# Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1)

Kim Papp, MD, PhD,[a] Kristian Reich, MD, PhD,[b] Craig L. Leonardi, MD,[c] Leon Kircik, MD,[d,k] Sergio Chimenti, MD,[e] Richard G. B. Langley, MD,[f] ChiaChi Hu, EdM, MS,[g] Randall M. Stevens, MD,[g] Robert M. Day, PhD,[g] Kenneth B. Gordon, MD,[h] Neil J. Korman, MD, PhD,[i] and Christopher E. M. Griffiths, MD, FMedSci[j]

*Waterloo, Ontario, and Halifax, Nova Scotia, Canada; Hamburg, Germany; Saint Louis, Missouri; Louisville, Kentucky; New York, New York; Rome, Italy; Summit, New Jersey; Chicago, Illinois; Cleveland, Ohio; and Manchester, United Kingdom*

***Background:*** Apremilast works intracellularly to regulate inflammatory mediators.

***Objective:*** ESTEEM 1 evaluated efficacy/safety of apremilast at 30 mg twice a day for moderate to severe plaque psoriasis.

***Methods:*** This phase III, multicenter, double-blind, placebo-controlled study randomized adults (2:1) to apremilast or placebo. At week 16, the placebo group switched to apremilast through week 32, followed by a randomized treatment withdrawal phase to week 52. Binary end points were analyzed using $\chi^2$ test; continuous end points used analysis of covariance.

***Results:*** In all, 844 patients were randomized (n = 282, placebo; n = 562, apremilast). At week 16, significantly more patients taking apremilast achieved 75% or greater reduction from baseline Psoriasis Area and Severity Index score (PASI-75) (33.1%) versus placebo (5.3%, $P < .0001$; primary end point). Most (61.0%) patients rerandomized to apremilast at week 32 achieved PASI-75 at week 52 versus 11.7% rerandomized to placebo. Of patients rerandomized to apremilast at week 32, mean percentage change from baseline PASI score was −88% to −81% (weeks 32-52). During the placebo-controlled period, 55.7% and 69.3% of patients randomized to placebo and apremilast, respectively, had 1 or more adverse events. Most adverse events were mild/moderate in severity. No new significant adverse events emerged with continued apremilast exposure versus the placebo-controlled period.

***Limitations:*** Data were limited to 52 weeks and may not generalize to nonplaque psoriasis.

From Probity Medical Research, Waterloo[a]; Dermatologikum Hamburg[b]; Department of Dermatology, Saint Louis University School of Medicine[c]; Mount Sinai Medical Center, New York[k] and Physicians Skin Care, PLLC, Louisville[d]; University of Rome Tor Vergata[e]; Dalhousie University, Halifax[f]; Celgene Corporation, Summit[g]; Northwestern University, Chicago[h]; University Hospitals Case Medical Center, Cleveland[i]; and Dermatology Center, Salford Royal Hospital, University of Manchester.[j]

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Correspondence to: Kim Papp, MD, PhD, Probity Medical Research, 135 Union St E, Waterloo, Ontario N2J 1C4, Canada. E-mail: kapapp@probitymedical.com.

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***Conclusions:*** Apremilast was effective in moderate to severe plaque psoriasis. (J Am Acad Dermatol 2015;73:37-49.)

***Key words:*** apremilast; clinical trial; ESTEEM; phosphodiesterase 4 inhibitor; psoriasis; treatment.

**CAPSULE SUMMARY**

- Many psoriasis patients discontinue treatment because of ineffectiveness, intolerability, or injection issues.
- In ESTEEM 1, oral apremilast was effective in moderate to severe plaque psoriasis for up to 52 weeks and was well tolerated.
- Apremilast offers an oral treatment option for patients with psoriasis.

Cyclic adenosine monophosphate, a key modulator of immune cell responses, is predominantly regulated by phosphodiesterase 4 (PDE4).[1] Apremilast, an oral PDE4 inhibitor, works intracellularly to regulate inflammatory mediators, including pathways relevant to the pathogenesis of psoriasis.[2] PDE4 inhibition elevates intracellular cyclic adenosine monophosphate, which in turn down-regulates the inflammatory responses within T helper (Th) 1, Th17, and type 1 interferon pathways and modulates production of anti-inflammatory cytokines, such as interleukin (IL)-10. In clinical studies, apremilast treatment decreased the number of myeloid dendritic cells and T cells infiltrating the epidermis and dermis of psoriatic lesions and caused a significant reduction in gene expression of IL-12/IL-23p40, IL-22, IL-8, beta-defensin 4, myxovirus resistance protein 1, IL-17A, and IL-23p19.[3,4] PDE4 inhibition can also affect other organ systems, such as adipose tissue, which may contribute to effects such as weight loss.[5,6] Apremilast (Otezla, Celgene Corporation, Summit, NJ) was approved by the US Food and Drug Administration (FDA) in 2014 and by the European Commission in 2015 for treatment of psoriasis and psoriatic arthritis.[7,8] Apremilast is the first oral drug to receive FDA approval for psoriasis since 1996.[9-12]

The Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) phase III program comprises 2 randomized, placebo-controlled studies evaluating apremilast in patients with moderate to severe plaque psoriasis. This article reports results of ESTEEM 1.

## METHODS

### Patients

Patients aged 18 years or older were eligible if they had chronic plaque psoriasis defined as a Psoriasis Area and Severity Index (PASI) score of 12 or higher, body surface area involvement 10% or more, static Physician Global Assessment (sPGA) score of 3 or higher (moderate to severe), and were candidates for phototherapy/systemic therapy. Main exclusion criteria were: other clinically significant or major uncontrolled disease, significant infection, active or history of incompletely treated tuberculosis (testing for latent tuberculosis was not required), use of biologics within 12 to 24 weeks, use of active topical agents for psoriasis within 2 weeks, and prolonged sun or ultraviolet exposure.

The following topical therapies were permitted except within 24 hours before each visit: weak or low-potency topical corticosteroids (class 6 or 7) restricted to treatment of face, axillae, and groin psoriasis lesions; coal tar shampoo and/or salicylic acid for scalp lesions; and unmedicated moisturizers. Patients previously treated with phototherapy/systemic therapy (small molecule or biologic) including treatment failures were permitted in the study. Live vaccinations were permitted during the study.

### Study design and treatment regimens

ESTEEM 1 (registered on clinicaltrials.gov NCT01194219; PSOR-1) was a phase III, multicenter, randomized, double-blind, placebo-controlled study conducted from September 2010 to December 2012 at 72 sites and consisted of 3 treatment periods (periods A, B, and C) (Fig 1). In period A (placebo-controlled phase, weeks 0-16), eligible patients were randomized (2:1) to apremilast at 30 mg twice a day or placebo. During period B (maintenance phase, weeks 16-32), placebo patients were switched to apremilast, with titration. Apremilast dosing was maintained from weeks 16 through 32. In period C (treatment withdrawal phase, weeks 32-52), patients initially randomized to apremilast at baseline who achieved 75% or greater reduction from baseline PASI score (PASI-75) at week 32 were rerandomized (1:1, blinded) to continue apremilast or switch to placebo. To mitigate potential dose-dependent adverse events (AEs), apremilast was titrated in 10-mg increments (beginning with 10 mg once daily) over the first week. Patients rerandomized to placebo at week 32 resumed apremilast (without titration) when they lost PASI-75 response. Patients

*Abbreviations used:*

| | |
|---|---|
| AE: | adverse event |
| ESTEEM: | Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis |
| FDA: | Food and Drug Administration |
| IL: | interleukin |
| PASI: | Psoriasis Area and Severity Index |
| PASI-75: | 75% or greater reduction from baseline Psoriasis Area and Severity Index score |
| PDE4: | phosphodiesterase 4 |
| SAE: | serious adverse event |
| sPGA: | static Physician Global Assessment |
| Th: | T helper |

initially randomized to placebo at baseline who achieved PASI-75 at week 32 were maintained on apremilast through week 52. For patients initially randomized to placebo or apremilast who did not achieve a PASI-75 response at week 32 (n = 135, placebo; n = 245, apremilast), topical therapies/ultraviolet B could be added at the discretion of the investigator. Of these patients, 91 (67.4%) in the placebo group and 126 (51.4%) in the apremilast group received either a topical or ultraviolet B therapy during period C; the results for these patients are not reported in this article. Blinding was maintained until all patients discontinued or completed the week 52 visit. Patients were eligible to continue in a long-term extension to receive apremilast for up to 4 additional years. Patients who completed or discontinued early entered a 4-week posttreatment observational phase. Visits occurred at baseline and then every 4 weeks, with an additional visit 2 weeks after each randomization.

The primary efficacy end point was the proportion of patients achieving PASI-75 at week 16 with apremilast versus placebo. The major secondary efficacy end point was the proportion of patients achieving sPGA score of 0 (clear) or 1 (almost clear) with a point reduction of 2 or more from baseline at week 16 with apremilast versus placebo. Safety evaluations, including AEs, vital signs, laboratory evaluations, physical examinations, electrocardiograms, and chest radiographs, were performed.

Patients provided written informed consent before study-related procedures were performed, and the protocol and consent were approved by institutional review boards or ethics committees at all investigational sites. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

### Statistical analysis

Efficacy data were assessed for the full analysis set (all randomized patients). The safety population comprised all randomized patients who received 1 dose or more of study drug. Approximately 825 patients were planned to be randomized into the study to provide a sufficient safety database. This proposed sample size provided more than 90% power to detect a 20% difference between apremilast and placebo in PASI-75 response.

Statistical analyses were conducted in a hierarchical manner for the efficacy end points to control the overall type I error rate. Thus, end points were analyzed in sequence only if the previous end point was statistically significant. Descriptive statistics were provided to summarize end points not included in the prespecified step-down procedure. All analyses are 2-sided. Discrete variables were analyzed using a $\chi^2$ test and an analysis of covariance model with treatment as a factor and baseline value as a covariate was used for continuous variables. The time to loss of PASI-75 response was characterized using Kaplan-Meier estimates. Missing data were handled with the last-observation-carried-forward methodology for the primary and major secondary end points; multiple sensitivity analyses (including nonresponder imputation) were conducted to confirm the robustness of the study results. Safety end points were summarized using descriptive statistics. All statistical analyses were conducted using SAS, Version 9.2 (SAS Institute Inc, Cary, NC).

## RESULTS

In all, 844 patients were randomized: 282 to placebo and 562 to apremilast (Fig 2). Most patients were from North American sites. Demographic and baseline characteristics are presented in Table I. At baseline, mean (SD) PASI score was 19.4 (7.4) and 18.7 (7.2) for placebo and apremilast, respectively; mean (SD) psoriasis duration was 18.7 (12.4) and 19.8 (13.0) years, respectively. In the placebo and apremilast groups, respectively, 150 (53.2%) and 301 (53.6%) patients had been treated previously with systemic therapy, including 80 (28.4%) and 162 (28.8%) who had received biologics; 101 (35.8%) and 196 (34.9%) patients had not previously received systemic therapy/phototherapy, respectively.

### Period A (weeks 0-16)

Significantly more apremilast-treated patients (33.1%) achieved the primary end point (PASI-75 at week 16) than did placebo patients (5.3%) (95% confidence interval 23.1%-32.5% for difference between apremilast and placebo of 27.8%; $P < .0001$) (Table II). sPGA score of 0 or 1 with a point reduction of 2 or more from baseline at week 16, the major secondary end point, was achieved by significantly

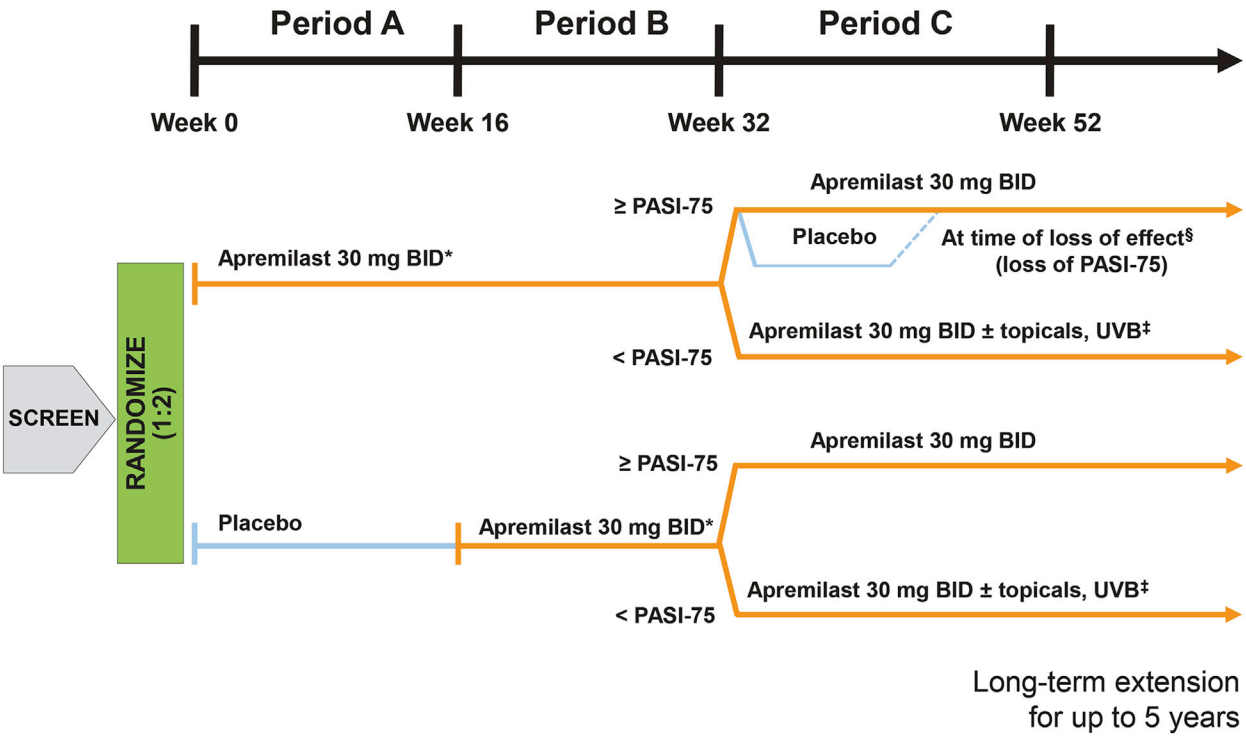


**Fig 1.** Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis 1 study design. *Doses of apremilast were titrated during the first week of administration and at week 16 when placebo patients were switched to apremilast. §Patients restarted apremilast at the time of loss of effect versus baseline (loss of 75% or greater reduction from baseline Psoriasis Area and Severity Index score [*PASI-75*]) but no later than week 52. ‡Patients initially on placebo or randomized to apremilast 30 mg twice a day (*BID*) who did not attain a PASI-75 were able to add topicals and/or ultraviolet (*UV*) B phototherapy at week 32 at the discretion of the investigator.

more patients taking apremilast than placebo (21.7% vs 3.9%) (95% confidence interval 13.7%-21.9% for difference between apremilast and placebo of 17.8%; $P < .0001$). Sensitivity analyses conducted to assess the impact of missing data (including non-responder imputation) also produced significantly greater responses ($P < .0001$) for PASI-75 and sPGA.

Of the other efficacy end points in the hierarchical testing sequence, the first 7 were statistically significant (all $P < .0001$) (Table II). At week 16, apremilast resulted in significantly greater improvement ($P < .0001$) compared with placebo in the following efficacy end points: mean percentage change in body surface area, mean percentage change in PASI score, 50% reduction from baseline PASI score, mean change in pruritus visual analog scale score (mm), and mean change in Dermatology Life Quality Index score (Table II). There was an approximately 50% decrease in severity of pruritus at week 16. In addition, the mean percentage change in Nail Psoriasis Severity Index and Scalp Physician Global Assessment responses were significantly greater for apremilast than for placebo ($P < .0001$) in patients with nail and scalp psoriasis at baseline (Fig 3 and Table II).

### Period B (weeks 16-32)

Higher response rates were observed at week 32 versus week 16 for PASI-75 response (Fig 4, *A*), mean percentage change from baseline in PASI score (Fig 4, *B*), and pruritus visual analog scale score (Fig 4, *C*) among patients who were switched from placebo to apremilast at week 16.

### Period C (weeks 32-52)

In all, 154 patients randomized to apremilast at baseline (period A) who achieved PASI-75 response at week 32 were rerandomized (1:1) to continue apremilast or switch to placebo. Of the 77 patients rerandomized to apremilast at week 32, 47 (61.0%) had PASI-75 response at week 52, and 58 (75.3%) had 70% or more improvement in PASI score from baseline. Mean percentage change from baseline PASI score was −88% to −81% from weeks 32 to 52 in these patients (Fig 5, *A*).

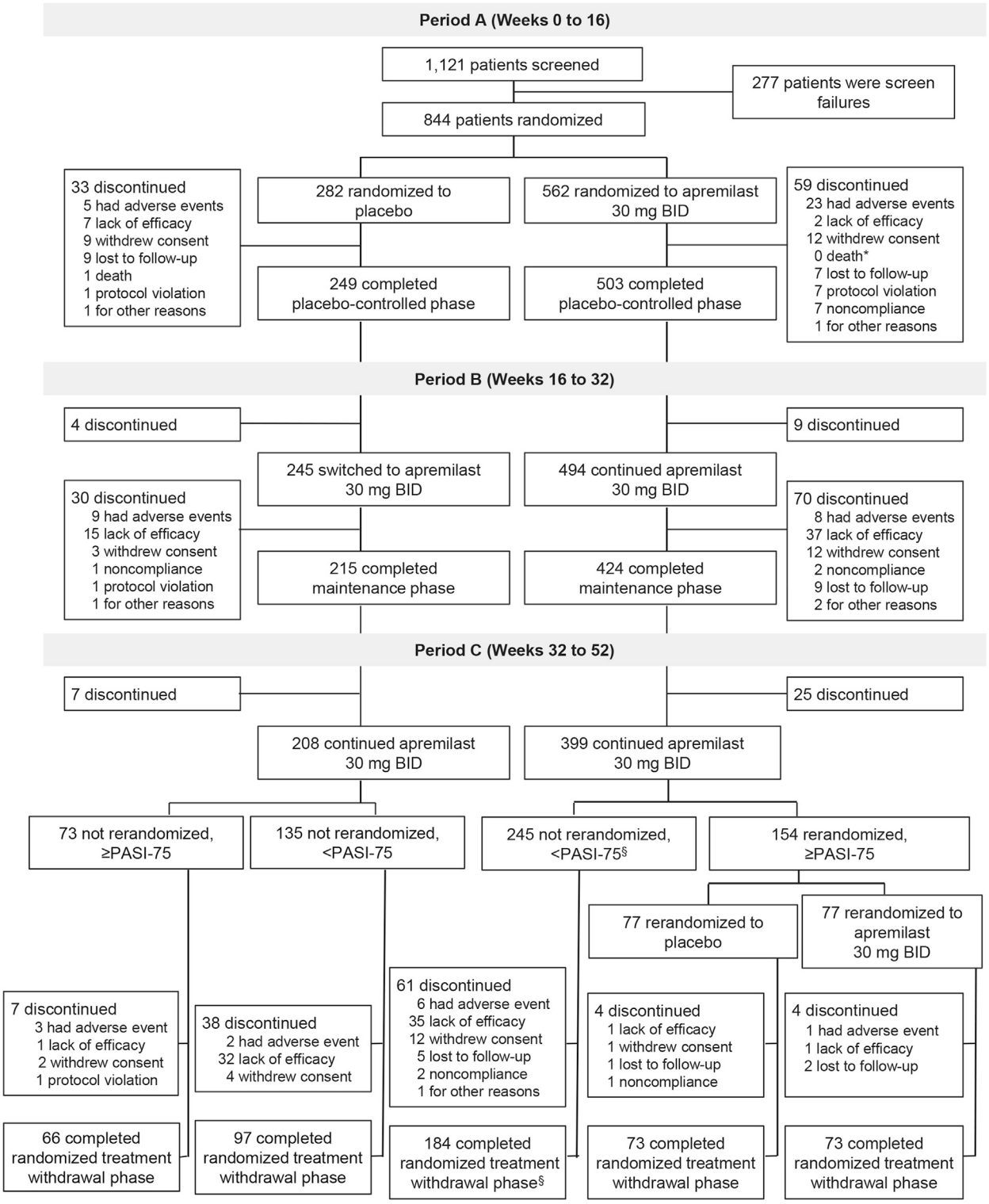


**Fig 2.** Patient disposition. *One death occurred in a patient randomized to apremilast after receiving the last dose of study medication in the placebo-controlled phase. The patient was considered to have completed the placebo-controlled phase. §Includes 4 patients who had a 75% or greater reduction from baseline Psoriasis Area and Severity Index score, were erroneously not rerandomized, and completed the study. *BID*, Twice a day.

**Table I.** Baseline demographics and disease characteristics: all randomized patients (N = 844)

| | Placebo n = 282 | Apremilast 30 mg BID n = 562 |
|---|---|---|
| Age, mean (SD), y | 46.5 (12.7) | 45.8 (13.1) |
| Male, n (%) | 194 (68.8) | 379 (67.4) |
| Female, n (%) | 88 (31.2) | 183 (32.6) |
| Race, n (%) | | |
| White | 250 (88.7) | 507 (90.2) |
| Asian | 16 (5.7) | 28 (5.0) |
| Black | 10 (3.5) | 18 (3.2) |
| Other | 6 (2.1) | 9 (1.6) |
| Body mass index, mean (SD), kg/m$^2$ | 31.3 (7.4) | 31.2 (6.7) |
| Weight, mean (SD), kg | 93.7 (23.2) | 93.2 (21.4) |
| Duration of plaque psoriasis, mean (SD), y | 18.7 (12.4) | 19.8 (13.0) |
| PASI score, mean (SD) | 19.4 (7.4) | 18.7 (7.2) |
| PASI score ≤20, n (%) | 195 (69.1) | 404 (71.9) |
| PASI score >20, n (%) | 87 (30.9) | 158 (28.1) |
| Body surface area, mean (SD), % | 25.3 (14.6) | 24.4 (14.7) |
| Body surface area ≤20%, n (%) | 133 (47.2) | 296 (52.7) |
| Body surface area >20%, n (%) | 149 (52.8) | 266 (47.3) |
| sPGA score 3 [moderate], n (%) | 192 (68.1) | 401 (71.4) |
| sPGA score 4 [severe], n (%) | 89 (31.6) | 161 (28.6) |
| Pruritus VAS score, mean (SD), mm | 65.2 (24.8) | 66.2 (25.5) |
| DLQI score, mean (SD) | 12.1 (6.7) | 12.7 (7.1) |
| Presence of nail psoriasis at baseline, n (%) | 195 (69.1) | 363 (64.6) |
| ScPGA score ≥3, n (%) | 189 (67.0) | 374 (66.5) |
| Prior systemic therapy [conventional and/or biologics], n (%) | 150 (53.2) | 301 (53.6) |
| Prior conventional systemic therapy, n (%) | 102 (36.2) | 212 (37.7) |
| Prior biologic therapy, n (%) | 80 (28.4) | 162 (28.8) |

n = number of randomized patients; actual number of patients available for each parameter may vary.
*BID*, Twice a day; *DLQI*, Dermatology Life Quality Index; *PASI*, Psoriasis Area and Severity Index; *ScPGA*, Scalp Physician Global Assessment; *sPGA*, static Physician Global Assessment; *VAS*, visual analog scale.

Of the 77 patients rerandomized to placebo, 64 (83.1%) lost PASI-75 response and reinitiated apremilast before week 52; of these, 45 (70.3%) regained PASI-75 response after retreatment (retreatment time: 3.4-22.1 weeks). Median time to first loss of PASI-75 after rerandomization at week 32 was 5.1 weeks (95% confidence interval 4.1-8.1) for patients who lost response.

Among patients initially randomized to placebo and switched to apremilast at week 16, 43 of 73 (58.9%) had PASI-75 at week 52. Mean (SD) percentage change in PASI score from baseline in these patients was −80.0% (14.4) (Fig 5, *B*).

In period A, 157 of 282 (55.7%) placebo patients and 388 of 560 (69.3%) patients taking apremilast had 1 or more AE (Table III). AEs were mild (reported in 31.2% of placebo and 39.5% of apremilast patients) or moderate (reported in 21.3% of placebo patients and 26.3% of apremilast patients) in severity. Severe AEs occurred in 9 (3.2%) placebo patients and 20 (3.6%) apremilast patients. Serious AEs (SAEs) occurred in 8 (2.8%) placebo patients and 12 (2.1%) apremilast patients.

Less than 8% of AEs led to drug discontinuation across the treatment groups. The most common AEs (occurring in ≥5% of patients in the placebo and apremilast treatment groups) were diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, tension headache, and headache (Table III). In apremilast-treated patients reporting diarrhea and nausea, 72.4% and 77.4%, respectively, occurred within 2 weeks after the first dose, 79.0% for diarrhea and 76.1% for nausea were mild in severity, and 61.0% for diarrhea and 65.6% for nausea resolved within 1 month. One patient each (0.4%) receiving placebo reported severe nausea and severe diarrhea, and 2 each (0.4%) receiving apremilast reported severe nausea and severe diarrhea.

Exposure-adjusted incidence of AEs did not increase over time in patients with 1 or more SAE, and no new significant AEs emerged with continued apremilast exposure compared with the placebo-controlled period (period A). In all, 633 (78.7%) patients had 1 or more AE; the most common AEs (≥5%) were the same as those reported during the placebo-controlled period (Table III). SAEs were

**Table II.** Clinical response across efficacy end points

| | Placebo-controlled phase (wk 16) | |
|---|---|---|
| | Placebo n = 282 | Apremilast 30 mg BID n = 562 |
| Primary end point, n (%) | | |
| PASI-75 (LOCF) | 15 (5.3) | 186 (33.1)* |
| PASI-75 (NRI) | 14 (5.0) | 183 (32.6) |
| Major secondary end point, n (%) | | |
| sPGA response (LOCF)† | 11 (3.9) | 122 (21.7)* |
| sPGA response (NRI)† | 11 (3.9) | 118 (21.0) |
| Additional end points | | |
| Percentage change in psoriasis affected BSA, mean (SD) | −6.9 (38.9) | −47.8 (38.4)* |
| Percentage change in PASI score from baseline, mean (SD) | −16.7 (31.52) | −52.1 (32.81)* |
| PASI-50, n (%) | 48 (17.0) | 330 (58.7)* |
| Change in pruritus VAS score [mm], mean (SD)‡ | −7.3 (27.08) | −31.5 (32.43)* |
| Change in total DLQI score from baseline, mean (SD) | −2.1 (5.69) | −6.6 (6.66)* |
| Patients with nail psoriasis at baseline | n = 195 | n = 363 |
| Percentage change in NAPSI from baseline, mean (SD)§ | 6.5 (60.57) | −22.5 (54.86)* |
| Patients with scalp psoriasis at baseline | n = 189 | n = 374 |
| ScPGA score 0 (clear) or 1 (minimal), n (%)¶ | 33 (17.5) | 174 (46.5)* |
| Other end points# | | |
| PASI-90, n (%) | 1 (0.4) | 55 (9.8) |
| NAPSI-50, n (%)§ | 29 (14.9) | 121 (33.3) |
| Patients with baseline DLQI >5 | n = 236 | n = 459 |
| DLQI response, n (%)‖ | 79 (33.5) | 322 (70.2) |
| DLQI response + PASI-50 response, n (%)** | 26 (11.0) | 221 (48.1) |
| Patients achieving DLQI ≤5, n (%) | 54 (23.6) | 251 (55.2) |

Wk 16 missing data were handled with LOCF methodology.

*BID*, Twice a day; *BSA*, body surface area; *DLQI*, Dermatology Life Quality Index; *LOCF*, last observation carried forward; *NAPSI*, Nail Psoriasis Severity Index; *NAPSI-50*, ≥50% improvement from baseline Nail Psoriasis Severity Index score; *NRI*, nonresponder imputation; *PASI*, Psoriasis Area and Severity Index; *PASI-50*, 50% or greater reduction from baseline Psoriasis Area and Severity Index score; *PASI-75*, 75% or greater reduction from baseline Psoriasis Area and Severity Index score; *PASI-90*, 90% or greater reduction from baseline Psoriasis Area and Severity Index score; *ScPGA*, Scalp Physician Global Assessment (0 = clear, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe); *sPGA*, static Physician Global Assessment (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe); *VAS*, visual analog scale.

*$P < .0001$ vs placebo.

†sPGA score of 0 (clear) or 1 (almost clear) with a ≥2-point reduction from baseline.

‡Pruritus VAS ranges from 0-100. Higher scores correspond to worse pruritus. Patients with a baseline value and ≥1 post baseline value are included, n = 277 (placebo) and n = 559 (apremilast 30 mg BID).

§Patients with nail psoriasis (score of ≥1) at baseline. A reduction in the NAPSI indicated improvement.

‖Decrease of ≥5 points in DLQI total score in patients with baseline DLQI total score >5. A reduction in score indicated improvement.

¶Patients with ScPGA score of ≥3 at baseline.

#Other supportive end points were not included in the prespecified step-down procedure to test for statistical significance and are presented descriptively.

**Decrease of ≥5 points in DLQI total score and PASI-50 achievement in patients with baseline DLQI total score >5.

reported in 34 (4.2%) patients, but no SAE was reported by more than 3 patients (Table III). Exposure-adjusted incidence rates for SAEs were 6.1 for the 52-week apremilast exposure period compared with 7.5 for the 16-week placebo-controlled period (period A). Incidence of SAEs was not driven by any single preferred term or specific individual organ toxicity. SAEs occurring in more than 1 patient receiving apremilast for up to 52 weeks were coronary artery disease and nephrolithiasis (n = 3, each), and urinary tract infection, acute myocardial infarction, and chronic obstructive pulmonary disease (n = 2, each) (Table III). Each AE leading to discontinuation occurred in less than 2% of patients (Table III).

No tuberculosis reactivation or systemic vasculitis was reported in the study. Changes in laboratory parameters were transient and were not clinically significant.

Body weight was measured in ESTEEM 1 at regular intervals. During the long-term apremilast-exposure period, the median (mean) weight loss was 1.40 (2.08) kg, with 19.0% of patients having weight loss greater than 5%. Weight decrease was reported as an AE in 1.0% of patients treated with apremilast. No patient reported an SAE of weight decrease and no patient treated with apremilast discontinued because of an AE of weight decrease. Weight loss did not lead to any overt medical sequelae or

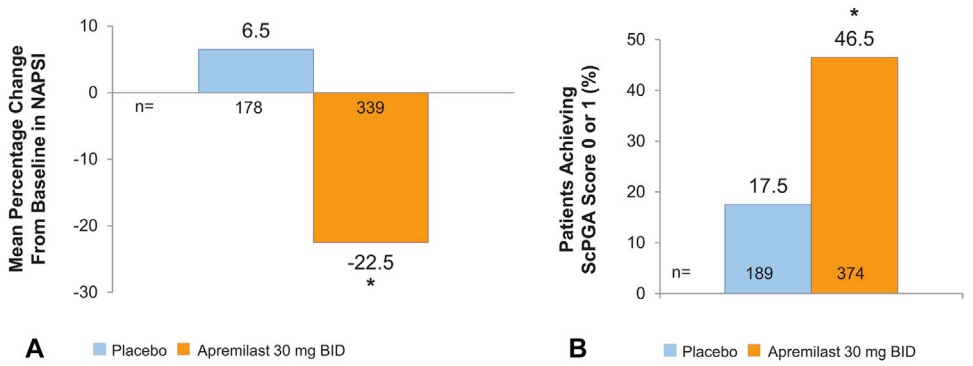


**Fig 3.** **A**, Mean percentage change in Nail Psoriasis Severity Index (*NAPSI*) score. Reduction in NAPSI score indicates improvement. Patients with a non-zero baseline value and 1 or more postbaseline values are included. **B**, Proportion of patients achieving Scalp Physician Global Assessment (*ScPGA*) score 0 (clear) or 1 (minimal) at week 16. Patients with ScPGA score of 3 or more (moderate to very severe) at baseline and 1 or more postbaseline values are included. *BID*, Twice a day. *$P < .0001$ versus placebo.

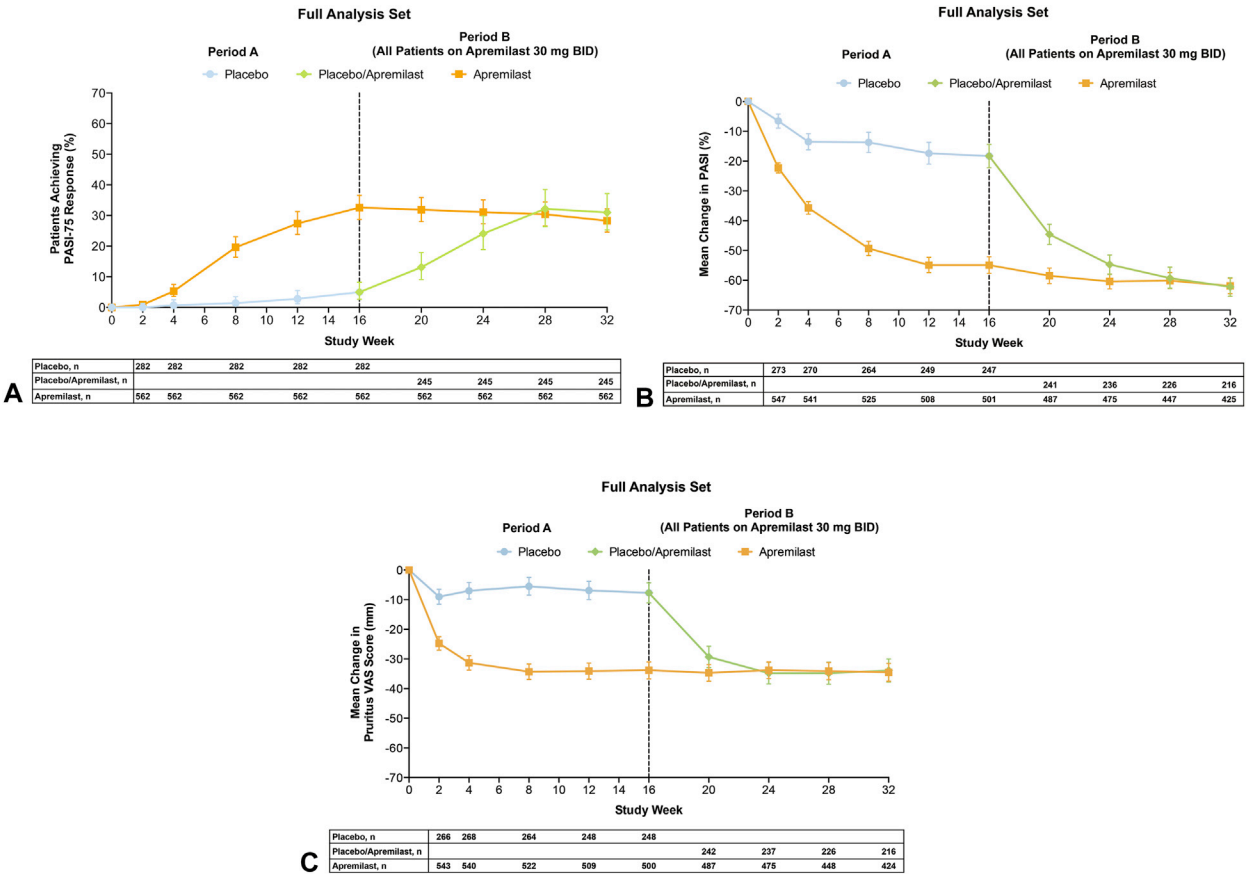


**Fig 4.** **A**, Proportion of patients achieving 75% or greater reduction from baseline Psoriasis Area and Severity Index (*PASI*) score (*PASI-75*) response over 32 weeks. **B**, Mean percentage improvement in PASI from baseline over 32 weeks. **C**, Mean change (mm) in pruritus visual analog scale (*VAS*) score from baseline over 32 weeks. Two-sided 95% confidence intervals are shown. *BID*, Twice a day.

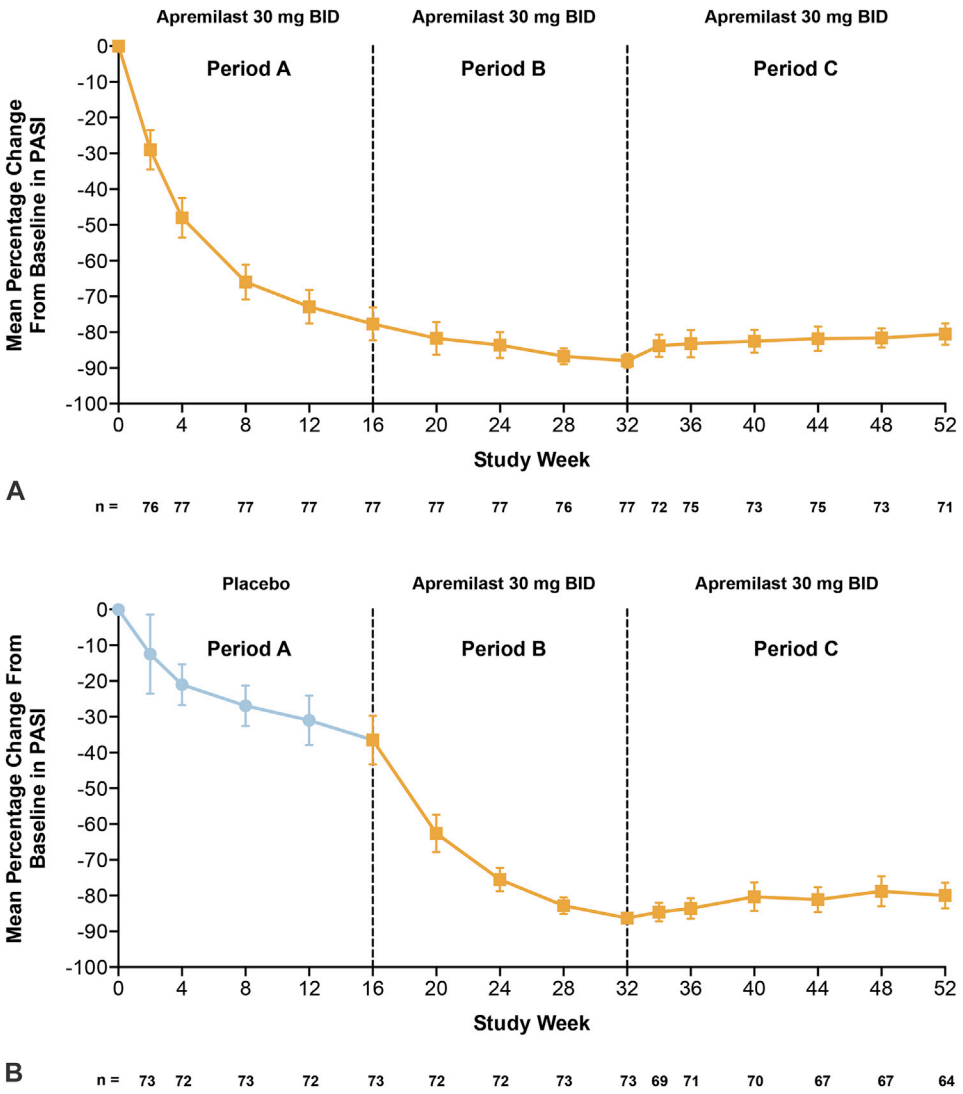


**Fig 5.** Mean percentage change (2-sided 95% confidence intervals) in Psoriasis Area and Severity Index (*PASI*) over 52 weeks. **A**, Patients randomized to apremilast at baseline with 75% or greater reduction from baseline PASI score (PASI-75) response at week 32 who were rerandomized to apremilast (data for patients who were rerandomized to placebo during the randomized treatment withdrawal phase are not shown). **B**, Patients randomized to placebo at baseline who were PASI-75 responders at week 32 and entered the randomized treatment withdrawal phase. Patient numbers begin at week 2. *BID*, Twice a day.

manifestations through the apremilast-exposure period.

## DISCUSSION

Two recent major surveys[13,14] demonstrate that many patients with psoriasis discontinue treatment with conventional systemic agents or biologics, despite considering their disease to be moderate to severe, because of lack of tolerability, safety issues, lack or loss of effectiveness, burden of monitoring, or injections. Therefore, despite current treatment options, there is an unmet medical need for new psoriasis therapies that have an acceptable safety profile and are effective.

Apremilast, an oral PDE4 inhibitor, provides a novel therapeutic option for the treatment of patients with moderate to severe plaque psoriasis. Its effects on cyclic adenosine monophosphate–regulated intracellular signaling, gene expression, and subsequent protein levels allow apremilast to modulate the immune responses that cause the inflammation associated with psoriasis.[2,3] ESTEEM 1 is the first phase III study confirming the efficacy of apremilast in psoriasis. Apremilast demonstrated significant

**Table III.** Adverse events and laboratory abnormalities during the placebo-controlled period (wk 0-16) and the apremilast-exposure period (wk 0-52)

| | Placebo-controlled period wk 0-16 | | | | Apremilast-exposure period wk 0-52 | |
|---|---|---|---|---|---|---|
| **Patients** | **Placebo n = 282** | **EAIR/100 patient-y** | **Apremilast 30 mg BID n = 560** | **EAIR/100 patient-y** | **Apremilast 30 mg BID n = 804** | **EAIR/100 patient-y** |
| Overview, n (%) | | | | | | |
| ≥1 AE | 157 (55.7) | 322.6 | 388 (69.3) | 534.3 | 633 (78.7) | 329.2 |
| ≥1 Severe AE | 9 (3.2) | 11.3 | 20 (3.6) | 12.6 | 48 (6.0) | 8.6 |
| ≥1 Serious AE | 8 (2.8) | 10.1 | 12 (2.1) | 7.5 | 34 (4.2) | 6.1 |
| ≥1 AE leading to drug withdrawal | 9 (3.2) | 11.4 | 29 (5.2) | 18.3 | 59 (7.3) | 10.5 |
| ≥1 AE leading to death | 1 (0.4)* | 1.3 | 1 (0.2)† | 0.6 | 1 (0.1)† | 0.2 |
| Reported by ≥5% of patients in any treatment group, n (%) | | | | | | |
| Diarrhea | 20 (7.1) | 26.6 | 105 (18.8) | 78.2 | 150 (18.7) | 31.6 |
| Upper respiratory tract infection | 21 (7.4) | 27.3 | 57 (10.2) | 37.6 | 143 (17.8) | 28.8 |
| Nausea | 19 (6.7) | 25.0 | 88 (15.7) | 63.6 | 123 (15.3) | 25.0 |
| Nasopharyngitis | 23 (8.2) | 30.1 | 41 (7.3) | 26.6 | 108 (13.4) | 20.9 |
| Tension headache | 12 (4.3) | 15.5 | 41 (7.3) | 27.2 | 77 (9.6) | 14.8 |
| Headache | 13 (4.6) | 17.0 | 31 (5.5) | 20.2 | 52 (6.5) | 9.6 |
| Leading to discontinuation in >1 patient in any treatment group, n (%) | | | | | | |
| Nausea | 1 (0.4) | 1.3 | 10 (1.8) | 6.3 | 14 (1.7) | 2.5 |
| Diarrhea | 1 (0.4) | 1.3 | 7 (1.3) | 4.4 | 10 (1.2) | 1.8 |
| Psoriasis | 1 (0.4) | 1.3 | 2 (0.4) | 1.2 | 6 (0.7) | 1.1 |
| Vomiting | 0 (0.0) | 0.0 | 1 (0.2) | 0.6 | 4 (0.5) | 0.7 |
| Dyspepsia | 0 (0.0) | 0.0 | 3 (0.5) | 1.9 | 3 (0.4) | 0.5 |
| Headache | 0 (0.0) | 0.0 | 3 (0.5) | 1.9 | 3 (0.4) | 0.5 |
| Tension headache | 0 (0.0) | 0.0 | 2 (0.4) | 1.2 | 3 (0.4) | 0.5 |
| Dizziness | 1 (0.4) | 1.3 | 2 (0.4) | 1.2 | 2 (0.2) | 0.4 |
| Migraine | 0 (0.0) | 0.0 | 2 (0.4) | 1.2 | 2 (0.2) | 0.4 |
| Upper abdominal pain | 0 (0.0) | 0.0 | 2 (0.4) | 1.2 | 2 (0.2) | 0.4 |
| Frequent bowel movements | 0 (0.0) | 0.0 | 2 (0.4) | 1.2 | 2 (0.2) | 0.4 |
| Hematochezia | 0 (0.0) | 0.0 | 1 (0.2) | 0.6 | 2 (0.2) | 0.4 |
| Psoriatic arthropathy | 0 (0.0) | 0.0 | 1 (0.2) | 0.6 | 2 (0.2) | 0.4 |
| Asthenia | 0 (0.0) | 0.0 | 2 (0.4) | 1.2 | 2 (0.2) | 0.4 |
| Fatigue | 0 (0.0) | 0.0 | 2 (0.4) | 1.2 | 2 (0.2) | 0.4 |
| Squamous cell carcinoma of the skin | 1 (0.4) | 1.3 | 0 (0.0) | 0.0 | 2 (0.2) | 0.4 |
| Serious AE occurring in >1 patient in any treatment group,‡ n (%) | | | | | | |
| Coronary artery disease | 0 (0.0) | 0.0 | 0 (0.0) | 0.0 | 3 (0.4) | 0.5 |
| Nephrolithiasis | 0 (0.0) | 0.0 | 0 (0.0) | 0.0 | 3 (0.4) | 0.5 |
| Urinary tract infection | 0 (0.0) | 0.0 | 0 (0.0) | 0.0 | 2 (0.2) | 0.4 |
| Acute myocardial infarction | 0 (0.0) | 0.0 | 1 (0.2) | 0.6 | 2 (0.2) | 0.4 |
| Chronic obstructive pulmonary disease | 0 (0.0) | 0.0 | 1 (0.2) | 0.6 | 2 (0.2) | 0.4 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Select marked laboratory abnormalities,[§] n/m (%) | | | | | | | |
| ALT >3 × ULN, U/L | 1/274 (0.4) | 1.3 | 1/555 (0.2) | 0.6 | 4/798 (0.5) | | 0.7 |
| AST >3 × ULN, U/L | 1/274 (0.4) | 1.3 | 2/554 (0.4) | 1.3 | 7/797 (0.9) | | 1.2 |
| Total bilirubin >1.8 × ULN, μmol/L | 1/274 (0.4) | 1.3 | 1/555 (0.2) | 0.6 | 4/798 (0.5) | | 0.7 |
| Hemoglobin A1C >9% | 1/258 (0.4) | 1.3 | 1/527 (0.2) | 0.6 | 1/773 (0.1) | | 0.2 |
| Total cholesterol >7.8 mmol/L | 6/256 (2.3) | 7.9 | 2/528 (0.4) | 1.3 | 14/774 (1.8) | | 2.5 |
| Triglycerides >3.4 mmol/L | 30/256 (11.7) | 39.4 | 53/528 (10.0) | 34.1 | 125/774 (16.1) | | 23.8 |
| Lymphocytes <0.8 × $10^9$/L | 7/274 (2.6) | 9.0 | 7/553 (1.3) | 4.4 | 23/796 (2.9) | | 4.1 |
| Neutrophils <1 × $10^9$/L | 0/274 (0.0) | 0.0 | 0/553 (0.0) | 0.0 | 1/796 (0.1) | | 0.2 |

EAIR per 100 patient-y is defined as 100 times the number (n) of patients reporting the event divided by patient-y within the phase (up to the first event start date for patients reporting the event), which allows for a more comprehensive understanding of relative safety event risk in the study population, especially for studies with a short placebo exposure period and a small number of patients in the placebo group. The n/m represents patients with ≥1 occurrence of the abnormality (n)/patients with ≥1 postbaseline value (m). The apremilast-exposure period (wk 0-52) included all patients who received apremilast 30 mg BID, regardless of when treatment was initiated.

*AE,* Adverse event; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *BID,* twice a day; *EAIR,* exposure-adjusted incidence rate; *ULN,* upper limit of normal.

*A 28-year-old woman with a history of suicide attempts receiving placebo committed suicide.

†A 30-year-old woman on apremilast was found to have a body mass index that increased from 35.1 to 40.6 kg/$m^2$, lung congestion, and bilateral edema consistent with acute cardiac failure, sleep apnea, and morbid obesity at the time of death. No definitive cause of death was identified.

‡During the placebo-controlled period (wk 0-16), no serious AE occurred in >1 patient in either treatment group.

§All laboratory measurements are nonfasting values.

improvements in mean percentage change in PASI score and in pruritus. PASI response was maintained over 52 weeks with continued apremilast treatment. In addition, apremilast demonstrated improvements in nail and scalp psoriasis, both difficult-to-treat forms of psoriasis.[15,16] Most patients rerandomized to placebo who lost PASI-75 response regained it after apremilast reinitiation.

Apremilast has been studied in more than 4000 patients, and the safety profile is consistent across indications.[7,17-19] In this study, most AEs were mild or moderate in severity and discontinuation rates because of AEs were low. No new significant AEs emerged compared with the placebo-controlled period (period A), and rates did not appear to increase with longer apremilast exposure. Incidence of SAEs was low (2.1% for placebo and 2.8% for apremilast) during the placebo-controlled period. Exposure-adjusted incidence rates for SAEs did not increase with longer apremilast exposure. No reactivation of tuberculosis was reported in patients receiving apremilast. Changes in laboratory parameters were transient and were not clinically significant.

Data in this study were limited to 52 weeks and do not provide long-term efficacy or safety information. The results in this study population might not generalize to those with nonplaque forms of psoriasis, or those with comorbidities or medical histories who were excluded from this study. However, the study population herein appears to be representative of the general plaque psoriasis population given the prevalence of comorbidities.

Apremilast has demonstrated improvements in the signs and symptoms of psoriatic arthritis and improved physical function in patients with psoriatic arthritis.[17] In addition to psoriatic arthritis, apremilast provides a novel therapeutic option to treat patients with moderate to severe plaque psoriasis, which may address documented patient concerns regarding current treatment options. The findings from this study indicate the clinical benefit of apremilast for up to 52 weeks for the treatment of moderate to severe plaque psoriasis. Most AEs were mild or moderate in severity and discontinuation rates because of AEs were low.

## Conclusions

There is an unmet clinical need for new psoriasis treatments. Apremilast is the first oral PDE4 inhibitor to show efficacy in the management of psoriasis. The results from this study showed that apremilast significantly reduced the severity of moderate to severe plaque psoriasis over 16 weeks, with responses maintained through 52 weeks of treatment. Most AEs were mild or

moderate in severity and discontinuation rates because of AEs were low. Based on these data, apremilast provides a novel therapeutic option for the treatment of patients with moderate to severe plaque psoriasis.

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