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## ORIGINAL ARTICLE

# Efficacy and safety of apremilast in patients with limited skin involvement, plaque psoriasis in special areas and impaired quality of life: Results from the EMBRACE randomized trial

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## Abstract

**Introduction/Background:** Manifestations of psoriasis in special areas are difficult to treat and are associated with a high disease burden and significant quality of life (QoL) impairment. Topical therapies may be inadequate for these patients, necessitating systemic treatment.

**Objective:** The objective of EMBRACE was to evaluate the impact on QoL, efficacy and safety of apremilast 30 mg BID in patients with limited skin involvement with plaque psoriasis manifestations in special areas and impaired QoL.

**Methods:** EMBRACE (NCT03774875) was a phase 4, randomized, placebo-controlled, multinational study. Patients had plaque psoriasis not controlled by topical therapy; lack of response, contraindication or intolerance to conventional first-line systemic therapy; psoriasis in  $\geq 1$  special area (including visible locations, scalp, nails, genital areas or palmoplantar areas); Psoriasis Area and Severity Index (PASI)  $\geq 3$  to  $\leq 10$ ; and Dermatology Life Quality Index (DLQI)  $> 10$ . The primary endpoint was DLQI response ( $\geq 4$ -point reduction) at Week 16.

**Results:** Of 277 randomized patients (apremilast:  $n = 185$ ; placebo:  $n = 92$ ), 221 completed Week 16 (apremilast:  $n = 152$ ; placebo:  $n = 69$ ). The primary endpoint ( $\geq 4$ -point reduction in DLQI at Week 16) was met by significantly more patients receiving apremilast (73.3%) versus placebo (41.3%;  $p < 0.0001$ ). Significantly greater improvement in affected body surface area (BSA) and PASI was observed with apremilast versus placebo at Week 16. There were also significantly greater improvements with apremilast versus placebo in itch numeric rating scale ( $-2.5$  vs.  $-0.9$ ,  $p < 0.0001$ ) and skin discomfort/pain visual analog scale ( $-21.5$  vs.  $-5.4$ ,  $p = 0.0003$ ) and greater achievement of Patient Benefit Index  $\geq 1$  (77% vs. 40%,  $p < 0.0001$ ) at Week 16. No new safety signals were observed.

**Conclusions:** Apremilast significantly improved skin-related QoL in patients with limited skin involvement with plaque psoriasis in special areas and highly impaired QoL. The safety profile was consistent with prior apremilast studies.

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## INTRODUCTION

Manifestations of plaque psoriasis can occur in special areas, including the scalp, nails, palms, soles, genitals or visible locations such as the face, neck, hairline or dorsal hand. These manifestations are common; psoriasis of the scalp and face each occur in >50% of patients, and genital psoriasis is reported in up to 63% of patients.<sup>1–3</sup> Special areas are difficult to treat and are associated with a high disease burden.<sup>1</sup> Significant disease-related quality-of-life (QoL) impairment as a result of psoriasis in special areas can be disproportionate to the extent of body surface area involved.<sup>4,5</sup> For example, scalp psoriasis and psoriasis in visible locations may lower patients' self-esteem and affect their social activities, and pain from nail and palmoplantar psoriasis (psoriasis on the palms and soles) can limit the ability to do daily tasks.<sup>1</sup>

Although topical therapies are the first line of treatment for psoriasis, they often provide inadequate response (i.e. insufficient efficacy and/or tolerability issues) in patients with psoriasis in special areas, and application of topical preparations can be messy and burdensome.<sup>1,6,7</sup> According to a European consensus, the presence of specific disease manifestations in visible areas, the scalp, genitals, palms and/or soles, or nails that are not adequately controlled by topical therapy alone in patients with otherwise mild disease may shift the psoriasis classification towards greater disease severity.<sup>8</sup> According to the International Psoriasis Council, patients may require systemic treatment if psoriasis is present in special areas.<sup>9</sup> The recognition of impactful psoriasis manifestations is considered best practice according to the people-centred healthcare concept of the World Health Organization.<sup>10</sup>

Apremilast is an oral phosphodiesterase 4 inhibitor that has been shown to be effective in treating psoriasis, including symptoms of scalp and nail psoriasis.<sup>11,12</sup> Here, we report the improvement in QoL and other efficacy endpoints as well as safety with apremilast in EMBRACE, a phase 4 study in patients with limited skin involvement with plaque psoriasis manifestations in special areas and impaired QoL.

## METHODS

### Study design

EMBRACE (NCT03774875) was a phase 4, multinational, randomized, double-blind, placebo-controlled, parallel-group trial. Enrolment was conducted in six countries in Western Europe (France, Germany, Great Britain, Italy, Spain and Switzerland). Patients were randomized 2:1 to receive apremilast or placebo. After 5 days of dose titration, patients received apremilast 30 mg BID or placebo for 16 weeks, followed by a 36-week active treatment phase (Fig. S1). Randomization was stratified by five special areas of plaque psoriasis: lesions in visible areas (i.e. dorsal hand,

face, neck or hairline), scalp, nails, genital areas and palmoplantar areas.

The study was approved by the institutional review board/ethics committee before commencement and conducted in compliance with Good Clinical Practice, the International Council for Harmonisation Guideline E6, the Declaration of Helsinki and applicable regulatory requirements. Patients provided written informed consent before study-related procedures.

### Eligibility criteria

EMBRACE enrolled patients with chronic plaque psoriasis for  $\geq 6$  months prior to baseline that was not controlled by topical therapy and had a lack of response, contraindication, or intolerance to conventional first-line systemic therapy. Patients had involvement in  $\geq 1$  special area (defined as lesions in visible locations [i.e. dorsal hand, face, neck or hairline], scalp, nails, genital areas, palmoplantar areas); a DLQI total score  $> 10$ ; and a PASI score  $\geq 3$  to  $\leq 10$ . For more details on criteria for psoriasis involvement in special areas, see the Appendix S1.

### Concomitant medications

Concomitant psoriasis medications, including topicals, conventional systemic therapies, biologic agents and phototherapies, were not permitted. Unmedicated skin moisturizers were permitted for body lesions only but could not contain urea or salicylic acid.

### Endpoints

The primary endpoint was DLQI response of  $\geq 4$ -point reduction from baseline at Week 16. The DLQI is a 10-item questionnaire with a score range of 0 (best QoL) to 30 (worst QoL).<sup>13</sup> Secondary endpoints included reduction from baseline in DLQI at Week 16, percentage change from baseline in affected BSA, proportion of patients achieving PASI  $< 3$ , reduction from baseline in itch numeric rating scale (NRS), reduction from baseline in skin discomfort/pain visual analog scale (VAS) and achievement of Patient Benefit Index (PBI)  $\geq 1$ . The PBI evaluates patient-perceived benefit of treatment on a scale ranging from 0 (no benefit) to 4 (maximum benefit).<sup>14</sup> Improvements in manifestations of plaque psoriasis in special areas were also assessed as an exploratory endpoint. In an ad hoc analysis, change from baseline in mean DLQI at Week 16 was categorized (worse [score increase], no change [0–1-point decrease], small [2–5-point decrease], moderate [6–10-point decrease], very large [11–20-point decrease], extremely large [21–30-point decrease])<sup>15</sup> and stratified by baseline score. Safety assessments included treatment-emergent adverse events (TEAEs) through Week 16.

## Statistical analysis

Discrete endpoints were analysed by Cochran–Mantel–Haenszel test adjusted for the stratification factor at randomization (i.e. the five plaque psoriasis special areas). Continuous endpoints were analysed by analysis of covariance with treatment and randomization strata as fixed effects and corresponding baseline value as a covariate. Multiple imputation was used for missing data.

## RESULTS

### Patient population

Of the 277 patients randomized (apremilast: 185; placebo: 92), 221 completed Week 16 (apremilast: 152; placebo: 69; Fig. S2). Mean age of the population was 49 years, 58.8% were men, and the mean duration of psoriasis was 17 years. In the overall population, 30.3% (84/277) of patients had one special area affected, 37.9% (105/277) had two, and 31.8% (88/277) had three or more. The most common special area affected was visible locations (26.7%), followed by the scalp (24.5%), nails (21.7%), genitals (15.5%) and palmoplantar areas (11.6%). Baseline demographics and clinical characteristics were similar between treatment groups (Table 1).

### Improvements in QoL

Mean DLQI was high at baseline (apremilast: 18.1; placebo: 18.5; Table 1), indicating that psoriasis had a very large effect on patient QoL. Significantly greater proportions of patients treated with apremilast (73.3%) versus placebo (41.3%) achieved the primary endpoint of DLQI response ( $\geq 4$ -point reduction) at Week 16 ( $p < 0.0001$ ; Fig. 1a). A significant treatment difference (95% CI) of  $-5.3$  ( $-7.2, -3.4$ ) (apremilast – placebo,  $p < 0.0001$ ) was observed for DLQI least-squares (LS) mean change from baseline to Week 16 (Fig. 1b).

When patients were stratified into groups according to baseline DLQI and categorized based on the extent of change at Week 16 (i.e. worse, no change, small, moderate, very large and extremely large<sup>15</sup>), at least 50% of patients in each baseline score group had a moderate or greater improvement in DLQI at Week 16 with apremilast treatment (Fig. 2a). The majority of patients receiving placebo had little to no change or had worsening in DLQI (Fig. 2b). In general, apremilast patients with higher baseline DLQI showed greater improvement in DLQI at Week 16 than did those with lower baseline DLQI (Fig. 2a); however, only a small number of patients had higher baseline DLQI. Among patients with DLQI between 17 and 28 at baseline ( $n = 86$ ), at least half experienced a very large or extremely large improvement in DLQI after 16 weeks of apremilast treatment. Among patients with baseline DLQI between 11 and 16, 29.7% (22/74) experienced a very large

**TABLE 1** Baseline demographics and clinical characteristics

Patients, <i>n</i> (%)	Placebo ( <i>n</i> = 92)	Apremilast ( <i>n</i> = 185)
Age, mean (SD), years	50.9 (13.7)	47.4 (14.3)
Men, <i>n</i> (%)	57 (62)	106 (57)
BMI, mean (SD), kg/m <sup>2</sup>	29.4 (5.7)	28.1 (5.6)
Duration of plaque psoriasis, mean (SD), years	18.4 (13.4)	16.3 (13.1)
Presence of plaque psoriasis, <i>n</i> (%)		
Visible locations	24 (26)	50 (27)
Dorsal hand <sup>a</sup>	14 (58)	31 (62)
Face <sup>a</sup>	11 (46)	26 (52)
Hairline <sup>a</sup>	15 (63)	21 (42)
Neck <sup>a</sup>	4 (17)	11 (22)
Scalp	23 (25)	45 (24)
Nail	20 (22)	40 (22)
Genitals	15 (16)	28 (15)
Palmoplantar	10 (11)	22 (12)
Number of special areas, mean	2.1	2.1
DLQI, mean (SD)	18.5 (4.9)	18.1 (4.9)
PASI, mean (SD)	6.8 (2.0)	6.8 (1.9)
BSA %, mean (SD)	7.3 (4.3)	7.0 (3.5)

Note: *N* represents the intent-to-treat population; the number of patients may vary. Abbreviations: BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; SD, standard deviation.  
<sup>a</sup>Percentages are based on the number of patients with psoriasis in visible locations (placebo:  $n = 24$ ; apremilast:  $n = 50$ ).

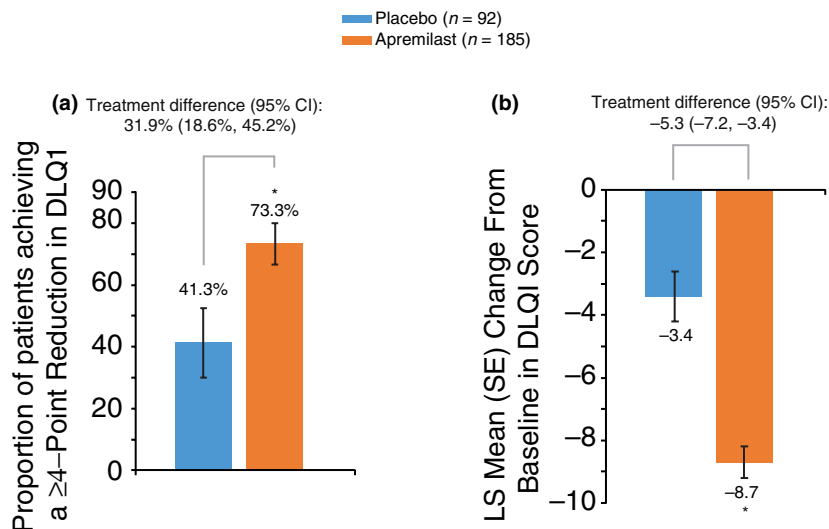
improvement and 28.4% (21/74) achieved a moderate improvement (Fig. 2a).

### Improvements in skin psoriasis

At baseline, mean affected BSA and PASI were 7.0% (range: 1.5%–21.0%) and 6.8, respectively, for patients randomized to apremilast and 7.3% (range: 1.3%–30.0%) and 6.8 for patients randomized to placebo (Table 1). Significantly greater improvement in BSA was seen with apremilast versus placebo (Fig. 3a); patients receiving apremilast experienced a LS mean decrease from baseline in BSA of  $-19.8\%$  at Week 16 whereas patients receiving placebo experienced a LS mean increase of  $18.5\%$  (difference in LS means:  $-38.4\%$ ,  $p = 0.0085$ ). In addition, significantly greater proportions of patients achieved PASI  $< 3$  with apremilast versus placebo at Week 16 (39.7% vs. 26.3%,  $p = 0.0328$ , Fig. 3b).

### Patient-reported outcomes

Mean itch NRS scores were high at baseline: 7.5 in the apremilast group and 7.4 in the placebo group. Significantly greater decreases in itch NRS score were seen with



**FIGURE 1** Improvement in QoL at Week 16. (a) Patients with a  $\geq 4$ -point reduction in DLQI (primary endpoint). Intent-to-treat population. Multiple imputation used for missing data. Error bars represent 95% CI. \* $p < 0.0001$  versus placebo by Cochran–Mantel–Haenszel test adjusting for the stratification factor. (b) Change from baseline in DLQI. Intent-to-treat population. Multiple imputations used for missing data. \* $p < 0.0001$  versus placebo by ANCOVA with treatment and stratification factor as independent variables and the baseline value as a covariate variable. ANCOVA, analysis of covariance; CI, confidence interval; DLQI, Dermatology Life Quality Index; LS, least squares; SE, standard error

apremilast versus placebo ( $-2.5$  vs.  $-0.9$ ,  $p < 0.0001$ ) at Week 16 (Fig. 4a). Baseline skin discomfort/pain VAS scores in apremilast and placebo groups were 61.3 and 61.8, respectively. Significantly greater decreases in skin discomfort/pain VAS score were seen with apremilast versus placebo ( $-21.5$  vs.  $-5.4$ ,  $p = 0.0003$ ) at Week 16 (Fig. 4b). In accordance with these improvements in itch and skin pain, 76.6% of patients achieved a PBI score  $\geq 1$  at Week 16 with apremilast versus 39.9% of patients with placebo ( $p < 0.0001$ ; Fig. 4c).

## Safety

Overall, 82.2% of patients receiving apremilast and 59.3% of patients receiving placebo experienced any TEAE during the study (Table 2). The majority of TEAEs through Week 16 were mild to moderate in intensity and did not lead to treatment discontinuation. The most common TEAEs were diarrhoea (apremilast: 33.0%; placebo: 6.6%), nausea (apremilast: 20.0%; placebo: 5.5%) and headache (apremilast: 20.0%; placebo: 5.5%). Depression occurred in one patient in each group, and there were no reports of suicidal ideation. Common TEAEs and the overall safety profile were consistent with the known safety profile of apremilast.<sup>11,16</sup>

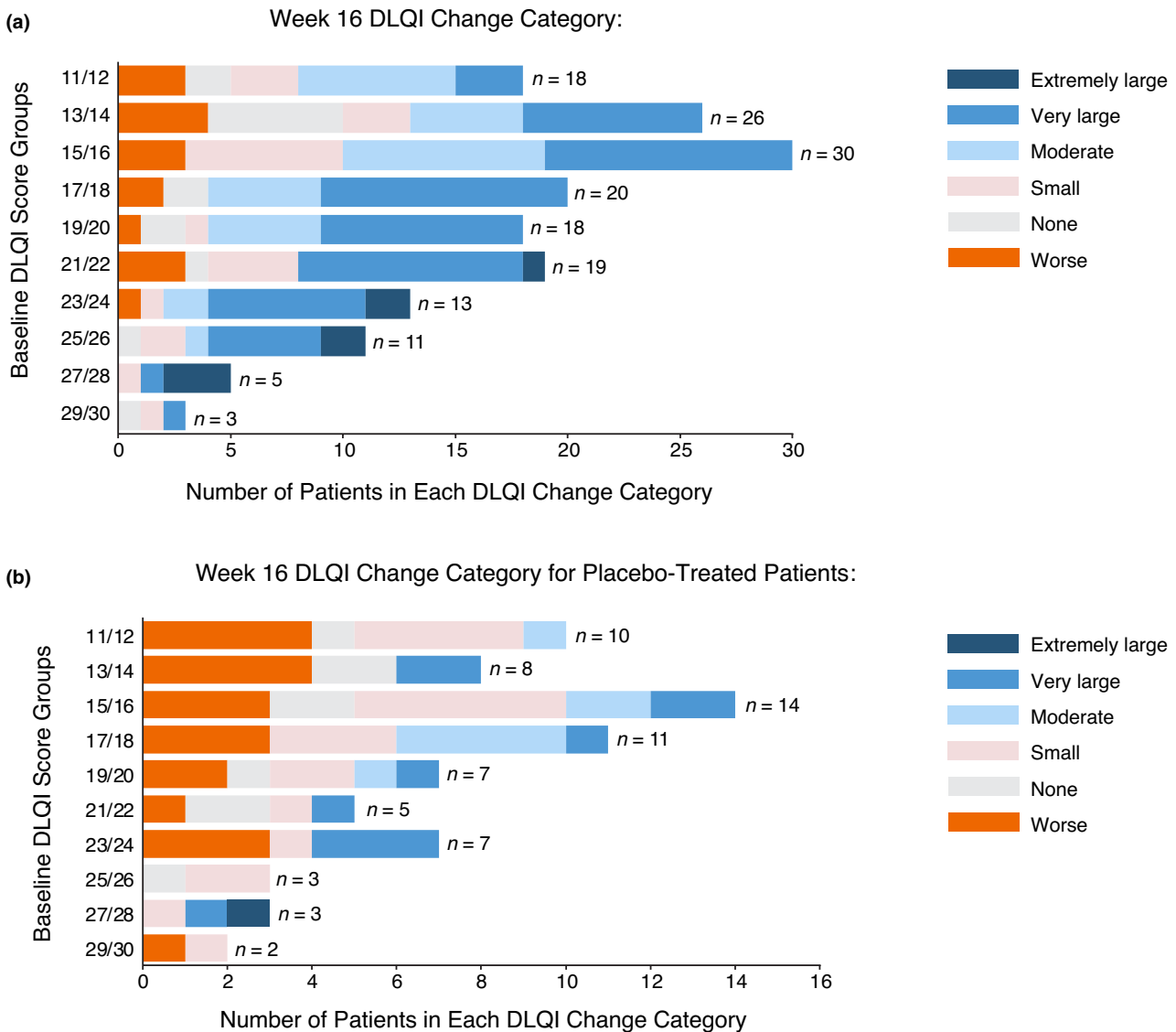
Two cases of COVID-19 pneumonia were reported during the study, both in the apremilast group. Dosing was interrupted in both patients. One of the cases was reported in an obese patient with type 2 diabetes. Both cases resolved and were determined to be unrelated to study treatment.

## DISCUSSION

Quality-of-life and other patient-reported outcomes (PROs) are important goals of psoriasis treatment and a focus of real-world studies.<sup>17</sup> Although many clinical studies include assessments of QoL, few have focused on a QoL measurement as the primary endpoint as in the EMBRACE study. EMBRACE is therefore unique in including DLQI as the primary endpoint and requiring eligible patients to have  $\geq 1$  special area affected. In EMBRACE, patients with limited skin involvement with manifestations of plaque psoriasis in special areas and impaired QoL who were receiving apremilast showed significantly improved QoL compared with placebo at Week 16. Approximately three-quarters of patients who received apremilast achieved a  $\geq 4$ -point decrease in DLQI, compared with less than half of patients who received placebo. This is similar to rates in phase 3 studies in patients with moderate to severe psoriasis, in which 63%–70% of patients achieved a  $\geq 5$ -point decrease in DLQI with apremilast versus 34%–42% of patients with placebo.<sup>11,12,18</sup> It is often difficult to reproduce findings from clinical trials in real-world studies. The consistency across EMBRACE and clinical trials provides strong support for apremilast as an effective treatment to reduce the impact of psoriasis on QoL.

The patient population in EMBRACE was unique as a result of the inclusion criterion of DLQI  $> 10$ . Even though skin involvement was limited, patients in EMBRACE had greatly impaired QoL (mean baseline DLQI of  $\sim 18$ ) compared with clinical trials of apremilast in patients with



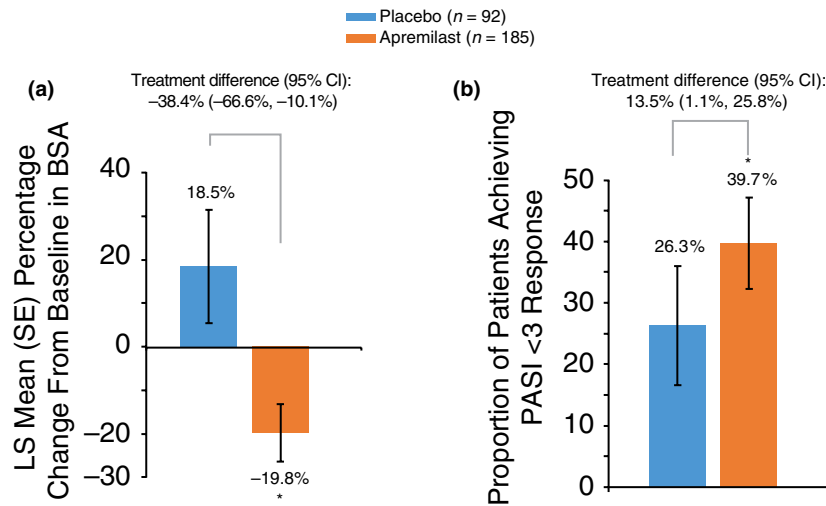


**FIGURE 2** Number of patients in each DLQI change category at Week 16 by baseline DLQI. (a) Apremilast-treated patients. (b) Placebo-treated patients. DLQI change categories were defined as worse (score increase), no change (0–1-point decrease), small (2–5-point decrease), moderate (6–10-point decrease), very large (11–20-point decrease) and extremely large (21–30-point decrease).<sup>15</sup> DLQI, Dermatology Life Quality Index

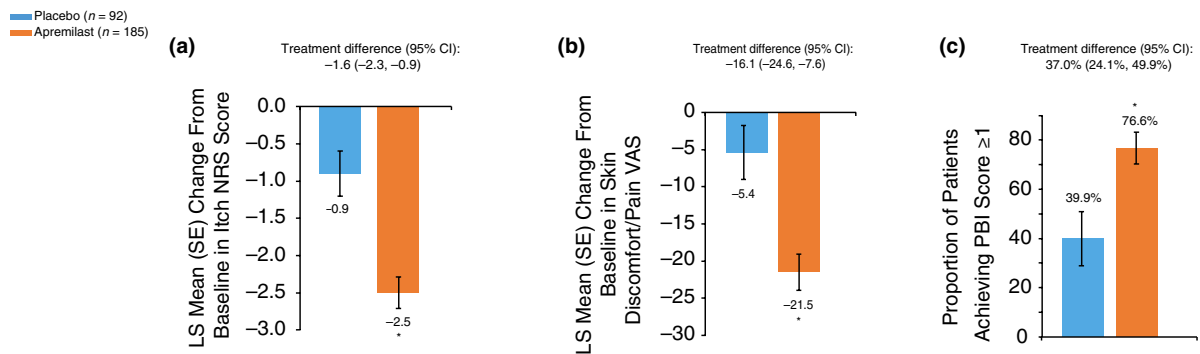
moderate to severe psoriasis in which mean baseline DLQI was no greater than 14.<sup>11,12,18</sup> This level of QoL impairment exemplifies the high burden of disease conferred by psoriasis in special areas despite low BSA involvement. According to the European consensus definition, DLQI > 10 in these patients warrants classification as having moderate to severe disease and the option to begin systemic treatment, despite the fact that mean BSA and PASI were < 10 in this population.<sup>8</sup>

Greater improvements in skin involvement were also seen at Week 16 with apremilast versus placebo. A reduction in affected BSA of 19.8% was observed with apremilast treatment compared with an increase of 18.5% with placebo, and a greater proportion of patients achieved PASI < 3 with apremilast (39.7%) versus placebo (26.3%).

The level of skin discomfort/pain at baseline in patients in EMBRACE was higher than that of patients with moderate to severe psoriasis in LIBERATE (~61 vs. 44–52) despite much lower BSA involvement in patients in EMBRACE (~7% vs. 27%).<sup>12</sup> This highlights the disproportionate impact of psoriasis in special areas. Patients receiving apremilast had significantly greater decreases in itch and skin pain than those receiving placebo. Decreases in skin discomfort/pain in EMBRACE were similar to results seen in LIBERATE (–21.5 and –26.2, respectively). This is important, as itch is reported as the most bothersome symptom of psoriasis.<sup>4</sup> Overall, the majority of patients receiving apremilast achieved PBI ≥ 1, indicating a perceived benefit from treatment, compared with less than half of patients receiving placebo.



**FIGURE 3** Improvement in skin involvement at Week 16. (a) Percentage change from baseline in affected BSA. Intent-to-treat population. Multiple imputations used for missing data.  $*p = 0.0085$  versus placebo by ANCOVA with treatment and stratification factor as independent variables and the baseline value as a covariate variable. ANCOVA, analysis of covariance; BSA, body surface area; CI, confidence interval; LS, least squares; SE, standard error. (b) Proportion of patients achieving PASI <3. Intent-to-treat population. Multiple imputation used for missing data. Error bars represent 95% CI.  $*p = 0.0328$  versus placebo by Cochran–Mantel–Haenszel test adjusting for the stratification factor. CI, confidence interval; PASI, Psoriasis Area and Severity Index.



**FIGURE 4** Improvement in additional patient-reported outcome measures at Week 16. (a) Change from baseline in itch NRS score. Intent-to-treat population. Multiple imputations used for missing data.  $*p < 0.0001$  versus placebo by ANCOVA with treatment and stratification factor as independent variables and the baseline value as a covariate variable. ANCOVA, analysis of covariance; CI, confidence interval; NRS, Numeric Rating Scale; LS, least squares; SE, standard error. (b) Change from baseline in skin discomfort/pain VAS score. Intent-to-treat population. Multiple imputations used for missing data.  $*p = 0.0003$  versus placebo by ANCOVA with treatment and stratification factor as independent variables and the baseline value as a covariate variable. ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; SE, standard error; VAS, visual analog scale. (c) Proportion of patients achieving PBI  $\geq 1$ . Intent-to-treat population. Multiple imputation used for missing data. Error bars represent 95% CI.  $*p < 0.0001$  versus placebo by Cochran–Mantel–Haenszel test adjusting for the stratification factor. CI, confidence interval; PBI, Patient Benefit Index.

EMBRACE was unique in requiring patients to have involvement in at least one special area. In this study, the number of special areas affected ranged from 1 to 5. On average, two special areas were affected, and 31.8% of patients had involvement in three or more special areas. This suggests that only a fraction of patients have a single special area affected (30.3% in EMBRACE). The integration of multiple special areas in EMBRACE provides a more comprehensive assessment of disease burden than other studies, which largely focused on only one special area.

## Limitations

The lack of an active comparator did not allow for direct comparisons with other treatments. The DLQI is the most widely used PRO to assess skin-related QoL. However, the DLQI is not specific to psoriasis or special areas. The current analysis is limited to 16 weeks and does not provide insight on long-term efficacy in this patient population.

**TABLE 2** Overview and most frequently occurring treatment-emergent adverse events

Patients, n (%)	Placebo (n = 91)	Apremilast (n = 185)
Any TEAE	54 (59.3)	152 (82.2)
Any drug-related TEAE	26 (28.6)	113 (61.1)
Any serious TEAE <sup>a</sup>	0	8 (4.3)
TEAE leading to drug withdrawal	8 (8.8)	18 (9.7)
TEAEs occurring in ≥5% of patients in either treatment group		
Diarrhoea	6 (6.6)	61 (33.0)
Nausea	5 (5.5)	37 (20.0)
Headache	5 (5.5)	37 (20.0)
Nasopharyngitis	11 (12.1)	18 (9.7)
Abdominal pain upper	3 (3.3)	12 (6.5)
Psoriasis	10 (11.0)	5 (2.7)
Abdominal pain	1 (1.1)	10 (5.4)

Abbreviation: TEAE, treatment-emergent adverse event.

<sup>a</sup>Except for two cases of COVID-19 pneumonia, all other serious AEs were single occurrences.

## CONCLUSION

The results of the EMBRACE trial support apremilast as an effective treatment to improve skin-related QoL in patients with limited skin involvement with psoriasis in special areas and highly impaired QoL. Approximately three-quarters of patients achieved at least a 4-point reduction in DLQI with apremilast. Apremilast treatment was also associated with significant improvements in skin involvement, including itch and skin discomfort/pain at Week 16. Common TEAEs and the overall safety profile were consistent with the known safety profile of apremilast. The unique focus on patients with psoriasis manifestations not limited to one special area in EMBRACE makes this study highly informative for the treatment of patients with special area involvement. Further studies in this patient population are needed.

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## FUNDING INFORMATION

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## CONFLICT OF INTEREST

**UM:** AbbVie, Aditxt, Almirall, Amgen Inc., Aristeia, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dr. Reddy's, Eli Lilly, Foamix, Formycon, Immunic, Janssen, LEO Pharma, Medac, MetrioPharm, Novartis, Phi-Stone, Pierre Fabre, Sanofi-Aventis, UCB Pharma, and UNION

Therapeutics—advisor, received speakers' honoraria, received grants, and/or participated in clinical trials. **JB:** AbbVie, Almirall, Amgen Inc., Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Samsung, Sienna, Sun Pharma and UCB—participated in advisory boards, received consultancy fees, spoke at sponsored symposia, and/or received grant funding. **CC:** AbbVie, Actelion, Almirall, Amgen Inc., Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Janssen, LEO Pharma, Eli Lilly, MSD, Novartis, Pfizer, Samsung and UCB—honoraria and/or research grants. **DJ:** AbbVie, Almirall, Amgen Inc., Biogen, Boehringer Ingelheim, Celgene, Fresenius Kabi, Janssen-Cilag, LEO Pharma, Lilly, Medac, MSD, Novartis, Pfizer, Sanofi and UCB—consultant, speaker, investigator, scientific officer, steering committee member and/or advisory board member. **PG:** AbbVie, Amgen Inc., Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi and UCB—consultant and grant/research support. **AF:** ProUnlimited—employee, under contract for Amgen Inc. **JR, MP, HP and SJ:** Amgen Inc.—employees and stockholders. **MA:** Abbott/AbbVie, Almirall, Amgen Inc., Beiersdorf, Biogen Idec, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Dermira, Eli Lilly, Fresenius, Galderma, GlaxoSmithKline, Hexal, Incyte, Janssen-Cilag, LEO Pharma, Lilly, Medac, Merck, MSD, Mylan, Novartis, Pfizer, Regeneron, Sandoz, UCB and XenoPort—consultant, paid speaker and/or has received research grants/honoraria.

## DATA AVAILABILITY STATEMENT

Qualified researchers may request data from Amgen clinical studies. Complete details are available at <http://www.amgen.com/datasharing>.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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