

CLINICAL REPORT

Effects of Apremilast on Pruritus and Skin Discomfort/Pain Correlate With Improvements in Quality of Life in Patients With Moderate to Severe Plaque Psoriasis

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Pruritus and skin discomfort/pain negatively impact health-related quality of life (HRQoL). The effects of apremilast, an oral phosphodiesterase 4 inhibitor, on pruritus, skin discomfort/pain, and patient global assessment of psoriasis disease activity (PgAPDA) were assessed in patients with moderate/severe chronic plaque psoriasis in the phase 3 ESTEEM trials. Significant improvements in pruritus and skin discomfort/pain observed at Week 2 with apremilast versus placebo (both studies, $p < 0.0001$) were sustained through Week 32. Among apremilast-treated patients, improvements in pruritus visual analog scale (VAS) scores correlated with Dermatology Life Quality Index scores ($r_s = 0.55$ [Week 16]; $r_s \geq 0.51$ [Week 32]; both studies, $p < 0.001$). PgAPDA correlated with improvements in pruritus ($r_s \geq 0.56$ [Week 16]; $r_s \geq 0.53$ [Week 32]; both studies, $p < 0.001$) and skin discomfort/pain ($r_s \geq 0.54$ [Week 16]; $r_s \geq 0.53$ [Week 32]; both studies, $p < 0.001$) VAS scores. Apremilast provided rapid and sustained improvement in pruritus and skin discomfort/pain, symptoms not typically captured in psoriasis assessments (e.g., PASI) that contribute significantly to patients' disease severity and HRQoL perceptions. **Key words: apremilast; chronic plaque psoriasis; pain; phosphodiesterase 4 inhibitor; pruritus; quality of life.**

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Psoriasis is a chronic, systemic inflammatory disease that affects approximately 1–3% of adults worldwide, with prevalence varying by geographic region (higher in Europe, North America, and Australia versus African and Asian countries) (1–3). Pruritus and skin discomfort/pain are clinically important symptoms reported in patients with chronic plaque psoriasis (4–6). Among patients with psoriasis, approximately 85% experience pruritus associated with their disease and 77% experience pruritus

on a daily basis (7). In a recent population-based survey of >3,000 patients with psoriasis in North America and Europe, 43% of patients responded that itching was the most bothersome sign or symptom associated with their disease (5). Pruritus has been reported to increase the risk of depression in some patients (8–12) and can negatively affect patient health-related quality of life (HRQoL) (4, 8, 9, 13). Findings from surveys of patients with psoriasis receiving oral or biologic therapy indicate that patient satisfaction with the efficacy and/or safety of current treatment modalities remains low (4, 5, 13).

Apremilast is an oral small molecule phosphodiesterase 4 inhibitor that elevates cyclic adenosine monophosphate (cAMP) levels in immune cells, which in turn down-regulates the production of pro-inflammatory mediators such as TNF- α , IL-17, and IL-23 and increases the production of anti-inflammatory mediators (14, 15). Apremilast was approved by the US Food and Drug Administration in 2014 and by the European Commission in 2015 for the treatment of adult patients with active psoriatic arthritis and for patients with moderate to severe plaque psoriasis (16–18). Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) is a phase 3 clinical trial program comprising 2 randomized, placebo-controlled studies (ESTEEM 1 and ESTEEM 2) evaluating the efficacy and safety of apremilast in adult patients with moderate to severe plaque psoriasis. In these studies, apremilast 30 mg BID significantly reduced the severity of psoriasis, as assessed by achievement of a $\geq 75\%$ reduction from baseline in Psoriasis Area and Severity Index score (PASI-75) at Week 16 (both studies, $p < 0.001$; primary end point) (19, 20). Response was generally maintained in patients who had a PASI response at Week 32 (PASI-75 in ESTEEM 1; PASI-50 in ESTEEM 2) and continued receiving apremilast 30 mg BID through Week 52. In these studies, apremilast also demonstrated an acceptable safety profile and was well tolerated for up to 52 weeks (19, 20).

The effect of apremilast on pruritus severity and HRQoL at Week 16 in the ESTEEM 1 and 2 trials has been reported (19, 20). In the ESTEEM 1 and 2 trials,

apremilast was associated with significant improvements in mean change from baseline in pruritus visual analog scale (VAS) scores (in mm) compared with placebo (ESTEEM 1: -31.5 mm vs. -7.3 mm; ESTEEM 2: -33.5 mm vs. -12.2 mm; both studies, $p < 0.001$) (19, 20). Patient HRQoL, as assessed by mean change from baseline in the Dermatology Life Quality Index (DLQI) total score, was also significantly improved with apremilast versus placebo (ESTEEM 1: -6.6 mm vs. -2.1 mm; ESTEEM 2: -6.7 mm vs. -2.8 mm; both studies, $p < 0.001$) at Week 16 (19, 20).

In patients with psoriasis, improvement in disease severity as assessed by PASI is associated with improvement in HRQoL; however, a lack of a direct correlation between absolute PASI and DLQI values and patient-reported outcomes for HRQoL suggests that factors other than disease severity may mediate patients' HRQoL (21–23). To understand the impact of clinical symptoms of psoriasis on patient HRQoL, we sought to further characterize the effect of apremilast 30 mg BID on pruritus and skin discomfort/pain, 2 important clinical symptoms of psoriasis, through Week 32 of the ESTEEM trials. Additionally, to further understand the relevance of clinical symptoms and patient perceptions of disease severity on HRQoL, *post hoc* analyses were conducted to evaluate the relationship between improvement in pruritus, skin discomfort/pain, and patient global assessment of psoriasis disease activity (PgAPDA) in response to apremilast, and HRQoL at Weeks 16 and 32 in the ESTEEM 1 and 2 trials.

METHODS

Study design and participants

ESTEEM 1 (clinicaltrials.gov identifier NCT01194219) and ESTEEM 2 (clinicaltrials.gov identifier NCT01232283) were similarly designed phase 3, multicenter, randomized, double-blind, placebo-controlled studies of apremilast in patients with moderate to severe chronic plaque psoriasis (Fig. S1¹). Patients with a history of prior phototherapy or systemic treatment (small molecule or biologic), including primary and secondary treatment failure (defined as never responded or lost response, as reported by investigator or patient on case report forms), were allowed to participate. The primary end point of both studies was the proportion of patients who achieved a PASI-75 response at Week 16. The change from baseline in the pruritus VAS and change from baseline in the DLQI total score at Week 16 were prespecified secondary end points in ESTEEM 1 and 2. The change from baseline in the skin discomfort/pain VAS, change from baseline in PgAPDA, and achievement of the minimal clinically important difference (MCID) in DLQI were prespecified exploratory end points of ESTEEM 1 and 2 as defined in the clinical trial protocol. Full details of the study design, inclusion and exclusion criteria, patient population, and primary safety and efficacy results have been described previously (19, 20). All patients provided written informed consent. The protocol and consent were approved by 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.

Outcome measurements

In the ESTEEM 1 and 2 studies, the severity of pruritus and skin discomfort/pain was assessed using the VAS, a common tool used in clinical trials to evaluate the intensity of these symptoms (24–26). Patient-reported pruritus was measured using a 100-mm VAS, which has been shown to be a valid and reliable method for pruritus assessment in patients with psoriasis (24, 26, 27). Patients were asked to rate the severity of their pruritus in response to the following question: On average, how much itch have you had because of your condition in the past week? (0 mm = no itch at all; 100 mm = worst itch imaginable).

Patient-reported skin discomfort/pain was measured using a 100-mm VAS adapted from the horizontal VAS originally designed for the assessment of acute pain (28, 29). Patients were asked to describe their sensations related to psoriatic lesions on the skin in response to the following question: On average, how much skin discomfort/pain have you had because of your condition in the past week? (0 mm = no pain at all; 100 mm = worst possible pain). Patient global assessment of psoriasis disease activity was also assessed using a 100-mm VAS adapted from the standard pain VAS tool mentioned above. Patients were asked to rate their assessment of psoriasis disease severity over the past week using a 100-mm VAS in response to the following question: Considering all the ways your psoriasis affects you, on average, how have you been doing in the past week? (0 mm = very well; 100 mm = very poor). All assessments for VAS scores were obtained at baseline; Weeks 2, 4, and 8; and every 4 weeks thereafter up to Week 32. A $\geq 20\%$ decrease from baseline in the pruritus VAS score was considered to be the MCID threshold for improvement of pruritus severity (30).

The DLQI, a validated questionnaire commonly used in psoriasis clinical trials for the assessment of HRQoL in patients with skin disease (31–35), was used to evaluate patient HRQoL. The DLQI scores range from 0 to 30 (0 = no impairment; 30 = worst QoL). All assessments were obtained at baseline, at Week 4, and then every 8 weeks thereafter up to Week 32. A reduction of ≥ 5 points in the DLQI score in patients with a baseline DLQI total score of > 5 was considered to be the MCID threshold for the DLQI (34).

Statistical analysis

In ESTEEM 1 and 2, the extent of pruritus at baseline was tabulated for the full analysis set, which consisted of all patients who were randomized as specified in the protocol. Mean changes from baseline in pruritus, skin discomfort/pain, and PgAPDA were tabulated based on patients with a baseline value and a post-baseline value at Week 16 and Week 32. All missing values were handled using the last-observation-carried-forward (LOCF) methodology. Descriptive statistics (mean change from baseline and standard deviation [SD]) were determined for pruritus, skin discomfort/pain, and PgAPDA at baseline. Additionally, the decrease in pruritus severity from baseline to Week 16 and the proportion of patients concurrently achieving the MCID for pruritus and DLQI scores at Week 16 and Week 32 are presented as numbers and percentages; no statistical comparisons between treatment groups were performed.

Changes from baseline in pruritus and skin discomfort/pain at Week 16 were compared using analysis of covariance (ANCOVA) models with the treatment group as a factor and the baseline pruritus and skin discomfort/pain value as a covariate, respectively. If the slope was homogenous, then a common slope was implemented into the model to test the treatment dif-

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ference. The 2-sided *p*-value for slope homogeneity <0.05 was assessed. An *ad hoc* repeated measurement was conducted with treatment, visit (Weeks 2, 4, 8, 12, and 16), and treatment-by-visit interaction in the model using a mixed model with missing data as random algorithm. The repeated measurement model was used to assess the treatment effect with the adjustment of time (visit) during the whole placebo-controlled phase to confirm the robustness of the treatment at Week 16 outcome.

Additional *post hoc* analyses explored achievement of clinically meaningful changes in pruritus VAS using $\geq 20\%$ decrease from baseline for pruritus VAS (MCID) as well as a threshold of ≥ 40 -mm decrease from baseline in pruritus VAS in patients with baseline pruritus VAS score ≥ 40 mm. Between-group comparisons for achieving pruritus MCID or a ≥ 40 -mm decrease from baseline in pruritus VAS at Week 16 were assessed using the Fisher exact test. A *p*-value of <0.05 was considered statistically significant.

The Spearman rank order correlation coefficient was used to assess the relationships between the pruritus VAS and HRQoL (as measured by the DLQI total score) at baseline (pooled placebo and apremilast groups) and with apremilast at Week 16 and Week 32. The Spearman rank order correlation coefficient was also used to analyze the relationships between mean change in PASI and DLQI total score as well as the relationships between mean changes from baseline in PgAPDA and both pruritus and skin discomfort/pain with apremilast at Week 16 and Week 32 in the ESTEEM patient population (all patients).

RESULTS

Patients

The full analysis set included 844 patients from ESTEEM 1 (placebo: *n*=282; apremilast: *n*=562) and 411 patients from ESTEEM 2 (placebo: *n*=137; apremilast: *n*=274). Demographic and baseline characteristics have been previously published (19, 20) and are shown in Table S1¹. At baseline, approximately one-third of patients had severe disease and approximately half had >20% body surface area involvement. The mean baseline pruritus VAS scores observed in ESTEEM 1 and 2 ranged from ap-

proximately 65 to 68 mm (moderate pruritus, i.e., 40 to <70 mm) (24), and the mean baseline skin discomfort/pain VAS scores ranged from approximately 57 to 59 mm. The mean baseline score for the PgAPDA VAS ranged from approximately 50 to 52 mm (Table S1¹).

Changes in pruritus and skin discomfort/pain

Mean improvements from baseline in pruritus and skin discomfort/pain VAS (in mm) were seen as early as Week 2 (*p*<0.0001, ANCOVA) with apremilast and were maintained through Week 32 in both studies (Fig. 1). In ESTEEM 1, the mean (SD) pruritus VAS score was 66.2 (25.52) mm at baseline and 34.7 (31.19) mm at Week 16, a decrease of 31.5 (32.43) mm or 47.6%. In ESTEEM 2, the mean (SD) pruritus VAS score was 67.8 (25.21) mm at baseline and 34.3 (31.63) mm at Week 16, a decrease of 33.5 (35.46) mm or 49.4% (Fig. 1A). At Week 32, mean (SD) improvements in pruritus VAS scores were sustained in the apremilast/apremilast

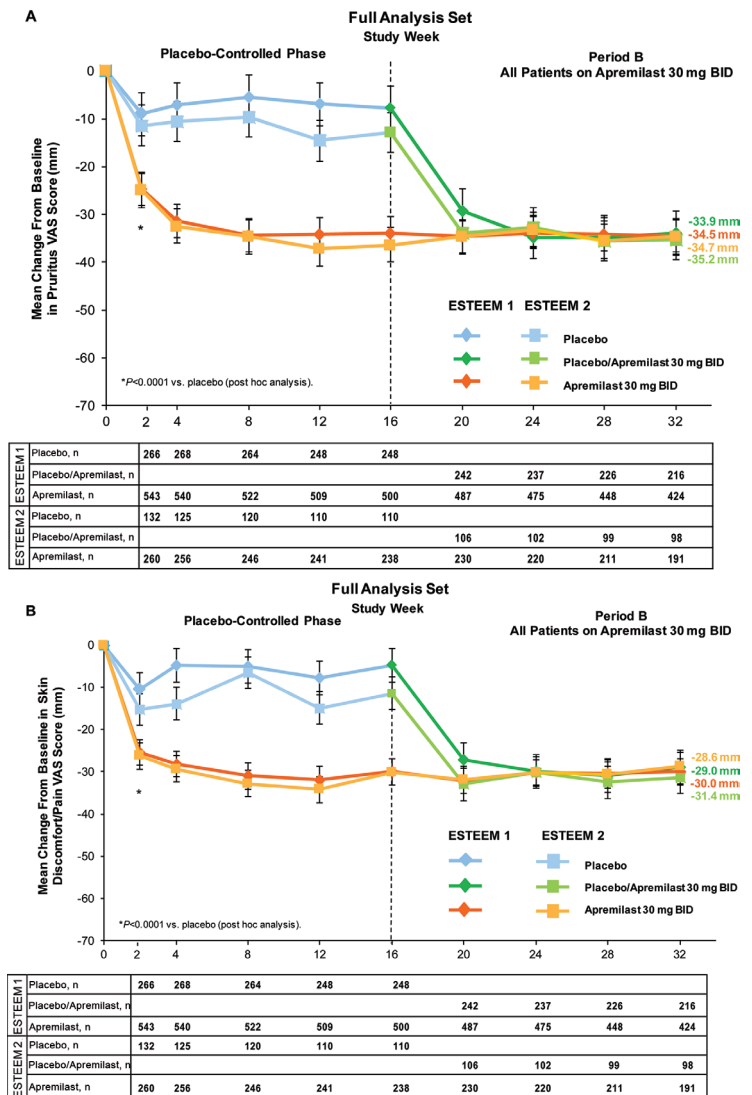


Fig. 1. (A) Mean change in pruritus VAS (mm) over 32 weeks, using data as observed from patients in the full analysis set. **p*<0.0001 versus placebo both ESTEEM 1 (standard error: 1.8560, degrees of freedom: 807) and ESTEEM 2 (standard error: 2.7558; degrees of freedom: 390) (ANCOVA, *post hoc* analysis). VAS: visual analog scale (100 mm). Mean (SD) baseline pruritus VAS values (as observed for patients in the full set analysis): ESTEEM 1: 65.0 (24.84) mm (placebo) and 66.1 (25.55) mm (apremilast 30 mg BID); ESTEEM 2: 65.3 (25.93) mm (placebo) and 67.7 (25.31) mm (apremilast 30 mg BID). (B) Mean change in skin discomfort/pain VAS (mm) over 32 weeks, using data as observed from patients in the full analysis set. **p*<0.0001 versus placebo both ESTEEM 1 (standard error: 2.0208, degrees of freedom: 807) and ESTEEM 2 (standard error: 2.9112; degrees of freedom: 390) (ANCOVA, *post hoc* analysis). VAS=visual analog scale (100 mm). Baseline mean (SD) skin discomfort/pain VAS values (as observed for patients in the full analysis set): ESTEEM 1: 56.8 (29.74) mm (placebo) and 58.0 (29.40) mm (apremilast 30 mg BID); ESTEEM 2: 57.1 (28.77) mm (placebo) and 58.7 (29.17) mm (apremilast 30 mg BID).

group (ESTEEM 1: -34.5 [31.16] mm; ESTEEM 2: -34.7 [32.80] mm [Fig. 1A]). The mean (SD) change from baseline in pruritus VAS score in the placebo/apremilast group was -33.9 (29.08) mm in ESTEEM 1 and -35.2 (32.38) mm in ESTEEM 2 at Week 32.

Apremilast resulted in an approximately 50% decrease in severity of skin discomfort/pain on VAS scores at Week 16 in both studies (Fig. 1B). In ESTEEM 1, the mean (SD) skin discomfort/pain VAS score was 58.1 (29.31) mm at baseline and 29.8 (30.85) mm at Week 16, a decrease of 28.3 (32.45) mm or 48.7% (Fig. 1B). Similar magnitude in the reduction from baseline was observed for apremilast in the severity of skin discomfort/pain VAS scores at Week 16 in ESTEEM 2 (Fig. 1B). At Week 32, mean (SD) improvements from baseline in skin discomfort/pain VAS scores were sustained in the apremilast/apremilast group (ESTEEM 1: -30.0 [31.85] mm; ESTEEM 2: -28.6 [34.13] mm). Mean (SD) changes from baseline in skin discomfort/pain VAS scores in the placebo/apremilast group were -29.0 (31.63) mm in ESTEEM 1 and -31.4 (32.94) mm in ESTEEM 2 at Week 32 (Fig. 1B).

Achievement of minimal clinically important difference

In ESTEEM 1, an MCID in pruritus VAS (improvement of ≥20%) was achieved by 70.6% (397/562) of patients receiving apremilast versus 33.7% (95/282) of patients receiving placebo ($p < 0.0001$, Fisher exact test) at Week 16 (Fig. 2A). Achievement of pruritus MCID was sustained in 57.8% (325/562) of patients in the apremilast/apremilast group; 58.5% (165/282) of patients in

the placebo/apremilast group achieved pruritus MCID at Week 32. Similar findings were observed for MCID achievement at Week 16 and Week 32 in ESTEEM 2 (Fig. 2A). Among patients with a pruritus VAS score ≥40 mm at baseline, a significantly greater proportion of patients achieved a ≥40-mm decrease from baseline in pruritus VAS with apremilast versus placebo at Week 16 in both studies ($p < 0.001$, Fisher exact test) (Fig. 2B). Additionally, a higher proportion of patients with improvement in pruritus severity had no itch or mild itch (pruritus VAS score ≤40 mm) with apremilast versus placebo at Week 16 (ESTEEM 1, 55.7% vs. 23.0%; ESTEEM 2, 57.7% vs. 28.5%, $p < 0.0001$ for both, Fisher exact test). At Week 32, 40.4% and 40.6% of patients achieved a ≥40-mm decrease from baseline in pruritus VAS in the placebo/apremilast and apremilast/apremilast groups, respectively, in ESTEEM 1; 45.0% and 40.5% of patients achieved a ≥40-mm decrease from baseline in pruritus VAS in the placebo/apremilast and apremilast/apremilast groups, respectively, in ESTEEM 2 (Fig. 2B).

Correlation between pruritus severity and Dermatology Life Quality Index scores

During the placebo-controlled phase, a similar trend was observed in the mean improvement from baseline in pruritus VAS and DLQI scores in patients receiving apremilast (Fig. 3). Achievement of the MCID for both pruritus and DLQI at Week 16 was numerically greater for apremilast versus placebo (ESTEEM 1: 261/562 [46.4%] vs. 36/282 [12.8%]; ESTEEM 2: 129/274 [47.1%] vs. 34/137 [24.8%]). A moderate positive correlation was noted between pruritus severity and DLQI scores at baseline ($r_s = 0.55$ [ESTEEM 1] and $r_s = 0.48$ [ESTEEM 2]), pooled treatment groups; both studies, $p < 0.0001$). At Week 16, a significant positive correlation existed between mean changes from baseline in pruritus VAS and DLQI total scores among patients receiving apremilast ($r_s = 0.55$ in both studies; $p < 0.001$) (Table I). The significant positive correlation between mean changes from baseline in pruritus VAS and DLQI scores was also observed with apre-

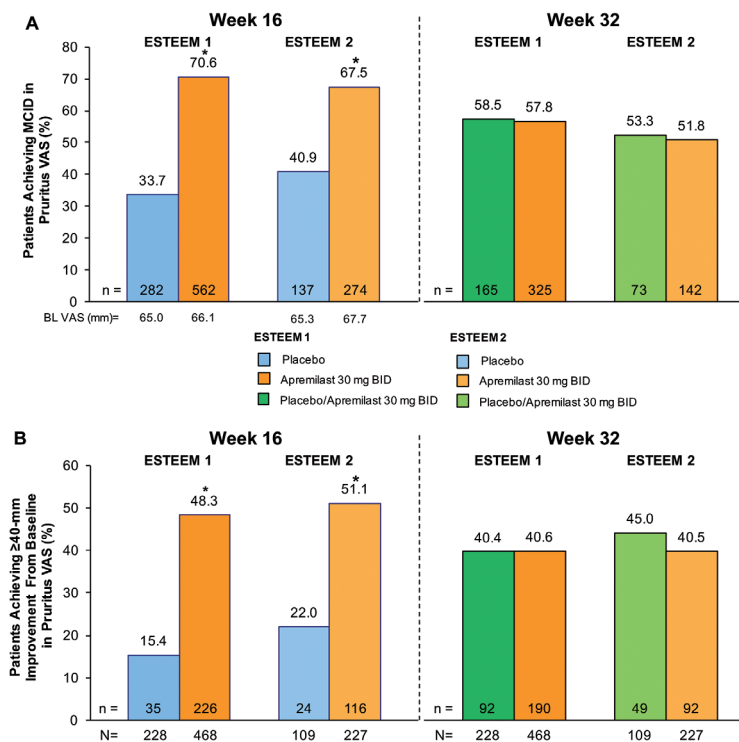


Fig. 2. (A) Proportion of patients achieving an MCID in pruritus VAS score at Week 16 and Week 32 in ESTEEM 1 and 2; and (B) proportion of patients achieving a ≥40-mm decrease in pruritus VAS score from baseline at Week 16 and Week 32 in ESTEEM 1 and 2. Patients in the full analysis set with a baseline pruritus VAS score ≥40 mm are included as observed. Patients in the full analysis set were included, using last observation carried forward (LOCF) for missing data; mean changes from baseline were based on patients in the full analysis set with a non-zero baseline value and at least one post-baseline value. * $p < 0.0001$ versus placebo; Fisher exact test. VAS: visual analog scale (100 mm).

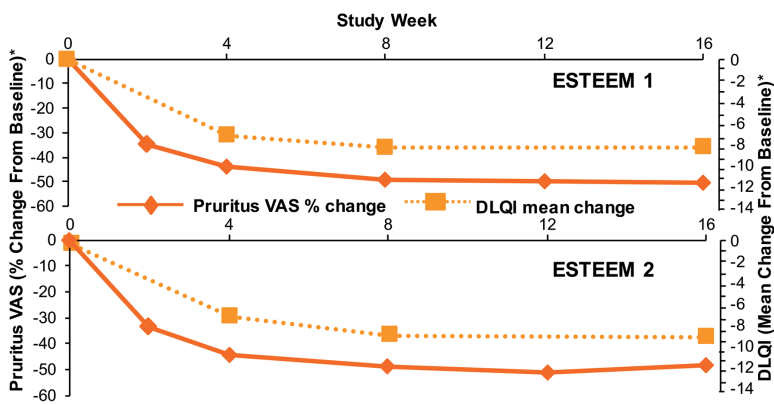


Fig. 3. Percent change from baseline in pruritus VAS and mean change from baseline in DLQI through Week 16. VAS: visual analog scale (100 mm); DLQI: Dermatology Life Quality Index; MCID: minimal clinically important difference. *Mean (SD) baseline pruritus VAS values: ESTEEM 1: 66.1 (25.55) mm (apremilast); ESTEEM 2: 67.7 (25.31) mm (apremilast). Mean (SD) baseline DLQI scores: ESTEEM 1: 12.7 (7.06) (apremilast); ESTEEM 2: 12.6 (7.18) (apremilast).

milast at Week 32 ($r_s \geq 0.51$; $p < 0.001$). In contrast, a weak correlation was observed between mean change from baseline in DLQI and PASI scores at Week 16 and Week 32 among patients receiving apremilast (Table I).

Improvements in patient global assessment of psoriasis disease activity

At Week 16, apremilast resulted in a significantly greater improvement from baseline in mean (SD) PgAPDA VAS score compared with placebo in ESTEEM 1 (-19.0 [30.12] mm vs. -1.1 [28.07] mm; $p < 0.0001$, ANOVA) and ESTEEM 2 (-20.8 [32.86] mm vs. -4.8 [30.26] mm; $p < 0.0001$, ANOVA). A moderate positive correlation existed between baseline VAS scores for PgAPDA and pruritus and skin discomfort/pain in both studies ($r_s \geq 0.43$, all patients; $p < 0.001$). At Week 16, significant positive correlations were observed between mean changes from baseline in VAS scores for PgAPDA and pruritus (ESTEEM 1: $r_s = 0.58$; ESTEEM 2: $r_s = 0.56$; both studies, $p < 0.001$; Table I) or skin discomfort/pain (ESTEEM 1: $r_s = 0.60$; ESTEEM 2: $r_s = 0.54$; both studies, $p < 0.001$; Table I). These significant positive correlations between mean changes from baseline in PgAPDA VAS and pruritus VAS or skin discomfort/pain VAS were maintained at Week 32 in both studies (Table I). Of note, the slope of

the mean improvement from baseline for PgAPDA and pruritus or skin discomfort/pain was similar at Week 16 and Week 32 (Fig. S2¹).

DISCUSSION

In the ESTEEM 1 and 2 studies, apremilast was effective in improving pruritus and skin discomfort/pain. The rapid and significant improvement in both pruritus and skin discomfort/pain achieved at Week 16 was sustained in patients who continued to receive apremilast through Week 32. In both studies, approximately 70% of the reduction in pruritus VAS scores achieved with apremilast was observed by the first post-baseline visit (i.e., Week 2); approximately 80% of the reduction in skin discomfort/pain VAS scores achieved with apremilast also occurred by Week 2. In this population of patients with moderate to severe pruritus at baseline, most patients achieved an MCID in pruritus VAS score at Week 16 with apremilast; MCID was sustained in approximately 50% of patients who continued to receive apremilast through Week 32. In addition, approximately half of patients receiving apremilast with a baseline score ≥ 40 mm experienced a ≥ 40 -mm decrease from baseline in the pruritus VAS score at Week 16. These improvements in pruritus and skin discomfort/pain were sustained up to Week 32 among patients receiving apremilast 30 mg BID from baseline; improvements were also observed in patients who were randomized to placebo at baseline and switched to apremilast 30 mg BID at Week 16. Consistent with improvements in mean changes from baseline in pruritus and skin discomfort/pain severity with apremilast versus placebo, a significant improvement in mean change from baseline in PgAPDA VAS was observed at Week 16 with apremilast versus placebo.

Limited data from clinical trials are available on the correlation between pruritus severity and patient HRQoL in patients with moderate to severe chronic plaque psoriasis. An *ad hoc* analysis of the PRISTINE trial, which evaluated different schedules of etanercept in 270 patients with chronic psoriasis, demonstrated

Table I. Summary of correlations for efficacy outcomes in ESTEEM 1 and ESTEEM 2

Outcome correlations*	ESTEEM 1 <i>n</i> = 499		ESTEEM 2 <i>n</i> = 238	
	Week 16	Week 32	Week 16	Week 32
	Pruritus VAS and DLQI change from baseline, r_s	0.55	0.53	0.55
PASI and DLQI change from baseline, r_s	0.34	0.32	0.42	0.29
Patient assessment of disease activity and pruritus VAS change from baseline, r_s	0.58	0.53	0.56	0.54
Patient assessment of disease activity and skin discomfort/pain VAS change from baseline, r_s	0.60	0.54	0.54	0.53

* $p < 0.001$ for all correlations.

DLQI: Dermatology Life Quality Index; VAS: visual analog scale.

a correlation between pruritus and patient HRQoL, both at baseline and after treatment of psoriasis (even after adjusting for improvement in PASI scores) (36). However, this analysis was limited because there was no placebo arm for comparison with active treatment. More recently, Zhu et al. (23) found a statistically significant association between improvement in pruritus and improvement in DLQI total score after adjusting for improvement in PASI, suggesting that pruritus is an important mediator between disease severity and patient HRQoL. The analysis from ESTEEM 1 and 2 reported here confirms these findings and represents one of the largest analyses of pruritus and patient HRQoL in a placebo-controlled clinical trial of patients with moderate to severe psoriasis. A positive correlation was observed between mean change from baseline in pruritus severity and HRQoL as assessed by the DLQI. *Post hoc* analyses demonstrated correlations between pruritus VAS and DLQI scores at baseline and change from baseline in these measures at Week 16 and Week 32. Such findings indicate that decreased pruritus severity is associated with improved patient HRQoL, as measured by the DLQI. Additional findings from *post hoc* analyses demonstrated a positive correlation between PgAPDA VAS score and both pruritus and skin discomfort/pain VAS scores at Week 16 and Week 32. Taken together, these findings indicate that rapid and sustained relief of symptoms associated with pruritus and skin discomfort/pain with apremilast can have a significant impact on patient HRQoL and patients' perception of psoriasis disease severity.

Although providing useful clinical information regarding apremilast in the treatment of moderate to severe chronic plaque psoriasis, this analysis from the ESTEEM trials had limitations. A steep reduction in pruritus severity at the first post-baseline assessment (Week 2) suggests that the effect of apremilast on pruritus may have occurred prior to the first assessment at Week 2. Thus, the effect of apremilast on pruritus earlier than Week 2 warrants study in future clinical studies. Additionally, assessments of pruritus and skin discomfort/pain were limited to VAS and do not provide detailed information concerning the location and nature of these signs and symptoms. Another limitation is the inherent weaknesses of the currently available tools used to assess pruritus outcomes in this analysis. The VAS is a widely used scale for assessment of pruritus; however, it has been noted in clinical studies evaluating the pruritus VAS that rating of a subjective sensation on a linear scale may be a complex process for patients, and some patients may tend to rate the middle of scale (24–27). The potential effect of external/internal factors on pruritus severity, as well as the subjective nature of the patient-reported outcome data collected, may possibly influence correlations between different outcomes reported in this study (24–27). However, similar results

were observed between the 2 independent studies, suggesting that the potential influence was minor.

In conclusion, apremilast significantly reduced pruritus and skin discomfort/pain severity, with most patients achieving a clinically meaningful response at Week 16. Improvements in pruritus severity occurred as early as Week 2 with apremilast and were maintained over 32 weeks. These findings indicate that apremilast provides a clinically meaningful decrease in severity of pruritus and skin discomfort/pain, not typically captured in psoriasis clinical assessments (e.g., PASI), which may lead to a significant improvement in the HRQoL of patients with chronic psoriasis.

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