$; Table 2). The major secondary end point, sPGA score of 0 or 1 at week 16, was also achieved by significantly more patients receiving apremilast vs. placebo (20·4% vs. 4·4%; $P < 0·001$). Significantly more patients receiving apremilast achieved PASI 50 and PASI 90 responses vs. placebo (55·5% vs. 19·7%; $P < 0·001$ and 8·8% vs. 1·5%; $P = 0·0042$) at week 16. The results of the nonresponder imputation sensitivity analyses were similar to those of the primary analysis (Table 2). The mean/median percentage change from baseline in PASI was −50·9%/−56·0% for apremilast vs. −15·8%/−18·0% for placebo ($P < 0·001$, mean change) at week 16. Nonoverlapping 95% confidence intervals between apremilast and placebo in the mean percentage improvement in PASI from baseline were detected as early as week 2, the first postbaseline visit.

Significant improvements at week 16 were seen with apremilast vs. placebo based on other efficacy end points, including Dermatology Life Quality Index (DLQI) score and response, with clinically meaningful improvement in DLQI (decrease from baseline DLQI ≥ 5 points) achieved in 70·8% of patients who had baseline DLQI > 5 (both $P < 0·001$; Table 2). At week 16, among patients with nail psoriasis (Nail Psoriasis Severity Index, NAPSI ≥ 1), the mean percentage improvement in NAPSI was significantly greater with apremilast than placebo ($P = 0·0052$; Table 2 and Fig. 3a), and NAPSI 50 achievement was also greater for patients receiving

Table 1 Baseline demographics and disease characteristics: full analysis set (N = 411)

	Placebo (n = 137)	Apremilast 30 mg BID (n = 274)
Prior systemic therapy (conventional and/or biologics), n (%)	73 (53·3)	157 (57·3)
Prior conventional systemic therapy, n (%)	53 (38·7)	106 (38·7)
Prior biologic therapy, n (%)	44 (32·1)	92 (33·6)
Age (years), mean ± SD	45·7 ± 13·4	45·3 ± 13·1
Male, n (%)	100 (73·0)	176 (64·2)
White, n (%)	128 (93·4)	250 (91·2)
Region, n (%)		
U.S.A.	65 (47·4)	141 (51·5)
Canada	30 (21·9)	62 (22·6)
Europe	42 (30·7)	71 (25·9)
Body mass index (kg m^{-2}), mean ± SD	30·7 ± 7·1	30·9 ± 6·7
Weight (kg), mean ± SD	90·5 ± 22·5	91·4 ± 23·0
Duration of plaque psoriasis (years), mean ± SD	18·7 ± 12·1	17·9 ± 11·4
PASI, mean ± SD	20·0 ± 8·0	18·9 ± 7·1
PASI > 20, n (%)	49 (35·8)	81 (29·6)
Body surface area (%), mean ± SD	27·6 ± 15·8	25·5 ± 15·4
Body surface area > 20%, n (%)	80 (58·4)	143 (52·2)
sPGA of 4 (severe), n (%)	49 (35·8)	75 (27·4)
Target nail NAPSI, n (%)[a]	91 (66·4)	175 (63·9)
ScPGA ≥ 3 (moderate to very severe), n (%)	93 (67·9)	176 (64·2)
PPPGA ≥ 3 (moderate to severe), n (%)	16 (11·7)	26 (9·5)
Pruritus VAS score (mm), mean ± SD	65·0 ± 26·0	67·8 ± 25·2
Skin discomfort/pain VAS score (mm), mean ± SD	56·9 ± 28·9	58·9 ± 28·9

The value *N* reflects the number of randomized patients; the actual number of patients available for each parameter may vary. BID, twice daily; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PPPGA, Palmoplantar Psoriasis Physician's Global Assessment; ScPGA, Scalp Physician's Global Assessment; sPGA, static Physician's Global Assessment; VAS, visual analogue scale. [a]Patients had to have target nail psoriasis at baseline (i.e. target nail NAPSI score ≥ 1). Target nail NAPSI scores range from 0 to 8.

apremilast vs. placebo (Table 2). Among patients with scalp psoriasis (Scalp Physician's Global Assessment, ScPGA ≥ 3) at baseline, an ScPGA score of 0 or 1 was achieved by significantly more patients receiving apremilast vs. placebo (P < 0·001; Table 2 and Fig. 3b). Among patients with palmoplantar psoriasis at baseline (Palmoplantar Psoriasis Physician's Global Assessment ≥ 3), a score of 0 or 1 was achieved by significantly more patients receiving apremilast vs. placebo (P = 0·032; Table 2).

At week 16, mean improvements from baseline in pruritus and skin discomfort/pain visual analogue scale (VAS) scores (in mm) were significantly greater with apremilast vs. placebo (P < 0·001; Table 2), with a decrease of approximately 50% from baseline in the severity of pruritus and skin discomfort/pain at week 16. A minimal clinically important difference in pruritus VAS (improvement of ≥ 20%)[15] was achieved by 67·5% of patients receiving apremilast vs. 40·9% of patients receiving placebo at week 16 (P < 0·001). Improvements in pruritus and skin discomfort/pain from baseline were detected as early as week 2 (P < 0·001 vs. placebo; post hoc analyses).

Period B: weeks 16–32

The PASI 50, PASI 75 and PASI 90 responses to apremilast for weeks 16–32 are shown in Figure 4. At week 32, the PASI, sPGA and DLQI responses and mean change in pruritus VAS of patients initially randomized to placebo at baseline

Table 2 Clinical response across efficacy end points at week 16 (period A, placebo-controlled phase)

	Placebo (n = 137)	Apremilast 30 mg BID (n = 274)	P-value
Primary end point			
PASI 75, % (LOCF)	5·8	28·8	< 0·001
PASI 75, % (NRI)	5·1	28·1	< 0·001
PASI 75 by prior systemic therapy, %			
No prior conventional systemic	3·6	33·3	< 0·001
No prior biologic	6·5	31·9	< 0·001
Prior biologic	4·5	22·8	0·0069
Major secondary end point			
sPGA score 0 or 1, % (LOCF)[a]	4·4	20·4	< 0·001
sPGA score 0 or 1, % (NRI)	3·6	19·7	< 0·001
Other end points			
PASI 50, % (LOCF)	19·7	55·5	< 0·001
PASI 50, % (NRI)	17·5	53·6	< 0·001
PASI 90, % (LOCF)	1·5	8·8	0·0042
PASI, mean % change	−15·8	−50·9	< 0·001
PASI, median % change	−18·0	−56·0	
DLQI, mean change	−2·8	−6·7	< 0·001
Pruritus VAS (mm), mean change	−12·2	−33·5	< 0·001
Skin discomfort/pain VAS (mm), mean change	−9·5	−28·5	< 0·001
Patients with baseline DLQI > 5	n = 119	n = 226	
DLQI response (decrease of ≥ 5 points), %[b]	42·9	70·8	< 0·001
DLQI (decrease of ≥ 5 points) + PASI 50 response, %[c]	13·4	49·1	< 0·001
Patients with nail psoriasis	n = 91	n = 175	
NAPSI, mean % change[d]	−7·1	−29·0	0·0052
NAPSI 50, %[d]	18·7	44·6	< 0·001
Patients with scalp psoriasis	n = 93	n = 176	
ScPGA score 0 (clear) or 1 (minimal), %[e]	17·2	40·9	< 0·001
Patients with palmoplantar psoriasis	n = 16	n = 26	
PPPGA score 0 (clear) or 1 (almost clear), %[f]	31·3	65·4	0·032

Week 16 missing data were handled with last-observation-carried-forward (LOCF) methodology, except where noted for nonresponder imputation (NRI). Decreases in Dermatology Life Quality Index (DLQI), pruritus visual analogue scale (VAS), skin discomfort/pain VAS and Nail Psoriasis Severity Index (NAPSI) indicate improvement. NAPSI 50, ≥ 50% reduction from baseline in NAPSI score; PASI, Psoriasis Area and Severity Index; PASI 50, ≥ 50% reduction from baseline in PASI score; PASI 90, ≥ 90% reduction from baseline in PASI score; PPPGA, Palmoplantar Psoriasis Physician's Global Assessment; ScPGA, Scalp Physician's Global Assessment; sPGA, static Physician's Global Assessment. [a]sPGA score of 0 (clear) or 1 (almost clear) with ≥ 2-point reduction from baseline. [b]Decrease of ≥ 5 points in DLQI total score in patients with a baseline total DLQI score > 5. [c]Decrease of ≥ 5 points in DLQI total score and PASI 50 achievement in patients with baseline total DLQI score > 5. [d]Patients with nail psoriasis (score ≥ 1) at baseline. [e]Patients with ScPGA score of ≥ 3 (moderate to very severe) at baseline. [f]Patients with PPPGA score ≥ 3 (moderate to severe) at baseline.

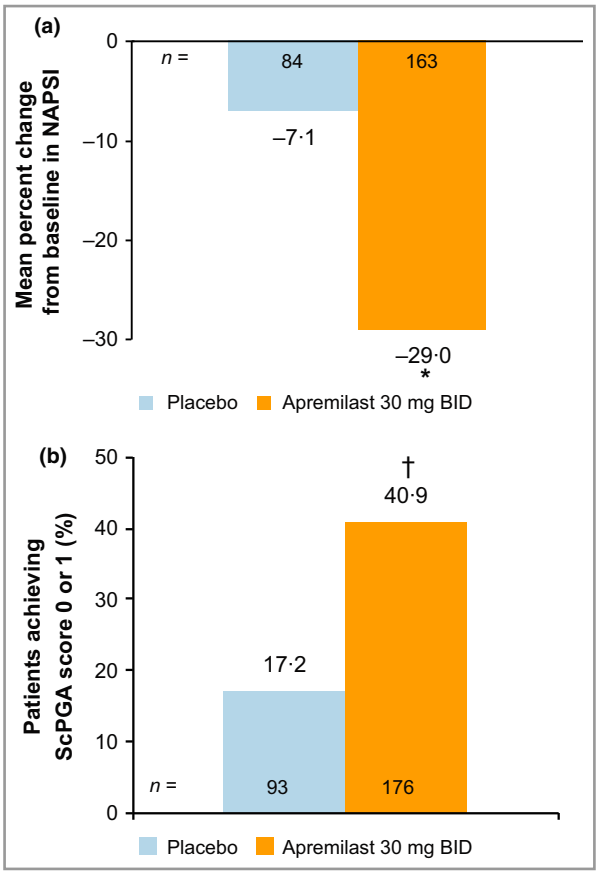


Fig 3. (a) Mean percentage change in Nail Psoriasis Severity Index (NAPSI). *P = 0·0052 vs. placebo. A reduction in NAPSI indicates improvement. Patients with a nonzero baseline value and ≥ 1 postbaseline value are included. (b) Proportion of patients achieving Scalp Physician's Global Assessment (ScPGA) 0 (clear) or 1 (minimal) at week 16. †P < 0·001 vs. placebo. Patients with ScPGA score of ≥ 3 (moderate to very severe) and ≥ 1 postbaseline value at baseline are included. BID, twice daily.

who were switched to apremilast at week 16 mirrored those of patients who received apremilast from baseline (Fig. 5a–e).

Period C: weeks 32–52

Patients randomized to apremilast or placebo at baseline who were PASI 50 responders at week 52: among the 123 patients initially randomized to apremilast who achieved PASI 50 at week 32, 61 and 62 patients were rerandomized to apremilast and placebo, respectively.

Of the patients rerandomized to apremilast, 80% had a PASI 50 response at week 52; the mean percentage change in PASI in these patients at week 52 was −74·4% (Fig. 6a). Of the 61 patients rerandomized to apremilast, 36 were PASI 75 responders at week 32; two-thirds of these patients had PASI 75 response at week 52. Of the 62 patients who were rerandomized to placebo at week 32, 30 (48%) patients never lost 50% or more of their PASI improvement obtained at week 32 during period C, and thus did not resume apremilast treatment prior to week 52. Of the 32 patients who did lose ≥ 50% of their PASI improvement while on placebo, 21 (66%) regained PASI 50 response upon retreatment with apremilast prior to the end of period C (week 52).

For patients rerandomized to placebo, the median time to first loss of response was 12·4 weeks among patients who lost response. Approximately 40% of the patients rerandomized to placebo had a PASI response of 24% or lower, and most had < 12 weeks of retreatment with apremilast to regain a PASI 50 response prior to week 52, as the retreatment time ranged from 2·6 to 18·3 weeks (median 12·0). Patients initially randomized to placebo at baseline who were PASI 50 responders at week 32 and remained on apremilast had a similar PASI response at week 52 to that seen for PASI 50 responders who had been rerandomized to apremilast at week 32 (Fig. 6b).

Safety

In period A (weeks 0–16), 60·3% of patients receiving placebo and 68·0% receiving apremilast reported at least one AE (Table 3). Most AEs were mild to moderate in severity. Incidences of serious AEs were low and comparable across groups,

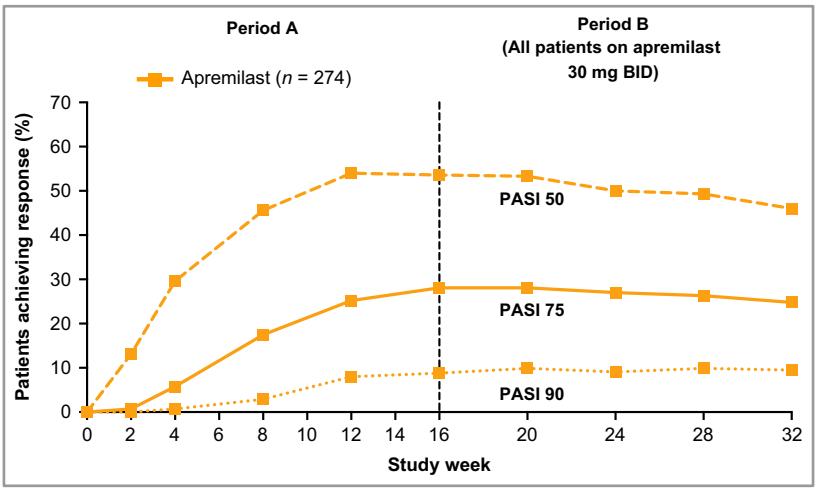
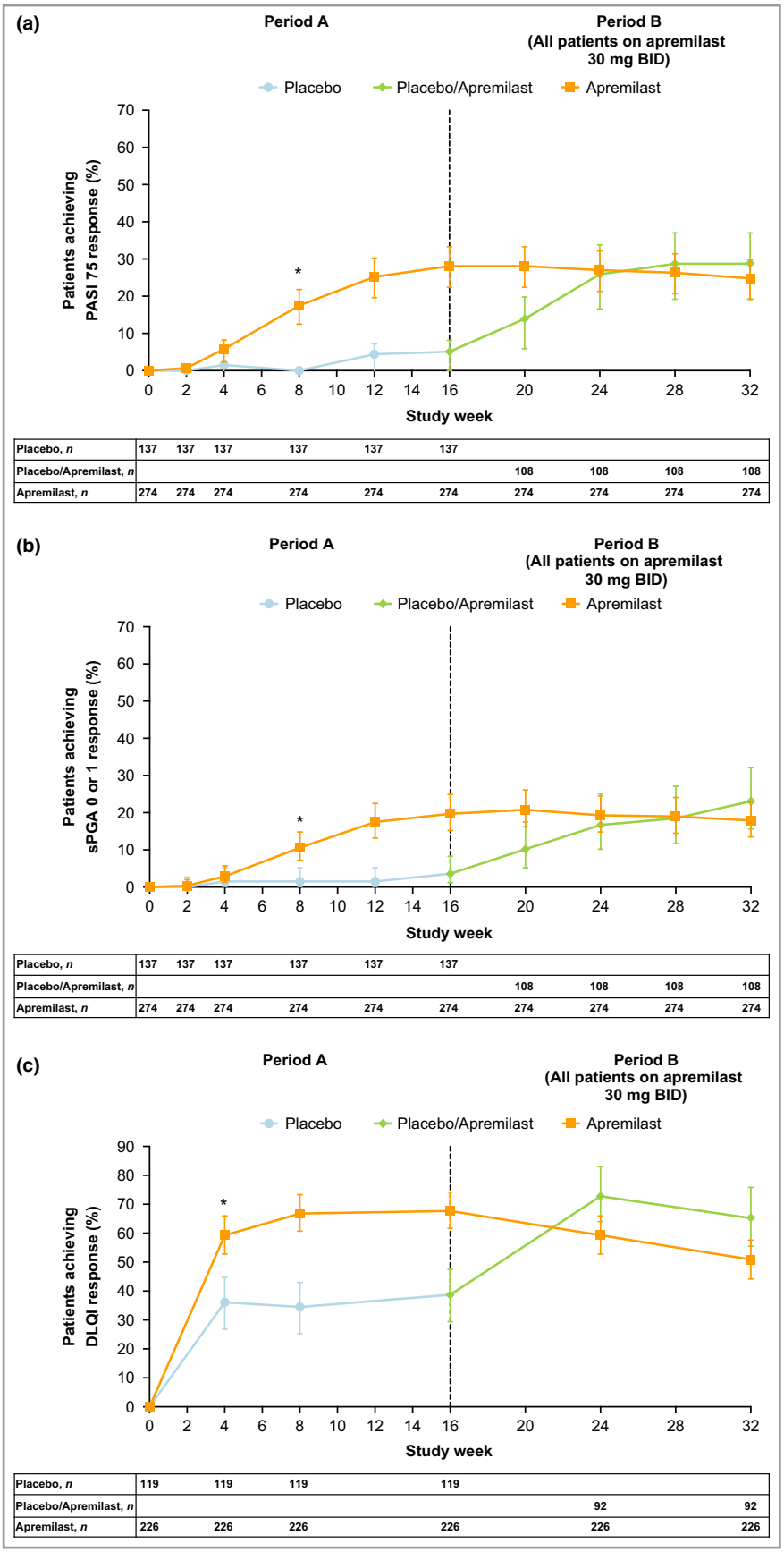


Fig 4. Proportion of patients achieving ≥ 50% reduction from baseline in Psoriasis Area and Severity Index (PASI 50), PASI 75 and PASI 90 over 32 weeks (patients who received apremilast from baseline). Data represent the modified intention-to-treat population, using nonresponder imputation at each time point. BID, twice daily.



Placebo, *n*	137	137	137	137	137	137				
Placebo/Apremilast, *n*							108	108	108	108
Apremilast, *n*	274	274	274	274	274	274	274	274	274	274

Placebo, *n*	137	137	137	137	137	137				
Placebo/Apremilast, *n*							108	108	108	108
Apremilast, *n*	274	274	274	274	274	274	274	274	274	274

Placebo, *n*	119	119	119	119			
Placebo/Apremilast, *n*					92	92	
Apremilast, *n*	226	226	226	226	226	226	

Fig 5. (a) Proportion of patients achieving ≥ 75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75) response. Data represent the modified intention-to-treat (mITT) population, using nonresponder imputation (NRI) at each time point. (b) Proportion of patients achieving static Physician's Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear) with a ≥ 2-point reduction from baseline. Data represent the mITT population, using NRI at each time point. (c) Proportion of patients achieving a decrease of ≥ 5 points in Dermatology Life Quality Index (DLQI) total score in patients with baseline DLQI total score > 5 over 32 weeks. Data represent the mITT population, using NRI at each time point. (d) Mean percentage improvement in PASI from baseline. Data represent the mITT population, as observed at each time point. In (a–d) * indicates the first time point significantly differentiating apremilast 30 mg twice daily (BID) from placebo [i.e. nonoverlapping two-sided 95% confidence intervals (CIs)]. (e) Mean change from baseline in pruritus visual analogue scale (VAS) score. Bars represent two-sided 95% CIs.*$P < 0{\cdot}001$ vs. placebo (*post hoc* analysis). Data represent the mITT population, as observed at each time point.

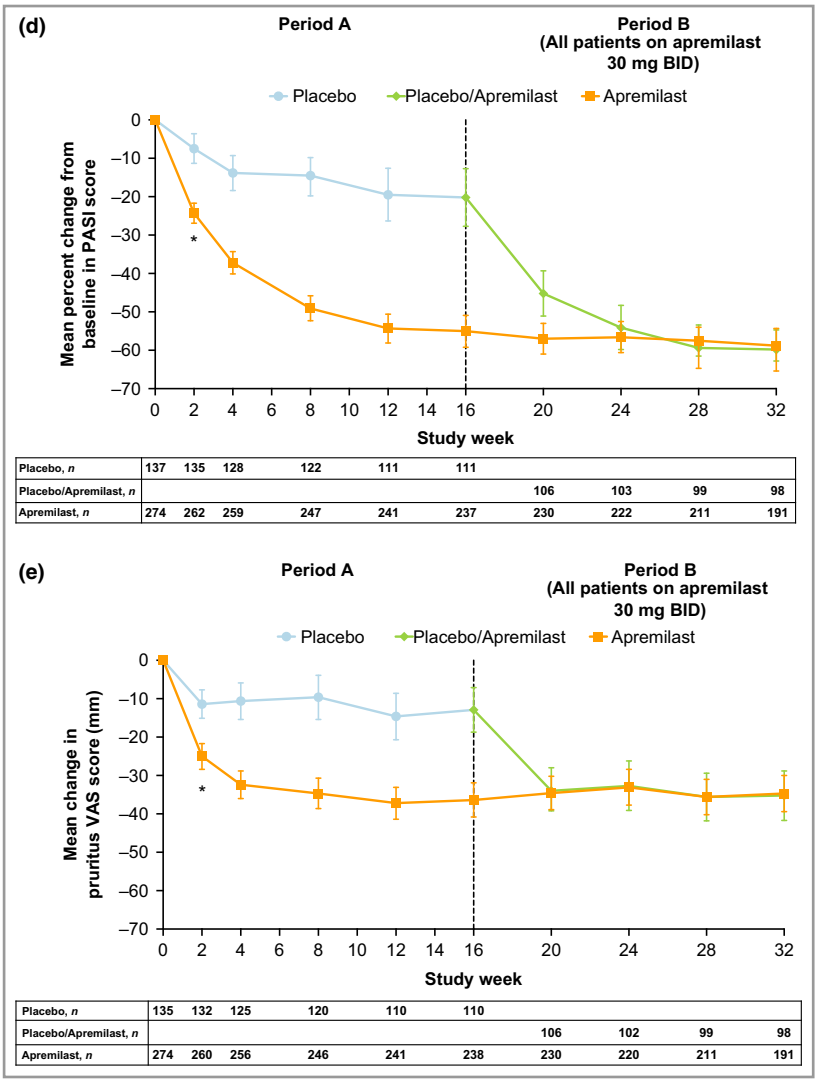


Fig 5. continued

occurring in three (2·2%) placebo and five (1·8%) apremilast patients. Discontinuation rates due to AEs were low (placebo 5·1%, apremilast 5·5%).

The most common AEs were nausea, diarrhoea, nasopharyngitis, tension headache and headache. Diarrhoea and nausea reported in apremilast-treated patients were predominantly mild in severity. Approximately half of these incidences occurred within the first week of dosing and were resolved within 1 month. No patient in either treatment group reported severe nausea or severe diarrhoea. During period A, the proportions of patients reporting any type of infection were similar between groups (placebo 20·6%, apremilast 24·6%). Most of these AEs were mild or moderate in severity.

Similar safety findings were observed during the apremilast exposure period (weeks 0–52), which included all patients receiving at least one dose of apremilast whether initiated at baseline or week 16. The exposure-adjusted incidence of AEs

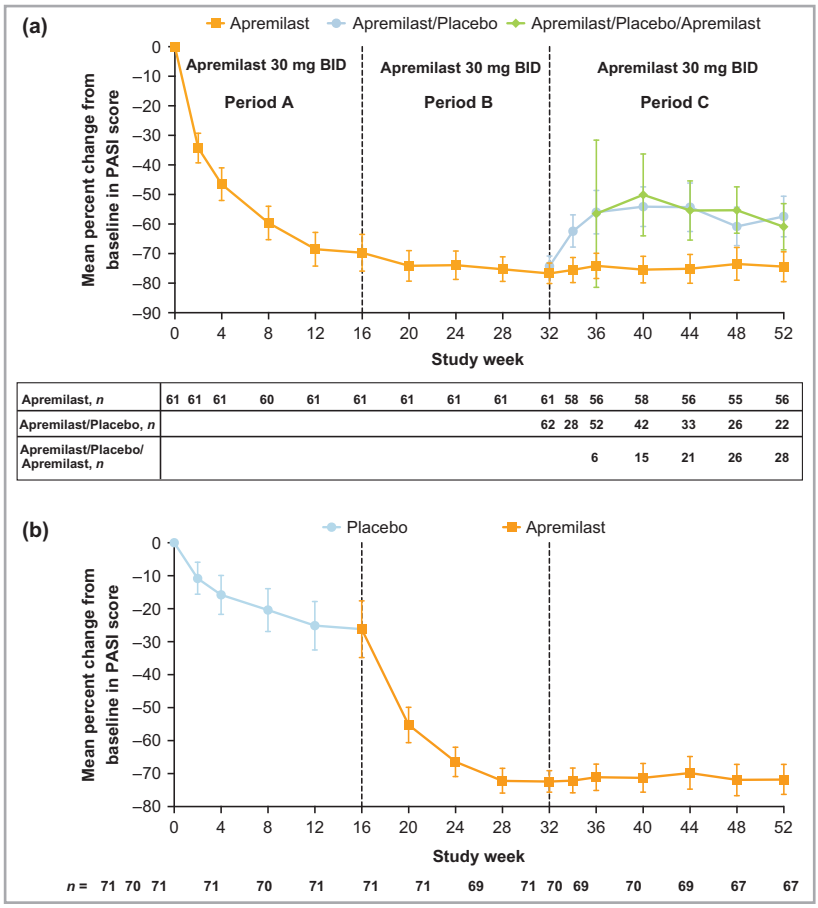


Fig 6. Mean percentage change (two-sided 95% confidence interval) in Psoriasis Area and Severity Index (PASI) over 52 weeks. (a) Patients randomized to apremilast at baseline who were PASI 50 responders at week 32 (denoted R) who were rerandomized to apremilast (apremilast/apremilast/apremilast-R) or placebo. Data are as observed at each time point. (b) Patients randomized to placebo at baseline who were PASI 50 responders at week 32 and were not rerandomized to placebo during period C (placebo/apremilast/apremilast-R). Data are as observed at each time point. PASI 50, ≥ 50% reduction from baseline in PASI score.

did not increase over time, and no new significant AEs emerged with continued apremilast exposure. Overall, 77·9% of patients had at least one AE, and most were mild or moderate. Serious AEs occurred in 4·7% of patients, and the incidence was not driven by any single AE or specific individual organ toxicity. Discontinuations due to AEs were low (7·1%). The profile of most common AEs was similar to that observed in period A (Table 3). Exposure-adjusted incidence rates of major adverse cardiac events, serious infections including systemic opportunistic infection, or malignancies in ESTEEM 1 and ESTEEM 2 (pooled analyses, n = 1184) were comparable between apremilast and placebo.

There were four cases of psoriasis reported as an AE among 62 patients who were rerandomized to placebo in period C; no additional systemic medications (other than study medications) were required to treat these AEs. The PASI score worsened to ≥ 125% of baseline in one of these patients; this worsening occurred following 5 weeks of treatment with placebo, after which the patient was restarted on apremilast. The patient's psoriasis improved to PASI 90 at week 52.

No cases of reactivation of tuberculosis were reported in this study. Overall, the incidence of marked laboratory abnormalities was comparable between treatment groups. Changes in haematology (e.g. haemoglobin, white blood cells, platelets) or clinical chemistry (e.g. creatinine, alanine aminotransferase, aspartate aminotransferase) laboratory parameters were transient and resolved with continued treatment; similar findings were observed with continued longer-term apremilast exposure (Table 3). There were no clinically meaningful changes in electrocardiogram findings during the study.

Body weight was prospectively measured in ESTEEM 2 at regular intervals. During the long-term apremilast exposure period, 20·2% of patients had weight loss > 5%. Weight decrease was reported as an AE in 2·4% of patients treated with apremilast. Two patients (0·5%) treated with apremilast discontinued due to an AE of weight decrease. Weight loss did not lead to any overt medical sequelae or manifestations through the apremilast exposure period. Based on an analysis of the relationship between weight loss and gastrointestinal AEs, there was no association between weight loss and diarrhoea or nausea/vomiting.

Discussion

The results of this phase III, long-term, placebo-controlled study (ESTEEM 2) establish the efficacy of oral apremilast in patients with moderate-to-severe plaque psoriasis, and are consistent with those reported in ESTEEM 1.[16,17] The primary end point in this study was met, with a significantly greater proportion of patients treated with apremilast achieving a PASI 75 response at week 16 vs. placebo. Across four phase IIb to IIIb studies of apremilast 30 mg twice daily, including the

Table 3 Adverse events and laboratory abnormalities during period A (weeks 0–16) and the apremilast exposure period (weeks 0–52)

	Placebo-controlled period, weeks 0–16				Apremilast exposure period, weeks 0–52	
Patients	Placebo (n = 136)	EAIR/100 patient years	Apremilast 30 mg BID (n = 272)	EAIR/100 patient years	Apremilast 30 mg BID (n = 380)	EAIR/100 patient years
Overview, n (%)						
≥ 1 AE	82 (60·3)	419·1	185 (68·0)	541·0	296 (77·9)	336·8
≥ 1 severe AE	6 (4·4)	16·7	12 (4·4)	16·2	33 (8·7)	13·6
≥ 1 serious AE	3 (2·2)	8·2	5 (1·8)	6·6	18 (4·7)	7·1
AE leading to drug withdrawal	7 (5·1)	19·3	15 (5·5)	19·8	27 (7·1)	10·6
AE leading to death[a]	0 (0·0)	0·0	0 (0·0)	0·0	0 (0·0)	0·0
Reported by ≥ 5% of patients in any treatment group, n (%)						
Nausea	9 (6·6)	26·0	50 (18·4)	78·2	63 (16·6)	29·3
Diarrhoea	8 (5·9)	23·1	43 (15·8)	65·9	55 (14·5)	25·1
Nasopharyngitis	6 (4·4)	16·9	20 (7·4)	27·3	55 (14·5)	23·8
Upper respiratory tract infection	6 (4·4)	16·7	13 (4·8)	17·3	35 (9·2)	14·7
Tension headache	2 (1·5)	5·6	20 (7·4)	28·1	29 (7·6)	12·3
Vomiting	5 (3·7)	14·1	14 (5·1)	19·1	24 (6·3)	9·8
Headache	1 (0·7)	2·7	17 (6·3)	23·5	22 (5·8)	9·0
Back pain	2 (1·5)	5·5	6 (2·2)	8·0	20 (5·3)	8·1
Psoriasis	7 (5·1)	19·5	4 (1·5)	5·3	12 (3·2)	4·8
Leading to discontinuation in > 1 patient in any treatment group, n (%)						
Nausea	0 (0·0)	0·0	3 (1·1)	3·9	3 (0·8)	1·2
Psoriasis	3 (2·2)	8·2	2 (0·7)	2·6	3 (0·8)	1·2
Headache	0 (0·0)	0·0	2 (0·7)	2·6	2 (0·5)	0·8
Decreased weight	–	–	–	–	2 (0·5)	0·8
Selected marked laboratory abnormalities, n/m (%)[b]						
ALT > 3 × ULN	0/130 (0·0)	0·0	0/263 (0·0)	0·0	2/370 (0·5)	0·8
AST > 3 × ULN	2/130 (1·5)	5·5	0/263 (0·0)	0·0	6/370 (1·6)	2·4
Total bilirubin > 1·8 × ULN	0/130 (0·0)	0·0	1/263 (0·4)	1·3	2/370 (0·5)	0·8
Total cholesterol > 7·8 mmol L^{-1} or > 301·6 mg dL^{-1}	2/121 (1·7)	5·8	4/248 (1·6)	5·5	7/357 (2·0)	2·8
Creatinine > 1·7 × ULN	0/130 (0·0)	0·0	1/263 (0·4)	1·3	1/370 (0·3)	0·4
Haemoglobin A1C > 9%	1/120 (0·8)	2·9	3/250 (1·2)	4·1	3/357 (0·8)	1·2
Triglycerides > 3·4 mmol L^{-1} or > 301·2 mg dL^{-1}	10/121 (8·3)	29·2	31/248 (12·5)	43·0	62/357 (17·4)	26·4
Haemoglobin						
Male < 10·5 or female < 8·5 g dL^{-1}	1/130 (0·8)	2·8	0/262 (0)	0·0	2/369 (0·5)	0·8
Male > 18·5 or female > 17·0 g dL^{-1}	0/130 (0·0)	0·0	0/262 (0)	0·0	0/369 (0)	0·0
Lymphocytes < 0·8 × 10^9 per L	5/130 (3·8)	13·8	2/262 (0·8)	2·6	8/369 (2·2)	3·2
Neutrophils < 1 × 10^9 per L	0/130 (0·0)	0·0	0/262 (0·0)	0·0	0/369 (0·0)	0·0
Platelets						
< 75 × 10^9 per L	0/130 (0·0)	0·0	0/262 (0·0)	0·0	0/369 (0·0)	0·0
> 600 × 10^9 per L	1/130 (0·8)	2·8	0/262 (0·0)	0·0	1/369 (0·3)	0·4

The apremilast exposure period (weeks 0–52) included all patients who received apremilast 30 mg twice daily (BID), regardless of when treatment was initiated. Exposure-adjusted incidence rate (EAIR) per 100 patient years is defined as 100 times the number of patients reporting the event divided by patient years within the phase (up to the first event start date for patients reporting the event). The value n/m represents patients with at least one occurrence of the abnormality (n)/patients with at least one postbaseline value (m). AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal. [a]One death was reported during the study: a 51-year-old woman who received placebo in the randomized treatment withdrawal phase following 224 days of treatment with apremilast died on study day 354 due to intracranial haemorrhage, 130 days after the last dose of apremilast (while on placebo). The investigator considered the death unrelated to apremilast. [b]All laboratory measurements are nonfasting values.

current study, PASI 75 responses at week 16 have ranged from 29% to 41%.[18–20]

Approximately 50% of patients achieved the European consensus treatment goal of a decrease of ≥ 5 points in DLQI total score and PASI 50 achievement in patients with baseline DLQI score > 5.[21] Thereby, the success criteria of the European Consensus on Treatment Goals were met.[22] Furthermore, 70% of patients had a clinically meaningful improvement in DLQI. Patients treated with apremilast also showed significantly reduced severity of difficult-to-treat nail, scalp and palmoplan-

tar psoriasis. Studies have indicated that pruritus is the most bothersome psoriasis symptom for patients,[23] and apremilast showed rapid and significant improvements in pruritus and skin discomfort/pain. Apremilast demonstrated a rapid onset of action, with clinically meaningful improvements in PASI, pruritus and skin discomfort/pain scores observed as early as week 2. PASI response was generally maintained over 52 weeks with continued apremilast treatment.

Apremilast demonstrated an acceptable safety profile. Most AEs were mild to moderate and did not lead to discontinuation. Nausea, diarrhoea and headache tended to occur more frequently during the first 2 weeks of apremilast dosing compared with subsequent weeks. The exposure-adjusted incidence of AEs did not increase over time, and no new significant AEs emerged with continued apremilast exposure. No increase in the risk for opportunistic serious infection was detected, and no reactivation of tuberculosis was reported during the study. Changes in laboratory parameters were transient, with no trends observed. Weight loss has been observed with apremilast; however, no patient had overt clinical consequences resulting from observed weight loss.

This safety profile, taken together with the efficacy results reported across studies, suggests that apremilast presents an alternative new therapeutic option for physicians and patients who require systemic therapy but prefer an oral option. In three recent major surveys, it was reported that both patients and physicians have acknowledged unmet treatment needs for chronic plaque psoriasis, including safety and tolerability concerns with current therapies and concerns of some patients regarding use of injectable therapies.[23–25] Moreover, the findings from these surveys indicate that a large number of patients are dissatisfied with and discontinue their current psoriasis therapies. The benefit–risk profile of apremilast, which shows moderate efficacy but is devoid of significant organ toxicity, may partially help to address these unmet needs. Of note, based on labelling recommendations, treatment with apremilast does not require laboratory prescreening or ongoing laboratory monitoring.

One limitation of the current study is that the data reported were limited to 52 weeks and do not provide longer-term safety or efficacy information. The results in this study population may not be generalizable to patients with nonplaque forms of psoriasis, or those with comorbidities or medical histories who were excluded from this study.

In conclusion, apremilast significantly reduced the severity of moderate-to-severe plaque psoriasis over 16 weeks, with response generally maintained in patients who were PASI 50 responders and who continued apremilast for 52 weeks. Apremilast was also effective in difficult-to-treat nail, scalp and palmoplantar psoriasis and was effective in improving pruritus and skin discomfort/pain. Apremilast demonstrated an acceptable safety profile, and no new significant AEs emerged with continued exposure for up to 52 weeks. Based on these data and data from ESTEEM 1, oral apremilast provides a new therapeutic option for the treatment of patients with moderate-to-severe plaque psoriasis and may help address unmet patient needs.

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Appendix

Conflicts of interest

C.P. has served as an investigator and consultant for AbbVie, Amgen, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis and Pfizer. J. Cather has been an investigator for Amgen, Celgene, Galderma, Merck, Novartis and Pfizer, and has served on advisory boards for AbbVie, Janssen, OrthoBiotech and Medac. M.G. has been an investigator for AbbVie, Allergan, Celgene, Dermira, Dr. Reddy's Laboratories, Eli Lilly, Galderma, Janssen Pharmaceutical, Kythera, Kyowa Hakko Kirin Pharma, LEO Pharma, Merck, Novartis, Pfizer, Regeneron and Takeda, and has served as a speaker for AbbVie, Actelion, Amgen, Astellas, Galderma, Janssen Pharmaceutical, LEO Pharma, Novartis and Pfizer. Y.P. has been an investigator for AbbVie, Amgen, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor/Janssen, Eli Lilly, Galderma, Isotechnika, LEO Pharma, Merck, Novartis, Pfizer, Pharmascience, Regeneron, Schering and Stiefel/GSK, and has served as a speaker for AbbVie, Amgen, Galderma, Janssen, LEO Pharma and Novartis. U.M. has been an advisor for and/or received speaker honoraria from and/or received grants from and/or participated in clinical trials for Abbott/AbbVie, Almirall-Hermal, Amgen, BASF, Biogen Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, Galderma, Janssen, LEO Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, Teva, VBL and XenoPort. C.F. has served on the advisory board for and/or received speaker honoraria from Celgene, Novartis, Janssen and AbbVie. J. Crowley has been an investigator for AbbVie, Amgen, AstraZeneca, Celgene, Janssen, Maruho, Merck, Pfizer and Regeneron; has served on the advisory board for AbbVie, Amgen, Celgene and Lilly; and has been a speaker for AbbVie and Amgen. C.H., R.M.S., K.S. and R.M.D. are employees of Celgene Corporation. G.G. has been an investigator for AbbVie, Amgen, Bioderma, Celgene, L'Oreal, MSD, Novartis and Pfizer, and has served as a consultant, speaker and/or advisory board member for AbbVie, Actelion, Almirall, Boehringer Ingelheim, Celgene, Dompé, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, Maruho, Merck-Serono, MSD, Novartis, Otsuka and Pfizer. A.B.G. is a consultant and/or advisory board member for Amgen Inc., Astellas, Akros, Centocor (Janssen) Inc., Celgene, Bristol-Myers Squibb Co., Beiersdorf Inc., Abbott Labs (AbbVie), Teva, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd, Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for Life, GlaxoSmithKline, XenoPort, Catabasis, Meiji Seika Pharma Co. Ltd, Takeda and Mitsubishi Tanabe Pharma Development America Inc, and is a recipient of research/educational grants paid to Tufts Medical Center by Centocor (Janssen), Amgen, Abbott (AbbVie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, Merck and XenoPort.