



Apremilast, an oral phosphodiesterase 4 inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: results of two phase III randomized, controlled trials

Citation

Thaçi, D., A. Kimball, P. Foley, Y. Poulin, E. Levi, R. Chen, and S.R. Feldman. 2016. "Apremilast, an oral phosphodiesterase 4 inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: results of two phase III randomized, controlled trials." *Journal of the European Academy of Dermatology and Venereology* 31 (3): 498-506. doi:10.1111/jdv.13918. <http://dx.doi.org/10.1111/jdv.13918>.

Published Version

doi:10.1111/jdv.13918

Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:32630489>

Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

Share Your Story

The Harvard community has made this article openly available.
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

ORIGINAL ARTICLE

Apremilast, an oral phosphodiesterase 4 inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: results of two phase III randomized, controlled trials

D. Thaçi,^{1,*} A. Kimball,² P. Foley,³ Y. Poulin,⁴ E. Levi,⁵ R. Chen,⁵ S.R. Feldman⁶

¹Comprehensive Center for Inflammation Medicine, University Hospital Schleswig-Holstein, Lübeck, Germany

²Harvard Medical School, Boston, MA, USA

³Skin & Cancer Foundation Inc., St. Vincent's Hospital, The University of Melbourne, Melbourne, Vic., Australia

⁴Centre de Recherche Dermatologique du Québec métropolitain, Québec, QC, Canada

⁵Celgene Corporation, Summit, NJ, USA

⁶Wake Forest University School of Medicine, Winston-Salem, NC, USA

*Correspondence: D. Thaçi. E-mails: diamant.thaci@uksh.de; thaci@ccim.uni-luebeck.de

Abstract

Background Apremilast, an oral phosphodiesterase 4 inhibitor, has an acceptable safety profile and is effective for treatment of plaque psoriasis and psoriatic arthritis.

Objectives To evaluate the impact of apremilast on health-related quality of life (HRQOL), general functioning and mental health using patient-reported outcome (PRO) assessments among patients with moderate to severe plaque psoriasis in the ESTEEM 1 and 2 trials.

Methods A total of 1255 patients were randomized (2 : 1) to apremilast 30 mg BID or placebo for 16 weeks; all received apremilast through Week 32. PRO assessments included the Dermatology Life Quality Index (DLQI), 36-Item Short-Form Health Survey version 2 mental/physical component summary scores (SF-36v2 MCS/PCS), Patient Health Questionnaire-8 (PHQ-8), EuroQol-5D (EQ-5D) and Work Limitations Questionnaire-25 (WLQ-25). *Post hoc* analyses examined relationships between Psoriasis Area and Severity Index (PASI) scores and PHQ-8 in the apremilast-treated population at Week 16.

Results Treatment with apremilast improved all HRQOL PROs at Week 16 (vs. placebo), except the SF-36v2 PCS, and improvements were sustained through Week 32. Mean DLQI and SF-36v2 MCS improvements exceeded minimal clinically important differences. Changes at Week 16 in PHQ-8 and PASI were weakly correlated, and only 35.8% of patients who achieved a $\geq 75\%$ reduction from baseline in PASI score (PASI-75) with apremilast treatment also achieved PHQ-8 scores of 0–4.

Conclusions Apremilast led to improvements in HRQOL PROs vs. placebo in patients with moderate to severe plaque psoriasis.

Received: 21 April 2016; Accepted: 23 June 2016

Conflicts of interest

D. Thaçi has served as a consultant, advisory board member and/or received honoraria for lecturing for AbbVie, Amgen, Almirall Biogen Idec, Celgene Corporation, Dignity, Eli Lilly, Galapagos, GSK, Janssen-Cilag, LEO Pharma, Maruho, Mitsubishi, MSD, Novartis, Pfizer, Regeneron, Sanofi, UCB and XenoPort. A. Kimball reports grants and/or personal fees from Celgene Corporation, Amgen, AbbVie, Pfizer, Merck, Janssen, Lilly and Novartis. Dr. Kimball is vice president of the International Psoriasis Council. P. Foley reports grants and/or personal fees as an investigator, advisory board member and/or speakers bureau member for AbbVie, Amgen, Celgene Corporation, Eli Lilly, Janssen, MSD, Novartis and Pfizer. Y. Poulin reports grants and other support from Amgen, and grants from AbbVie, Aquinox, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corporation, Galderma, GSK-Stiefel, Janssen/Centocor, LEO Pharma, Lilly, Merck, Novartis, Pfizer and Takeda. E. Levi and R. Chen are employees of Celgene Corporation. S. R. Feldman reports grants and/or personal fees as an investigator, consultant, researcher and/or speaker for AbbVie, Celgene Corporation, Janssen and Novartis.

Funding source

These studies were funded by Celgene Corporation.

Introduction

Psoriasis is a chronic inflammatory disease manifested in the skin with a worldwide prevalence of 1–3%.^{1,2} Patients with psoriasis often report significant impairments in health-related quality of life (HRQOL), which may include physical discomfort, psychosocial problems, emotional distress and limitations in activities of daily living.^{3–5} Patient-reported outcome (PRO) assessments of HRQOL, depression, pruritus, or impact on work productivity are important additions to the clinical measures of psoriasis severity as they provide a more comprehensive view of the impact the disease and its treatment have on the patient.⁶ The widely used psoriasis outcome measure Psoriasis Area and Severity Index (PASI) does not take into account the full breadth and depth of psoriatic disease, a finding that was highlighted in a recent report from the International Dermatology Outcome Measures (IDEOM) group, whose mission statement is to ‘establish patient-centered measurements to enhance research and treatment for those with dermatologic disease.’⁷

Apremilast, an oral selective phosphodiesterase 4 inhibitor, elevates intracellular cyclic adenosine monophosphate (cAMP) levels, regulating mediators implicated in the pathogenesis of psoriasis and psoriatic arthritis.⁸ Apremilast was approved by the US Food and Drug Administration and the European Commission for treatment of psoriasis and psoriatic arthritis.^{9,10} Approval for the treatment of psoriasis stemmed from the results of the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) phase III clinical trial programme. Both ESTEEM 1 and ESTEEM 2 demonstrated that apremilast was safe and effective in the treatment of patients with moderate to severe plaque psoriasis for up to 52 weeks.^{11,12} In phase II clinical trials of apremilast in patients with moderate to severe plaque psoriasis¹³ and in patients with moderate to severe psoriatic arthritis,¹⁴ significant improvements in HRQOL were observed with apremilast treatment.

This report describes the effects of apremilast on PROs describing HRQOL, general functioning and mental health in patients with moderate to severe psoriasis who participated in ESTEEM 1 and ESTEEM 2.

Materials and methods

Study design

ESTEEM 1 (NCT01194219) and ESTEEM 2 (NCT01232283) were similarly designed phase III, multicentre, randomized, double-blind, placebo-controlled studies in patients aged ≥ 18 years with moderate to severe chronic plaque psoriasis (PASI score ≥ 12 , body surface area involvement $\geq 10\%$, static Physician Global Assessment [sPGA] score ≥ 3 [moderate to severe]) who were candidates for phototherapy and/or systemic therapy. Full details of the ESTEEM 1 and 2 study designs, inclusion and exclusion

criteria, patient populations and primary safety and efficacy results have been published.^{11,12}

Assessments

Patient-reported outcome assessments included the Dermatology Life Quality Index (DLQI),¹⁵ 36-Item Short-Form Health Survey version 2 (SF-36v2),¹⁶ European Quality of Life-5 Dimensions Questionnaire (EQ-5D),¹⁷ Patient Health Questionnaire-8 (PHQ-8)¹⁸ and Work Limitations Questionnaire-25 (WLQ-25).¹⁹ Each was administered at baseline and Weeks 4, 8 and 16 (placebo-controlled phase, Period A), and Weeks 24 and 32 (maintenance phase, Period B), except the EQ-5D and WLQ-25 index, which were administered at baseline and the end of each treatment phase (Weeks 16 and 32).

The DLQI, a 10-item questionnaire assessing the impact of skin disease on HRQOL, was completed before other assessments. Total score ranges from 0 to 30; higher scores indicate poorer quality of life and scores of 11–20 indicate a large impact of skin disease on HRQOL.¹⁵ The minimal clinically important difference (MCID) in the DLQI is a decrease (i.e. improvement) of 5.0 points from baseline.^{20,21}

The SF-36v2, a 36-item general health status questionnaire, comprises eight domains (physical function, role limitations–physical, vitality, general health perceptions, bodily pain, social function, role limitations–emotional, and mental health). Domain scores range from 0 to 100; higher scores indicate better health.¹⁶ Domain scores are combined into physical (PCS) and mental (MCS) component summary scores, with normative values of 50 and standard deviations of 10. The MCIDs for each component summary score and for each domain score are 2.5 and 5.0 points respectively.¹³

The EQ-5D provides a self-assessment of general health status on the day completed. It comprises a single item assessing general health status, scored using a visual analogue scale (0–100 mm) and five items assessing mobility, self-care, pain, usual activities and psychological status, each scored as 1 (no problem), 2 (moderate problem) or 3 (severe problem).¹⁷

The PHQ-8, an 8-item questionnaire, assesses signs and symptoms of depression for the previous 2-week period.¹⁸ Items include lack of interest or pleasure in activities, feelings of depression or hopelessness, sleep difficulty, tiredness, changes in appetite, feelings of inadequacy, difficulty concentrating and slow speech or restlessness. Each item is scored from 0 (not at all) to 3 (nearly every day); total score ranges from 0 to 24. Scores of 5–9, 10–14, 15–19 and 20–24 indicate mild, moderate, severe and very severe depressive symptoms respectively.¹⁸

The WLQ-25 instrument assesses the degree to which employed individuals experience on-the-job limitations due to health problems, as well as health-related productivity loss over the previous 2-week period.¹⁹ Work limitations are categorized into four domains: physical demands scale (PDS), mental/interpersonal demands scale (MDS), time management scale (TMS)

and output demands scale (ODS). Domains are used to calculate the WLQ-25 index. WLQ-25 scale scores were also converted to a productivity loss estimate.

End points

Patient-reported outcomes were pre-specified as secondary/exploratory end points in the ESTEEM protocols. Secondary end points included changes from baseline at Week 16 in DLQI total score and SF-36v2 MCS score; exploratory end points included changes from baseline in SF-36v2 PCS score, PHQ-8 score, EQ-5D score, WLQ-25 score and proportions of patients achieving DLQI response (decrease from baseline ≥ 5.0 points in DLQI total score) and composite DLQI/PASI-50 response ($\geq 50\%$ reduction from baseline in PASI score) at Weeks 16, 24 and 32. *Post hoc* analyses were performed for an in-depth examination of the relationship between clinical improvement in psoriasis severity (measured by $\geq 75\%$ reduction from baseline in PASI score [PASI-75]) and improvement in depressive symptoms measured by PHQ-8 at Week 16 in a pooled population of apremilast-treated patients in both ESTEEM studies. These analyses included: (i) achievement of DLQI 0 (no impact) or 1 (minimal impact); (ii) correlation between changes from baseline in PASI and

PHQ-8 scores; (iii) among patients with PHQ-8 score ≥ 10 (at least moderate depressive symptoms) at baseline, mean change from baseline in PHQ-8 score in patients who achieved PASI-75 at Week 16 vs. those who did not; and (iv) among patients with PHQ-8 score ≥ 10 (at least moderate depressive symptoms) at baseline, percentage of patients achieving both PASI-75 and PHQ-8 score of 0–4 (no significant depressive symptoms). The impact of apremilast therapy on work productivity was examined, comparing patient responses on the WLQ-25 at baseline and Week 16. WLQ-25 improvements are represented as a negative change from baseline.

Statistical analysis

Pre-specified and exploratory PRO end points were evaluated in the full analysis set (FAS; all patients randomized as specified in the protocols). Continuous variables were analysed using an analysis of covariance model with treatment as factor and baseline value as covariate. Discrete variables were examined using a Cochran–Mantel–Haenszel χ^2 test. For pre-specified and exploratory end points, last observation carried forward (LOCF) methodology was used to account for missing data from Weeks 0 to 16 (Period A); thereafter, data as observed were evaluated

Table 1 Baseline demographic and disease characteristics of ESTEEM 1 and ESTEEM 2 populations

	ESTEEM 1		ESTEEM 2	
	Placebo <i>n</i> = 282	Apremilast 30 mg BID <i>n</i> = 562	Placebo <i>n</i> = 137	Apremilast 30 mg BID <i>n</i> = 274
Age, mean (SD), years	46.5 (12.7)	45.8 (13.1)	45.7 (13.4)	45.3 (13.1)
Male, <i>n</i> (%)	194 (68.8)	379 (67.4)	100 (73.0)	176 (64.2)
White, <i>n</i> (%)	250 (88.7)	507 (90.2)	128 (93.4)	250 (91.2)
Body mass index, mean (SD), kg/m ²	31.3 (7.4)	31.2 (6.7)	30.7 (7.1)	30.9 (6.7)
Weight, mean (SD), kg	93.7 (23.2)	93.2 (21.4)	90.5 (22.5)	91.4 (23.0)
Duration of plaque psoriasis, mean (SD), years	18.7 (12.4)	19.8 (13.0)	18.7 (12.1)	17.9 (11.4)
PASI score, mean (SD)	19.4 (7.4)	18.7 (7.2)	20.0 (8.0)	18.9 (7.1)
PASI score >20, <i>n</i> (%)	87 (30.9)	158 (28.1)	49 (35.8)	81 (29.6)
BSA, mean (SD), %	25.3 (14.6)	24.4 (14.7)	27.6 (15.8)	25.5 (15.4)
BSA >20%, <i>n</i> (%)	149 (52.8)	266 (47.3)	80 (58.4)	143 (52.2)
sPGA = 4 (severe), <i>n</i> (%)	89 (31.6)	161 (28.6)	49 (35.8)	75 (27.4)
DLQI (0–30), mean (SD)	12.1 (6.7)	12.7 (7.1)	12.8 (7.1)	12.5 (7.1)
SF-36v2 MCS (0–100), mean (SD)	47.0 (11.6)	45.8 (12.5)	45.3 (12.4)	45.4 (12.8)
SF-36v2 PCS (0–100), mean (SD)	48.8 (8.9)	48.8 (9.7)	48.5 (9.5)	48.5 (9.1)
EQ-5D index (0–1), mean (SD)	0.81 (0.16)	0.80 (0.17)	0.78 (0.19)	0.79 (0.18)
PHQ-8 (0–24), mean (SD)	5.2 (5.4)	5.4 (5.5)	5.4 (5.5)	5.3 (5.2)
WLQ-25 index, mean (SD)	0.037 (0.043)	0.040 (0.048)	0.038 (0.046)	0.045 (0.046)
Prior systemic therapy (conventional and/or biologic), <i>n</i> (%)	150 (53.2)	301 (53.6)	73 (53.3)	157 (57.3)
Prior conventional systemic therapy, <i>n</i> (%)	102 (36.2)	212 (37.7)	53 (38.7)	106 (38.7)
Prior biologic therapy, <i>n</i> (%)	80 (28.4)	162 (28.8)	44 (32.1)	92 (33.6)

The *n* reflects the number of randomized patients; actual number of patients available for each parameter may vary.

BSA, body surface area; DLQI, Dermatology Life Quality Index; EQ-5D, European Quality of Life-5 Dimensions Questionnaire; MCS, Mental Component Summary score; PASI, Psoriasis Area and Severity Index; PCS, Physical Component Summary score; PHQ-8, Patient Health Questionnaire-8; SF-36v2, 36-Item Short-Form Health Survey version 2; sPGA, static Physician Global Assessment; SD, standard deviation.

for Week 32 using descriptive statistics (Period B). *Post hoc* analyses were performed based on pooled ESTEEM 1 and 2 populations, except DLQI score of 0 or 1 at Week 16, which was performed in the separate ESTEEM 1 and 2 cohorts using LOCF; Spearman analyses were based on LOCF data in patients randomized to apremilast. For response rate analyses, missing values were accounted for using non-responder imputation (except where noted); between-group differences were compared using Fisher's exact tests. Statistical comparisons were conducted using two-sided tests at the 0.05 significance level.

Results

Patients

The FAS included 844 patients from ESTEEM 1 and 411 from ESTEEM 2. Baseline demographic and clinical characteristics were balanced between groups (Table 1). The mean baseline PASI score ranged from 18.7 to 20.0 and patients had psoriasis for a mean of 17.9–19.8 years; 36.2–38.7% had been treated previously for psoriasis with conventional systemic therapy, and 28.4–33.6% had received biologic therapy. More than half of all patients (53.2–57.3%) had received prior systemic therapy (conventional treatment and/or biologic).

Mean baseline DLQI scores (range: 12.1–12.8), SF-36v2 MCS scores (range: 45.3–47.0), SF-36v2 PCS scores (range: 48.5–48.8) and EQ-5D scores (range: 0.78–0.81) indicated a large negative impact of skin disease on patient-perceived physical and mental

health at baseline. Mean baseline PHQ-8 scores ranged from 5.2 to 5.4, consistent with mild depressive symptoms, in the ESTEEM 1 and 2 populations; overall, 246 (19.6%) patients had a baseline PHQ-8 score ≥ 10 , indicating depressive symptoms that were at least moderate. In line with these findings, 178 (14.2%) patients reported a history of depression, and 156 (12.4%) were taking antidepressant medication at baseline.

PRO assessments: Period A (Weeks 0–16)

DLQI At Week 16, the mean decrease from baseline in DLQI score was greater with apremilast vs. placebo in each study ($P < 0.0001$; Table 2). Greater proportions of patients receiving apremilast vs. placebo achieved the MCID for DLQI (i.e. DLQI response) and composite DLQI/PASI-50 response in both studies at Week 16 (all $P < 0.0001$; Fig. 1 and Table 2). The differences in response between the apremilast and placebo groups in DLQI improvement and DLQI response were seen by Week 4 (the first post-baseline QOL assessment) but emerged more gradually based on composite DLQI/PASI-50 response (Fig. 1). *Post hoc* analysis showed that a higher percentage of patients treated with apremilast achieved a DLQI score of 0 or 1 at Week 16 (ESTEEM 1: 25.8%; ESTEEM 2: 28.1%) vs. placebo-treated patients (ESTEEM 1: 6.7%; ESTEEM 2: 8.0%; both $P < 0.001$).

SF-36v2 MCS and PCS At Week 16, the mean change from baseline in SF-36v2 MCS score was greater with apremilast vs.

Table 2 PRO assessments at Week 16 (LOCF)

	ESTEEM 1		ESTEEM 2	
	Placebo <i>n</i> = 282	Apremilast 30 mg BID <i>n</i> = 562	Placebo <i>n</i> = 137	Apremilast 30 mg BID <i>n</i> = 274
Secondary end points				
DLQI total score, mean change (SD)	-2.1 (5.69)	-6.6 (6.66)*	-2.8 (7.22)	-6.7 (6.95)*
SF-36v2 MCS, mean change (SD)	-1.0 (9.16)	2.4 (9.50)*	0.0 (10.50)	2.6 (10.13)†
Exploratory end points				
DLQI response, <i>n</i> (%)¶,**	79 (33.5)	322 (70.2)*	51 (42.9)	160 (70.8)*
Composite DLQI/PASI-50 response, <i>n</i> (%)¶	26 (11.0)	221 (48.1)*	16 (13.4)	111 (49.1)*
DLQI 0 or 1 response, <i>n</i> (%)	19 (6.7)	145 (25.8)†	11 (8.0)	77 (28.1)†
SF-36v2 PCS, mean change (SD)	0.17 (6.22)	1.15 (7.20)	0.28 (7.29)	1.60 (7.24)
EQ-5D, mean change (SD)	-0.014 (0.171)	0.038 (0.166)*	-0.0005 (0.184)	0.051 (0.178)†
PHQ-8, mean change (SD)	0.3 (4.2)	-0.6 (4.3)†	0.2 (4.5)	-0.8 (4.5)‡
WLQ-25, mean change (SD)	0.006 (0.036)	-0.004 (0.039)§	-0.005 (0.036)	-0.006 (0.039)

P-values based on analysis of covariance model for changes from baseline with treatment as factor and baseline value as a covariate and on a two-sided chi-square test for DLQI responses and LOCF used for imputation of missing values.

* $P < 0.0001$; † $P \leq 0.0095$; ‡ $P = 0.0126$; § $P = 0.0148$.

¶DLQI response = decrease of ≥ 5.0 points in DLQI total score in patients with baseline DLQI total score > 5 (a reduction in score indicates improvement); composite DLQI/PASI-50 = decrease of ≥ 5.0 points in DLQI total score and PASI-50 achievement in patients with baseline DLQI total score > 5 .

**ESTEEM 1: placebo *n* = 236, apremilast *n* = 459; ESTEEM 2: placebo *n* = 119, apremilast *n* = 226.

DLQI, Dermatology Life Quality Index; EQ-5D, European Quality of Life-5 Dimensions Questionnaire; LOCF, last observation carried forward; MCS, Mental Component Summary score; PASI, Psoriasis Area and Severity Index; PCS, Physical Component Summary score; PHQ-8, Patient Health Questionnaire-8; SF-36v2, 36-Item Short-Form Health Survey version 2; SD, standard deviation; WLQ-25, 25-item Work Limitations Questionnaire.

placebo in ESTEEM 1 and 2 ($P < 0.0001$ and $P = 0.008$ respectively; Table 2). The improvement in SF-36v2 MCS scores with apremilast approached or exceeded the MCID of 2.5. The mean scores of 48.2 and 48.0 after 16 weeks of treatment with apremilast approached the US normative value of 50.0. Mean change in SF-36v2 PCS score, although numerically greater with apremilast than with placebo, did not reach statistical significance or the MCID threshold at Week 16 (Table 2).

PHQ-8 Patients treated with placebo reported a slight increase (worsening) of 0.3 and 0.2 points, whereas apremilast-treated patients saw an improvement of -0.6 ($P = 0.009$) and -0.8 ($P = 0.013$) points in the mean PHQ-8 score at Week 16 in ESTEEM 1 and 2 respectively (Table 2). Mean PHQ-8 scores at Week 16 in patients receiving apremilast in ESTEEM 1 (4.8) and ESTEEM 2 (4.5) were below the threshold of 5 for mild depression.

EQ-5D At Week 16, mean change from baseline in EQ-5D score was greater with apremilast vs. placebo in ESTEEM 1 ($P < 0.0001$) and ESTEEM 2 ($P = 0.010$; Table 2). Mean values for EQ-5D score in patients treated with placebo were essentially unchanged from baseline.

WLQ-25 At Week 16, mean change from baseline in WLQ-25 score was greater with apremilast vs. placebo in ESTEEM 1 ($P = 0.0148$) but not ESTEEM 2 (Table 2). Mean WLQ-25 values with placebo increased from baseline in ESTEEM 1 and decreased from baseline in ESTEEM 2.

Post hoc analyses: period A (Weeks 0–16), pooled ESTEEM population

WLQ-25 At Week 16, treatment with apremilast was associated with a greater mean improvement in the WLQ-25 index vs. placebo ($P = 0.031$), corresponding to a higher mean per cent improvement in productivity loss ($P = 0.035$; Fig. 2). In the subset of patients receiving apremilast who achieved PASI-75,

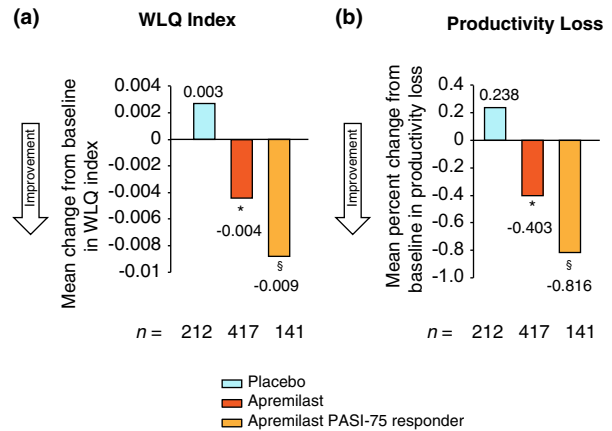


Figure 2 WLQ-25 index (a) and productivity loss (b) (pooled ESTEEM 1 and 2 population) at Week 16. (a) $*P = 0.031$ vs. placebo. $^{\$}P = 0.005$ vs. placebo. (b) $*P = 0.035$ vs. placebo. $^{\$}P = 0.006$ vs. placebo. WLQ-25, 25-item Work Limitations Questionnaire.

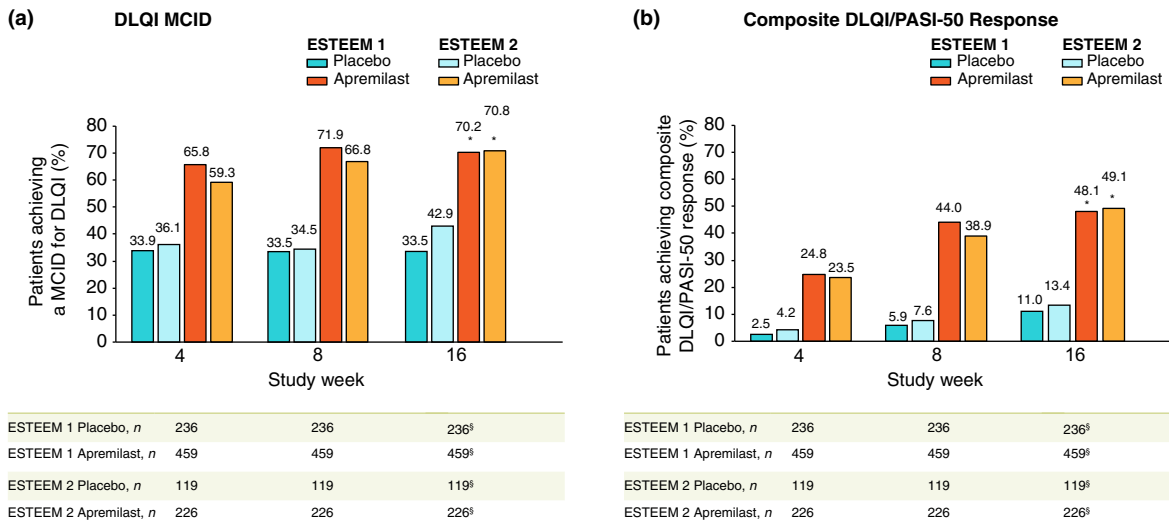


Figure 1 Proportion of patients who achieved MCID for DLQI (a) and composite DLQI/PASI-50 response (b) at Week 16. $*P < 0.0001$. $^{\$}$ Data based on LOCF at Week 16. n represents the number of patients with evaluable data at the time point indicated; data are as observed for Weeks 4 and 8. DLQI, Dermatology Life Quality Index; LOCF, last observation carried forward; MCID, minimal clinically important difference; PASI-50 = $\geq 50\%$ reduction from baseline in Psoriasis Area and Severity Index.

improvements were greater for both the WLQ-25 index and productivity loss vs. placebo (Fig. 2). Of the four scales of the WLQ-25 index, the PDS was not significantly improved with apremilast vs. placebo (-1.06 vs. -1.63). In contrast, patients treated with apremilast reported improvements vs. those treated with placebo in MDS (-1.78 vs. +0.86), TMS (-2.07 vs. +2.77, $P = 0.002$) and ODS (-1.51 vs. +1.05, $P = 0.046$). In the subset of patients who achieved PASI-75, apremilast was associated with additional improvements in MDS, TMS and ODS.

Relationships between changes in PHQ-8 and PASI at Week 16

At Week 16, in the pooled ESTEEM 1 and 2 population of patients receiving apremilast, changes from baseline in PHQ-8 and PASI scores were weakly correlated (Spearman $r = 0.174$) (Fig. 3).

Post hoc analyses were conducted in the pooled subset of patients treated with apremilast in both ESTEEM studies with at least moderate depressive symptoms at baseline (PHQ-8 ≥ 10).¹⁸ In patients who achieved PASI-75, improvement in PHQ-8 scores at Week 16 was higher (mean change PHQ-8: -6.7) than that observed in patients who did not achieve PASI-75 (mean change PHQ-8: -3.3; $P = 0.0018$) (Fig. 4). At Week 16, only 35.8% of patients who achieved PASI-75 also achieved PHQ-8 scores of 0-4.

PRO assessments: period B (Weeks 16-32)

Improvements in PRO measures during Weeks 0-16 were sustained with continued apremilast therapy during Period B (Table 3; Figs 5 and 6). Patients initially randomized to placebo and switched to apremilast during Weeks 16-32 exhibited improvements in all PRO measures, similar to those observed in patients treated with apremilast at randomization (Table 3; Figs 5 and 6).

Discussion

The ESTEEM 1 and 2 populations discussed in this report exhibited the adverse impact of psoriasis on quality of life, general

functioning and mental health consistently reported in patients with this chronic inflammatory disease. At baseline, the SF-36v2 MCS and PCS values were below the US norm of 50.0,²² and EQ-5D values were below both the US age- and gender-based norm of 0.87 and were even below the norm of 0.83 for US patients with psoriasis and related disorders.²³⁻²⁹ In line with reports of psoriasis, regardless of severity, being independently associated with major depression even when controlling for comorbidities,³⁰⁻³² 19.6% of patients in the current analysis had baseline PHQ-8 scores ≥ 10 , indicating at least moderate depressive symptoms. The burden of depression in the ESTEEM

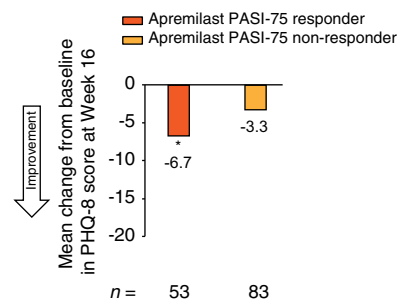


Figure 4 Change from baseline in PHQ-8 score in patients with at least moderate depressive symptoms (PHQ-8 ≥ 10) at baseline: apremilast-treated patients, Week 16, pooled ESTEEM 1 and 2 apremilast population, $n = 136$. * $P = 0.0018$. PHQ-8, Patient Health Questionnaire-8.

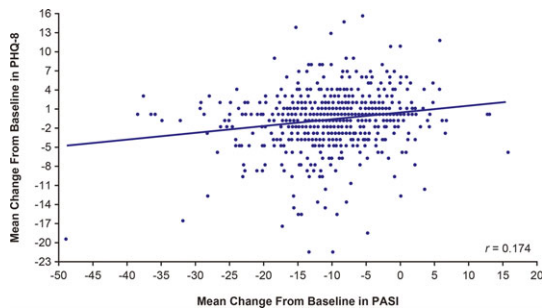
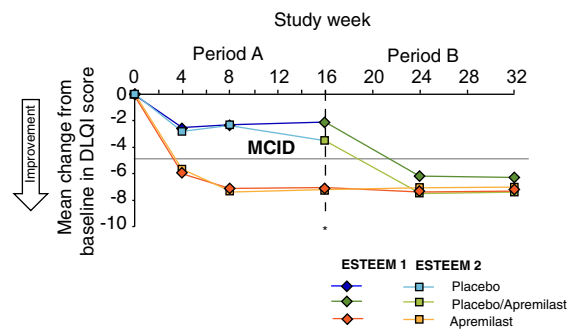


Figure 3 Correlation between changes from baseline in PASI and PHQ-8 scores: apremilast-treated patients, Week 16, pooled ESTEEM 1 and 2 population, $n = 735$. PASI, Psoriasis Area and Severity Index; PHQ-8, Patient Health Questionnaire-8.



ESTEEM 1				
Placebo, n	282	270	264	247
Placebo/Apremilast, n				237
Apremilast, n	561	536	523	500
ESTEEM 2				
Placebo, n	136	127	121	110
Placebo/Apremilast, n				103
Apremilast, n	274	257	246	239

Figure 5 Mean change in DLQI total score over 32 weeks. * $P < 0.0001$. n represents the number of patients with evaluable data at the time point indicated; data are as observed. DLQI, Dermatology Life Quality Index.

population is in keeping with the prevalence of depression reported in patients with psoriasis.³⁰

Treatment with apremilast was repeatedly associated with improvement in patient-reported measures assessed at Week 16 as compared with placebo. The mean changes from baseline in DLQI and SF-36v2 MCS exceeded the MCIDs, suggesting that these improvements were meaningful to patients. Moreover, approximately half of patients treated with apremilast achieved a composite DLQI/PASI-50 response by Week 16, which has been proposed as a psoriasis treatment goal.^{33,34} Treatment with apremilast also improved work productivity as measured by WLQ-25, particularly in patients who also achieved PASI-75. Improvements in HRQOL emerged by Week 4 (the first post-baseline QOL assessment) with apremilast, showed further improvement through 16 weeks and were generally sustained with continued apremilast therapy for up to 32 weeks. Patients who initially received placebo had similar improvements in HRQOL after switching to apremilast.

Apremilast carries a warning for depression due to an imbalance in AEs (as spontaneously reported by patients) noted at Week 16: 1.3% (12/920) of patients treated with apremilast reported depression vs. 0.4% (2/506) of those taking placebo.⁹ In the study population, apremilast treatment was associated with improvements in depressive symptoms as measured by the PHQ-8, and overall mental health as measured by SF-36v2 MCS score; however, analysis of these end points with longer term treatment beyond 32 weeks is needed to more fully assess durability of improvements.

In the *post hoc* analyses reported here, among patients with at least moderate depressive symptoms at baseline (PHQ-8 ≥10), patients who achieved clinically significant skin

clearance (PASI-75) had greater improvement in PHQ-8 scores than those not achieving PASI-75, and more than one-third of patients who achieved PASI-75 also achieved PHQ-8 scores of 0–4, indicating that skin clearance is associated with improvement in mental status of patients. Moreover, reducing psoriasis disease severity improves psoriasis patients' HRQOL and mental health.^{35–37}

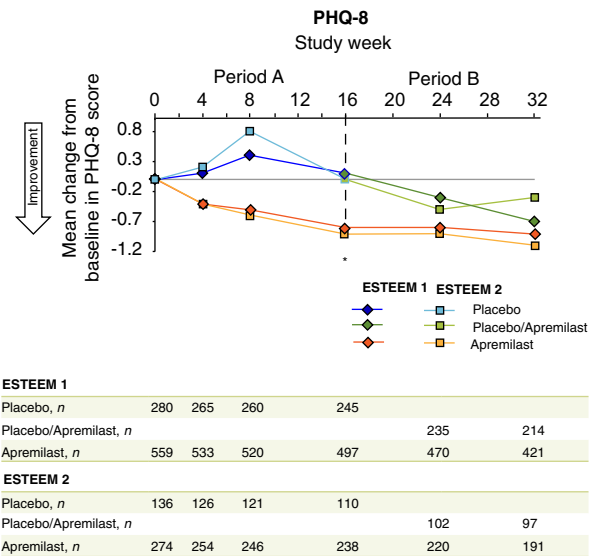


Figure 6 Mean change in PHQ-8 score over 32 weeks. **P* < 0.05. *n* represents the number of patients with evaluable data at the time point indicated; data are as observed. PHQ-8, Patient Health Questionnaire-8.

Table 3 PRO assessments at Week 32 (data as observed)

	ESTEEM 1		ESTEEM 2	
	Placebo/Apremilast 30 mg BID n = 245	Apremilast 30 mg BID n = 562	Placebo/Apremilast 30 mg BID n = 92	Apremilast 30 mg BID n = 226
Secondary end points				
DLQI total score, mean change (SD)	-6.3 (5.70)	-7.3 (6.62)	-7.4 (7.17)	-7.0 (6.43)
SF-36v2 MCS, mean change (SD)	2.1 (9.56)	3.0 (9.93)	2.7 (8.65)	3.5 (11.00)
Exploratory end points				
DLQI response, n (%)*, †	120 (58.3)	264 (57.5)	60 (65.2)	115 (50.9)
Composite DLQI/PASI-50 response, n (%)*	94 (45.6)	197 (42.9)	50 (54.3)	83 (36.7)
SF-36v2 PCS, mean change (SD)	0.76 (7.16)	1.21 (6.86)	2.8 (7.74)	1.8 (7.41)
EQ-5D, mean change (SD)	0.021 (0.155)	0.040 (0.161)	0.063 (0.171)	0.059 (0.181)
PHQ-8, mean change (SD)	-0.7 (4.28)	-0.9 (4.04)	-0.3 (3.82)	-1.1 (4.75)
WLQ-25, mean change (SD)	-0.000 (0.035)	-0.006 (0.042)	-0.006 (0.034)	-0.006 (0.035)

*DLQI response = decrease of ≥5.0 points in DLQI total score in patients with baseline DLQI total score > 5 (a reduction in score indicates improvement); composite DLQI/PASI-50 = decrease of ≥5.0 points in DLQI total score and PASI-50 achievement in patients with baseline DLQI total score.

†ESTEEM 1: placebo/apremilast *n* = 206, apremilast/apremilast *n* = 459; ESTEEM 2: placebo/apremilast *n* = 92, apremilast/apremilast *n* = 226.

DLQI, Dermatology Life Quality Index; EQ-5D, European Quality of Life-5 Dimensions Questionnaire; MCS, Mental Component Summary score; PASI, Psoriasis Area and Severity Index; PCS, Physical Component Summary score; PHQ-8, Patient Health Questionnaire-8; SF-36v2, 36-Item Short-Form Health Survey version 2; SD, standard deviation; WLQ-25, 25-item Work Limitations Questionnaire.

Examinations of the relationship between depressive symptoms and improvements in skin disease severity reported here revealed a weak correlation between overall change in PASI and PHQ-8 scores at Week 16, indicating that perhaps factors beyond clinical signs of psoriasis as assessed by PASI, such as pruritus and skin pain, play a role in depression associated with psoriasis. Subjective features of psoriatic lesions not captured by PASI scores – such as pain, pruritus and effects on psychosocial function – may also impact depressive symptoms.³⁸ A recent analysis of the ESTEEM 1 and 2 studies found that 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.³⁹ For example, a significant ($P < 0.001$) positive correlation existed between mean changes from baseline in pruritus VAS and DLQI total scores among patients receiving apremilast at Week 16, which was maintained at Week 32.³⁹

Apremilast represents a novel effective therapeutic option for patients with moderate to severe plaque psoriasis, with an acceptable safety and tolerability profile that has produced clinically meaningful improvements in HRQOL, general functioning and mental health of these patients. Consideration of factors beyond reduction in clinical disease severity, such as improvements in PROs, in this analysis may provide clinicians a more comprehensive view of the impact of the disease and its treatment on patients, potentially helping to guide treatment decisions.

Acknowledgments

The authors thank Irina Khanskaya, John Marcsisin, Claire Barcellona (clinical), Zuoshun Zhang (statistics), Monica Bilbault, Dale McElveen (clinical operations), Marlene Kachnowski (data management), Ann Marie Tomasetti, Trisha Zhang (programming) and Kamal Shah (safety) of Celgene Corporation for their contributions to the study and/or the manuscript. The authors received editorial support in the preparation of the manuscript from Karen Dougherty, PhD, and Kristin E. Larsen, PhD, of Peloton Advantage, LLC, funded by Celgene Corporation.

References

- Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013; **133**: 377–385.
- Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol* 2014; **70**: 512–516.
- de Korte J, Sprangers MA, Mommers FM, Bos JD. Quality of life in patients with psoriasis: a systematic literature review. *J Invest Dermatol Symp Proc* 2004; **9**: 140–147.
- Kimball AB, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. *Am J Clin Dermatol* 2005; **6**: 383–392.
- Meyer N, Paul C, Feneron D *et al.* Psoriasis: an epidemiological evaluation of disease burden in 590 patients. *J Eur Acad Dermatol Venereol* 2010; **24**: 1075–1082.
- Shikier R, Bresnahan BW, Stone SP, Thompson C, Koo J, Revicki DA. Validity and reliability of patient reported outcomes used in psoriasis: results from two randomized clinical trials. *Health Qual Life Outcomes* 2003; **1**: 53.
- Gottlieb AB, Levin AA, Armstrong AW *et al.* The International Dermatology Outcome Measures Group: formation of patient-centered outcome measures in dermatology. *J Am Acad Dermatol* 2015; **72**: 345–348.
- Schafer PH, Parton A, Capone L *et al.* Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. *Cell Signal* 2014; **26**: 2016–2029.
- Otezla [package insert]. Celgene Corporation, Summit, NJ; December 2015.
- Otezla [summary of product characteristics]. Celgene Europe Ltd, Uxbridge, UK; January 2015.
- Papp K, Reich K, Leonardi CL *et al.* 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]). *J Am Acad Dermatol* 2015; **73**: 37–49.
- Paul C, Cather J, Gooderham M *et al.* 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). *Br J Dermatol* 2015; **173**: 1387–1399.
- Strand V, Fiorentino D, Hu C, Day RM, Stevens RM, Papp KA. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study. *Health Qual Life Outcomes* 2013; **11**: 82.
- Strand V, Schett G, Hu CC, Stevens RM. Patient-reported health-related quality of life with apremilast for psoriatic arthritis: a phase II, randomized, controlled study. *J Rheumatol* 2013; **40**: 1158–1165.
- Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–216.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473–483.
- Rabin R, de Charro F. EQ-5D: a measure of health status from the Euro-Qol Group. *Ann Med* 2001; **33**: 337–343.
- Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord* 2009; **114**: 163–173.
- Lerner D, Amick BC III, Rogers WH, Malspeis S, Bungay K, Cynn D. The Work Limitations Questionnaire. *Med Care* 2001; **39**: 72–85.
- Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in dermatology life quality index scores [abstract P-59]. *Br J Dermatol* 2002; **147** (Suppl 62): 50.
- Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 2015; **230**: 27–33.
- Ware JE Jr. SF-36 Health Survey Update [WWW document]. URL <http://www.sf-36.org/tools/sf36.shtml>. (last accessed: 10 February 2016).
- Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006; **26**: 410–420.
- Fryback DG, Dunham NC, Palta M *et al.* US norms for six generic health-related quality-of-life indexes from the National Health Measurement study. *Med Care* 2007; **45**: 1162–1170.
- Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol* 2010; **146**: 891–895.
- Dommasch ED, Li T, Okereke OI, Li Y, Qureshi AA, Cho E. Risk of depression in women with psoriasis: a cohort study. *Br J Dermatol* 2015; **173**: 975–980.

- 27 Kulkarni AS, Balkrishnan R, Camacho FT, Anderson RT, Feldman SR. Medication and health care service utilization related to depressive symptoms in older adults with psoriasis. *J Drugs Dermatol* 2004; **3**: 661–666.
- 28 Langley RG, Feldman SR, Han C et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad Dermatol* 2010; **63**: 457–465.
- 29 McDonough E, Ayearst R, Eder L et al. Depression and anxiety in psoriatic disease: prevalence and associated factors. *J Rheumatol* 2014; **41**: 887–896.
- 30 Cohen BE, Martires KJ, Ho RS. Psoriasis and the risk of depression in the US population: National Health and Nutrition Examination Survey 2009–2012. *JAMA Dermatol* 2016; **152**: 73–79.
- 31 Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. *J Invest Dermatol* 2014; **134**: 1542–1551.
- 32 Dalgard FJ, Gieler U, Tomas-Aragones L et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol* 2015; **135**: 984–991.
- 33 Pathirana D, Ormerod AD, Saiag P et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; **23**(Suppl 2): 1–70.
- 34 Mrowietz U, Kragballe K, Reich K et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**: 1–10.
- 35 Krueger GG, Langley RG, Finlay AY et al. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. *Br J Dermatol* 2005; **153**: 1192–1199.
- 36 Lebwohl M, Papp K, Han C et al. Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. *Br J Dermatol* 2010; **162**: 137–146.
- 37 Kalb RE, Blauvelt A, Sofen HL et al. Effect of infliximab on health-related quality of life and disease activity by body region in patients with moderate-to-severe psoriasis and inadequate response to etanercept: results from the PSUNRISE trial. *J Drugs Dermatol* 2013; **12**: 874–880.
- 38 Mrowietz U, Chouela EN, Mallbris L et al. Pruritus and quality of life in moderate-to-severe plaque psoriasis: post hoc explorative analysis from the PRISTINE study. *J Eur Acad Dermatol Venereol* 2015; **29**: 1114–1120.
- 39 Sobell JM, Foley P, Toth D et al. Effects of apremilast on pruritus and skin discomfort/pain correlate with improvements in quality of life in patients with moderate to severe plaque psoriasis. *Acta Derm Venereol* 2016; **96**: 514–520.