

## Apremilast in the treatment of moderate-to-severe plaque psoriasis: results from the ESTEEM studies

Psoriasis is a chronic, systemic inflammatory disease that often has a negative impact on daily functioning and quality of life. Although many treatment options are available, patients are often dissatisfied with their current disease management. Apremilast, an oral PDE4 inhibitor, was recently approved in multiple countries for the treatment of patients with active psoriatic arthritis and patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. In Phase III pivotal clinical trials, apremilast demonstrated clinical efficacy and safety in the treatment of psoriasis as well as active psoriatic arthritis. Here, we discuss the clinical implications and future direction of psoriasis therapy, given the availability of a new oral treatment option.

**Keywords:** apremilast • disease burden • ESTEEM studies • pharmacodynamics • pharmacokinetics • plaque psoriasis • treatment

Psoriasis, a chronic, immune-mediated, systemic inflammatory disease of the skin, is associated with multiple comorbidities and reduced quality of life [1–3]. Psoriasis is common, and estimates of psoriasis prevalence range from 1 to 3% worldwide [4]. In the USA, psoriasis affects an estimated 3.1% of adults 20–59 years of age [5].

Plaque psoriasis manifests as raised, irregularly shaped and well-demarcated erythematous lesions often covered in silvery scales [1,6]. Psoriatic lesions may occur anywhere on the body surface, but frequently occur on the elbows, knees, trunk, sacrum and scalp [6]. The majority of individuals with psoriasis experience localized or mild disease; however, approximately one fifth of those affected have moderate-to-severe disease that affects more than 3% of their body surface area or involves areas of the body that have a particularly high impact on quality of life or physical functioning, such as the face, genitals, nails, hands or feet [5,6]. Lesions are often pruritic and painful, even for patients with localized disease [6]. In addition, 30–40% of patients with plaque psoriasis

have signs and symptoms of concomitant psoriatic arthritis [5,7]. Of interest, skin disease activity and joint disease activity do not necessarily correlate [8]. Psoriasis is also associated with a distinct set of comorbidities, including obesity, diabetes, cardiovascular disease, metabolic syndrome [2,7] and depression [5], all of which may increase the risk of morbidity. Moreover, patients with severe psoriasis are at an increased risk of myocardial infarction, stroke and cardiovascular mortality [9]. Psoriasis also has a negative impact on health-related quality of life and daily function, with more than 90% of patients in one US survey reporting that psoriasis was a problem in their daily life, regardless of their disease severity [3].

### Immunopathophysiology of psoriasis

In psoriasis, the inflammatory cytokine network becomes dysregulated, causing the release of proinflammatory mediators from innate and adaptive immune cells, which in turn leads to aberrant keratinocyte proliferation [10,11]. The exact etiology of psoriasis has

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yet to be elucidated, but it is considered to be a T-cell-mediated process, with the Th17 pathway emerging as the critical pathway in the immunogenesis of psoriasis [12,13]. Dendritic cells, endothelial cells, keratinocytes, monocytes and neutrophils have been shown to have important roles in psoriasis [14,15]. For example, research has shown that inflammatory myeloid dendritic cells secrete IL-23, IL-12 and IL-10; these cytokines (or the surface molecules they express) polarize naive T cells into Th1, Th2 and IL-17-producing T cells. In psoriasis, the Th1 and Th17 cell populations are expanded, and they overproduce cytokines IL-17 and IL-22, IFN- $\gamma$ , and TNF- $\alpha$ , resulting in the proliferation of keratinocytes and the amplification of psoriatic inflammation [15,16]. In individuals with psoriasis, cutaneous and systemic overexpression of proinflammatory ILs, TNF- $\alpha$ , IFN- $\gamma$  and growth factors has been observed [2,14]. In addition, abnormal differentiation and hyperproliferation of keratinocytes; hyperplastic, dilated blood vessels; and inflammatory infiltration of leukocytes into the dermis are histological hallmarks of psoriasis [12,13]. Biologic agents that target TNF- $\alpha$ , IL-17 and IL-23 have demonstrated clinical efficacy in controlling many of the clinical signs and symptoms in patients with psoriasis, further confirming the role of these cytokines in the etiology of psoriasis [15,17]. Of interest, the TNF- $\alpha$  inhibitors infliximab, etanercept and/or adalimumab have also been shown, in rare instances, to paradoxically trigger psoriasis in patients with rheumatologic conditions such as rheumatic arthritis and Crohn's disease [18].

The immune dysregulation that characterizes psoriasis likely arises from a combination of genetic and environmental factors [1]. Genome-wide association scans have identified a set of alleles called the psoriasis susceptibility locus (*PSORS1*), located within the major histocompatibility complex, which is associated with an increased risk of developing psoriasis [19]. The *PSORS1* allele *HLA-Cw\*0602* plays a prominent role in conferring risk for the most common plaque psoriasis phenotype; moreover, single nucleotide polymorphisms of *HLA-C* regulatory genes in patients with psoriasis influence *HLA-Cw\*0602* transcription [19]. Other findings from genome-wide association scans have identified variants in the gene for the *IL-23R* and in the untranslated region of the *IL-12B* *p40* gene, among others, as conferring increased risk for developing psoriasis [20–22].

Several environmental factors have been associated with an increased risk of psoriasis and may contribute to the psoriatic inflammatory cascade, including smoking, physical trauma and bacterial infection [1]. Similarly, comorbid conditions such as obesity, diabetes and cardiovascular disease are all linked to immune dysregulation

and/or systemic inflammation and may share common pathophysiologic mechanisms that seem likely to influence the course and severity of psoriasis disease [2].

### Treatment of plaque psoriasis

Given what is known about the heterogeneous nature of psoriasis, it has become clear that each patient presents a unique biologic canvas. The clinical presentation of psoriatic disease varies widely among patients, including age of onset, nature of symptoms, location, course and severity [1,13]. Accordingly, treatment should be individualized for optimal outcomes. Because of the chronic and lifelong, yet dynamic, nature of psoriasis, long-term therapy is generally required to achieve adequate disease control [6].

Treatment decisions for psoriasis are guided by clinical presentation, comorbidities, patient treatment history and lifestyle, disease-related psychosocial burden and safety considerations [17]. Topical therapies are useful for treating patients with localized disease affecting less than 3% of the body surface area. For patients with more extensive disease, options include phototherapy; traditional systemic therapy such as methotrexate, cyclosporine and acitretin; or biologic therapy [6,23–25]. In particular, biologic therapies have demonstrated marked improvements in the cutaneous manifestations of psoriasis as well as in the cutaneous and rheumatologic manifestations of psoriatic arthritis [6,15,17,24,26]. Moreover, biologic therapies are preferred over traditional systemic medications in women of childbearing potential [27]. However, despite all the medications in our armamentarium, additional treatments are needed for adequate disease control in some patients.

Although there are numerous therapies available for the treatment of psoriasis, three recent major surveys reported that a substantial proportion of patients are not satisfied with and discontinue their current psoriasis medications, primarily because of lack or loss of therapeutic effectiveness. This perceived lack of therapeutic effectiveness may actually be a result of undertreatment of psoriasis [28–30]. Other reasons cited for treatment discontinuation and dissatisfaction were lack of tolerability and perceived safety issues. Many traditional therapies have multiple contraindications, such as liver (methotrexate) or kidney (cyclosporine) disease, which may limit their use in some patients [6,24]. Methotrexate and acitretin are teratogens and cannot be used in women of childbearing potential who are or wish to become pregnant. In the presence of ethanol, acitretin can be converted to etretinate, which is also teratogenic and has a particularly long half-life; therefore, women must avoid becoming pregnant for at least 3 years following use. Methotrexate has several other black box warnings, including potentially fatal organ

system toxicity (e.g., gastrointestinal, bone marrow, liver and skin reactions). Many of the conventional oral therapies require frequent laboratory monitoring and have multiple drug interactions [24]. Biologic therapies are effective; however, despite their targeting specific immunologic pathways, the immunosuppressive effects may be associated with an increased risk of infections and malignancies [31–33]. In addition, some patients develop treatment resistance, which may limit the long-term efficacy of some biologic agents [34]. Also, some patients are uncomfortable committing to maintenance dosing.

The chronic nature of psoriasis requires long-term treatment with an effective agent that targets the pathophysiologic pathways of psoriasis [35] while providing acceptable tolerability. In addition, therapies that improve existing comorbidities or that at least do not worsen them are optimal. Apremilast (Otezla, Celgene Corporation, NJ, USA), an oral PDE4 inhibitor, was approved by the US FDA in 2014 and by the European Commission in 2015 for patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy and for adult patients with active psoriatic arthritis [36,37]. Apremilast is the first oral drug to receive FDA approval for treatment of psoriasis since 1996 [38–41], and the first in the class of small-molecule inhibitors of PDE4, an enzyme involved in the chronic inflammation associated with the development of skin symptoms in psoriasis. Apremilast has since been approved for the treatment of psoriasis and psoriatic arthritis in multiple countries, including Canada [42].

### Pharmacokinetics of apremilast

Several studies investigated the pharmacokinetics of apremilast in healthy volunteers [27,36,43–44] and in patients with severe plaque psoriasis [45]. In healthy volunteers, the mean half-life ( $t_{1/2}$ ) of apremilast was approximately 6–9 h [36]; the mean peak serum concentration ( $C_{max}$ ) ranged between 333 and 500 ng/ml; and the median time to reach maximum serum concentration ( $T_{max}$ ) was approximately 2.5 h [27,36,43–44]. Co-administration with food did not alter the extent of apremilast absorption [36]. In patients with severe plaque psoriasis who received oral apremilast 20 mg twice daily over 29 days, the mean steady-state  $t_{1/2}$  of apremilast was 8.2 h and the mean steady-state  $C_{max}$  was 207 ng/ml; median  $T_{max}$  was 2.0 h [45].

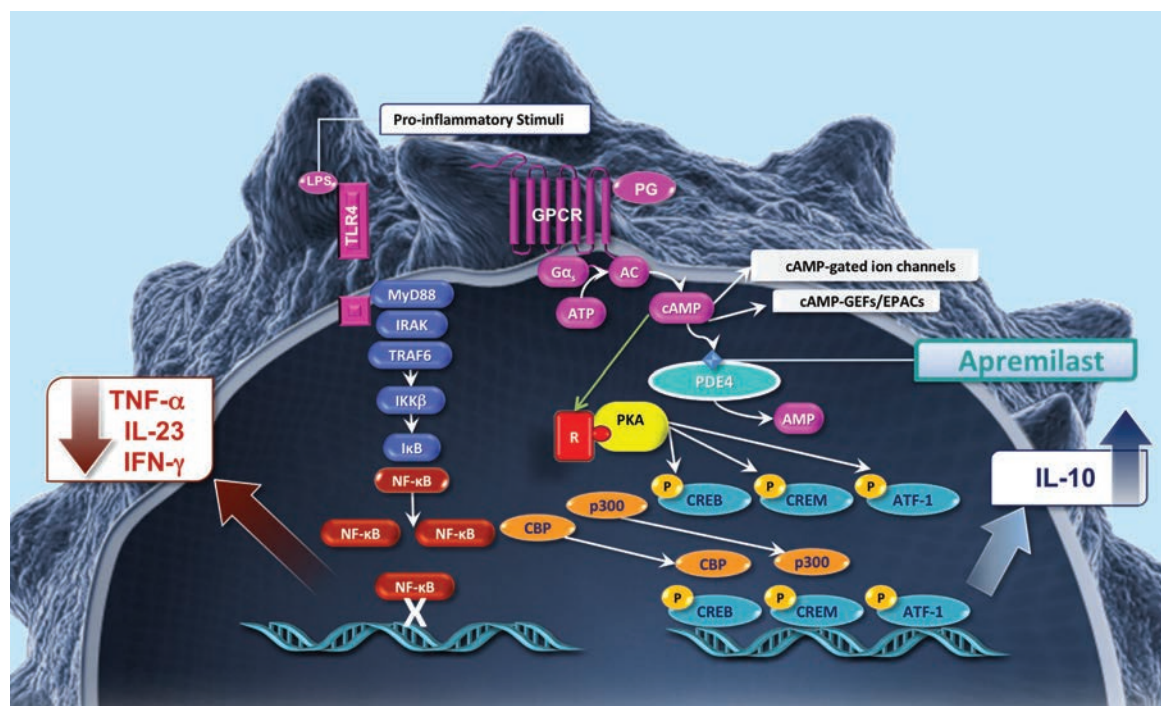
Other investigations have examined the potential for drug–drug interactions with apremilast [46,47]. Liu *et al.* found that, in patients with psoriatic arthritis ( $n = 3$ ) or rheumatoid arthritis ( $n = 12$ ) receiving stable doses of methotrexate (7.5–20 mg once weekly), co-administration of apremilast 30 mg twice daily for 6 days did not affect the pharmacokinetic profile of

either agent [46]. Because CYP450 (CYP)-oxidative metabolism plays a role in apremilast clearance [27], the impact of potential drug–drug interactions between apremilast and ketoconazole (a strong CYP3A4 inhibitor) or rifampicin (a potent CYP3A4 inducer) was also recently studied [47]. Co-administration of ketoconazole has been demonstrated to slightly decrease clearance of apremilast, resulting in a clinically insignificant increase (36%) in overall apremilast exposure [36,47]. Conversely, rifampin has been shown to increase the clearance of apremilast by more than threefold [36,47]. Based on these findings, strong CYP3A inducers like rifampin, phenobarbital or carbamazepine are not recommended for concomitant use with apremilast, as this may result in a loss of apremilast efficacy due to decreased drug exposure.

### Mechanism of action & pharmacodynamic impact of apremilast

The PDE4 inhibitor apremilast works intracellularly to regulate the production of multiple inflammatory mediators implicated in the pathogenesis of psoriasis (Figure 1) [11,48]. The PDE family of enzymes is the sole means of degrading cyclic AMP (cAMP) and cyclic GMP (cGMP), cyclic nucleotides found in all cell types and key second messengers that regulate most types of cells [49]. PDE4 is the predominant cAMP-specific phosphodiesterase in inflammatory cells, including mast cells, monocytes, macrophages, dendritic cells, eosinophils and T cells [49]. PDE4 inhibitors prevent the degradation of intracellular cAMP. PDE4 inhibition is the only known mechanism of action of apremilast [11]. With apremilast-mediated PDE4 inhibition, consequent rises in intracellular cAMP lead to changes in signaling pathways, including activation of protein kinase A (PKA) and phosphorylation of cAMP-responsive element binding (CREB) transcription factors, which ultimately both suppress expression of proinflammatory cytokines (e.g., TNF- $\alpha$  and IFN- $\gamma$ , and IL-2, IL-12 and IL-23) and enhance production of anti-inflammatory cytokines (Figure 1) [10,11].

Apremilast has demonstrated effective reduction in psoriatic lesion thickness and modulation of inflammatory responses in psoriatic lesions in clinical studies of patients with severe psoriasis [45,50]. In an early open-label study in patients with severe plaque psoriasis, apremilast 20 mg once daily for 29 days led to a  $\geq 20\%$  reduction in epidermal thickness of lesional skin in eight of 15 (53%) participants [45]. In this responder subgroup, the number of T cells was reduced by 28.8% in the dermis and by 42.6% in the epidermis in lesional skin biopsies [45]. In a Phase II study involving patients with recalcitrant psoriasis, apremilast 20 mg twice daily for 12 weeks significantly reduced myeloid den-



**Figure 1. The mechanism of action of apremilast.** Apremilast specifically targets PDE4 and modulates expression of a network of proinflammatory (i.e., TNF- $\alpha$ , IL-23 and IFN- $\gamma$ ) and anti-inflammatory (i.e., IL-10) mediators. cAMP is a key second messenger signaling molecule produced intracellularly in response to signals emanating from GPCRs such as those binding PG; binding of ligand to the GPCR acts via the stimulatory G $\alpha_s$  to activate AC, which converts ATP into cAMP. In immune cells such as monocytes and dendritic cells, PDE4 is the primary enzyme responsible for degrading cAMP to AMP. Thus, inhibition of PDE4 by apremilast increases intracellular cAMP levels. In turn, increased cAMP levels activate PKA, as well as cAMP-gated ion channels or EPAC. Downstream effects of PKA activation include phosphorylation of the CRE-binding family of transcription factors: CREB, CREM and ATF-1. In cell types such as monocytes, these phosphorylated transcription factors bind to CRE sites within promoters of genes such as the anti-inflammatory mediator IL-10, thus increasing gene expression. At the same time, CRE-driven transcriptional activation recruits coactivators such as CBP or the homologous protein p300, thus recruiting these coactivators away from NF- $\kappa$ B. NF- $\kappa$ B is activated in response to proinflammatory stimuli (e.g., LPS-stimulation of the TLR4 pathway), and is responsible for the transcriptional activation of proinflammatory mediators including TNF- $\alpha$ , IL-23 and IFN- $\gamma$ . Decreased availability of the coactivators (CBP and p300) reduces NF- $\kappa$ B-dependent gene expression. The resulting decreased inflammatory response may lead to lower levels of infiltration by other immune cells, as well as reduced activation and proliferation of keratinocytes and synoviocytes. Together, this may lead to decreased epidermal thickening in psoriasis and decreased synovial damage in rheumatoid arthritis. AC: Adenylyl cyclase; cAMP: Cyclic AMP; CREB: cAMP-responsive element binding protein; CREM: cAMP-responsive element modulator; EPAC: Exchange protein activated by cAMP; G $\alpha_s$ : G protein alpha subunit; GPCR: G-protein-coupled receptor; LPS: Lipopolysaccharide; PG: Prostaglandin; PKA: Protein kinase A. Reproduced with permission from [48].

dritic cell, T-cell and NK-cell or NK-T-cell infiltration into the dermis and epidermis of psoriatic lesions [50]. Reductions in multiple inflammatory mediators (TNF- $\alpha$ , inducible nitric oxide synthase [iNOS], IL-12/23 p40, IL-17A) were observed at week 4 and week 12. Median percentage change from the baseline Psoriasis Area and Severity Index (PASI) scores at week 12 significantly correlated with decreases in several such markers, including iNOS, IL-17A, DEFB4 and keratin 16; as early as week 4, significant correlations between reduction in PASI score and IL-12/IL-23p40, DEFB4 and myxovirus resistance protein 1 (a surrogate marker for lesional type 1 IFN activity) [18] were observed [50]. These findings suggest that the biologic

effects of apremilast may be due to a broader regulation of inflammatory response versus other classes of drugs that target a single component within a network of proinflammatory mediators.

The pharmacodynamic impact of apremilast was recently evaluated in a substudy of the PALACE Phase III clinical trial, PALACE 1. This substudy assessed plasma biomarkers associated with inflammation in peripheral blood plasma samples of patients with active psoriatic arthritis, and examined the relationship between changes in these select biomarkers and the primary clinical response (defined as a 20% improvement from baseline in modified American College of Rheumatology [ACR20] response). At weeks 16 and 24,



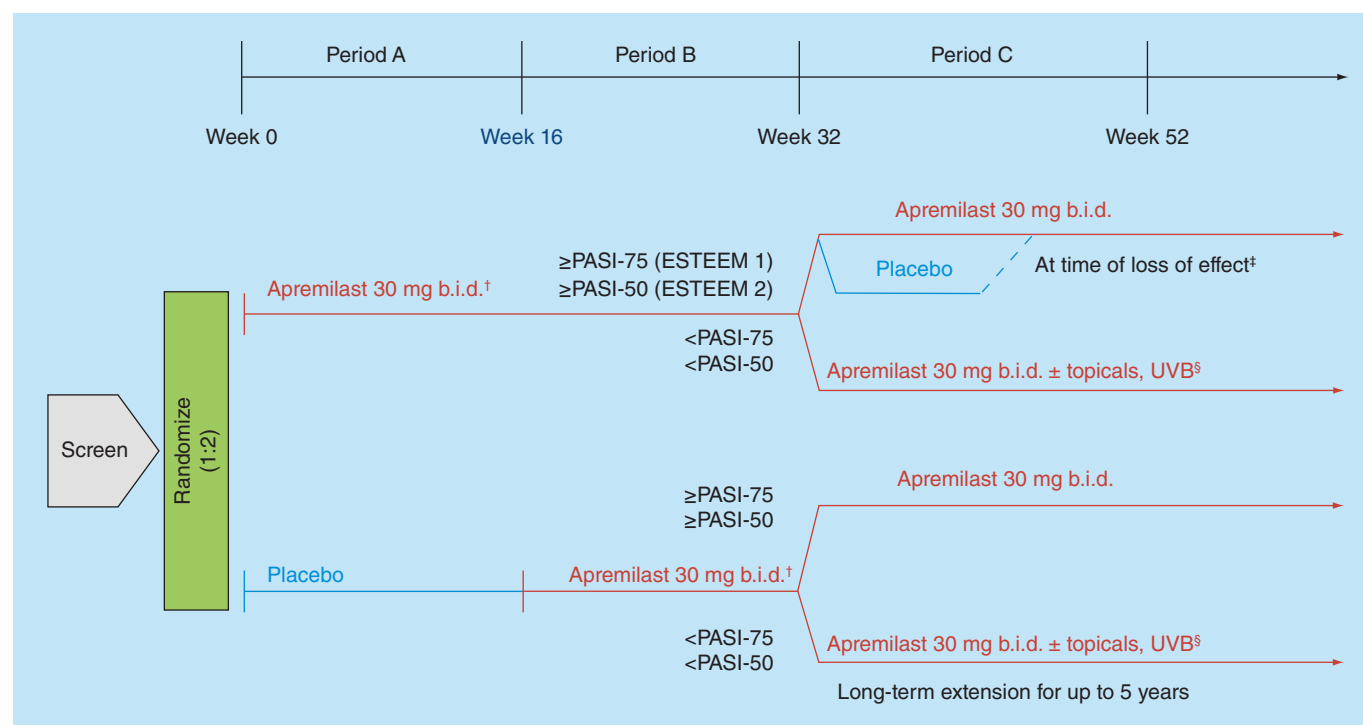
apremilast 20 mg twice daily or 30 mg twice daily significantly reduced TNF- $\alpha$ , IL-8, IL-6 and ferritin levels versus placebo ( $p < 0.05$ ), consistent with the regulation of multiple cytokines elicited by PDE4 inhibition. Logistic regression analyses demonstrated that changes in TNF- $\alpha$  with apremilast treatment were associated with ACR20 clinical response at week 16. By week 40, IL-6, IL-17, IL-23, IL-10, ferritin and IL-1 receptor antagonists (IL-1RA) all exhibited significant changes among patients treated with either 20 or 30 mg twice daily versus baseline; decreases in IL-6, IL-17 and IL-23 suggest long-term inhibition of the systemic Th-17 response, whereas increases in IL-10 and IL-1RA are indicative of an increase in anti-inflammatory mediator production.

### Pivotal clinical efficacy & safety studies of apremilast

#### Apremilast in plaque psoriasis: the ESTEEM Phase III studies

The safety and efficacy of apremilast 30 mg twice daily in the treatment of moderate-to-severe plaque psoriasis have been demonstrated in the ESTEEM Phase III

clinical trial program. ESTEEM 1 [51] and ESTEEM 2 [52], two similarly designed international, multicenter, randomized, double-blind, placebo-controlled studies, evaluated the safety and efficacy of apremilast in patients with moderate-to-severe plaque psoriasis (Figure 2). Patients were eligible to participate in the study if they were 18 years of age or older and had 10% or more involvement of the body surface area, static Physician Global Assessment (sPGA) rating of 3 or greater (moderate or severe disease), and PASI score of 12 or greater, and were candidates for phototherapy or systemic therapy. Patients were randomized (2:1) to receive apremilast 30 mg twice daily or placebo for 16 weeks (placebo-controlled phase, period A). At week 16, placebo patients were switched to apremilast. Dosing with apremilast was maintained for all patients from weeks 16–32 (maintenance phase, period B). Treatment from weeks 32–52 (randomized treatment withdrawal phase, period C) was based on the original treatment assignment and the PASI response at week 32, as shown in Figure 2. Blinding was maintained until all patients discontinued or completed their week



**Figure 2. The ESTEEM 1 and ESTEEM 2 study design.**

<sup>†</sup>Doses of apremilast were titrated during the first week of administration and at week 16 when placebo patients were switched to apremilast.

<sup>‡</sup>In ESTEEM 1, patients were switched to apremilast at the time of loss of PASI-75, but no later than week 52. In ESTEEM 2, patients were switched to apremilast at the time of loss of effect, defined as the time of loss of 50% of the PASI improvement obtained at week 32 compared with baseline, but no later than week 52.

<sup>§</sup>Patients initially on placebo or randomized to apremilast 30 mg twice daily who did not attain a PASI-75 (ESTEEM 1) or PASI-50 (ESTEEM 2) response were able to add topicals and/or UVB at week 32 at the discretion of the investigator.

b.i.d.: twice daily; PASI-75: 75% reduction from baseline Psoriasis Area and Severity Index score; PASI-50: 50% reduction from baseline Psoriasis Area and Severity Index score; UVB: Ultraviolet light B.

52 visit. In both ESTEEM studies, the primary end point was the proportion of patients who achieved a 75% reduction from baseline PASI score (PASI-75) at week 16. Baseline demographic and disease characteristics were well balanced between groups in both studies (Table 1).

In ESTEEM 1 (n = 844) and ESTEEM 2 (n = 411), patients receiving apremilast demonstrated statistically significant improvements in PASI-75 response at week 16 compared with patients receiving placebo ( $p < 0.0001$ ) (Figure 3). Nonoverlapping confidence intervals (representing a statistically significant difference) between apremilast and placebo in the mean percentage improvement in PASI were detected as early as week 2 [52,53]. The beneficial effects of apremilast were also seen at week 16 based on achievement of sPGA response (score of 0 or 1 with at least a two-point

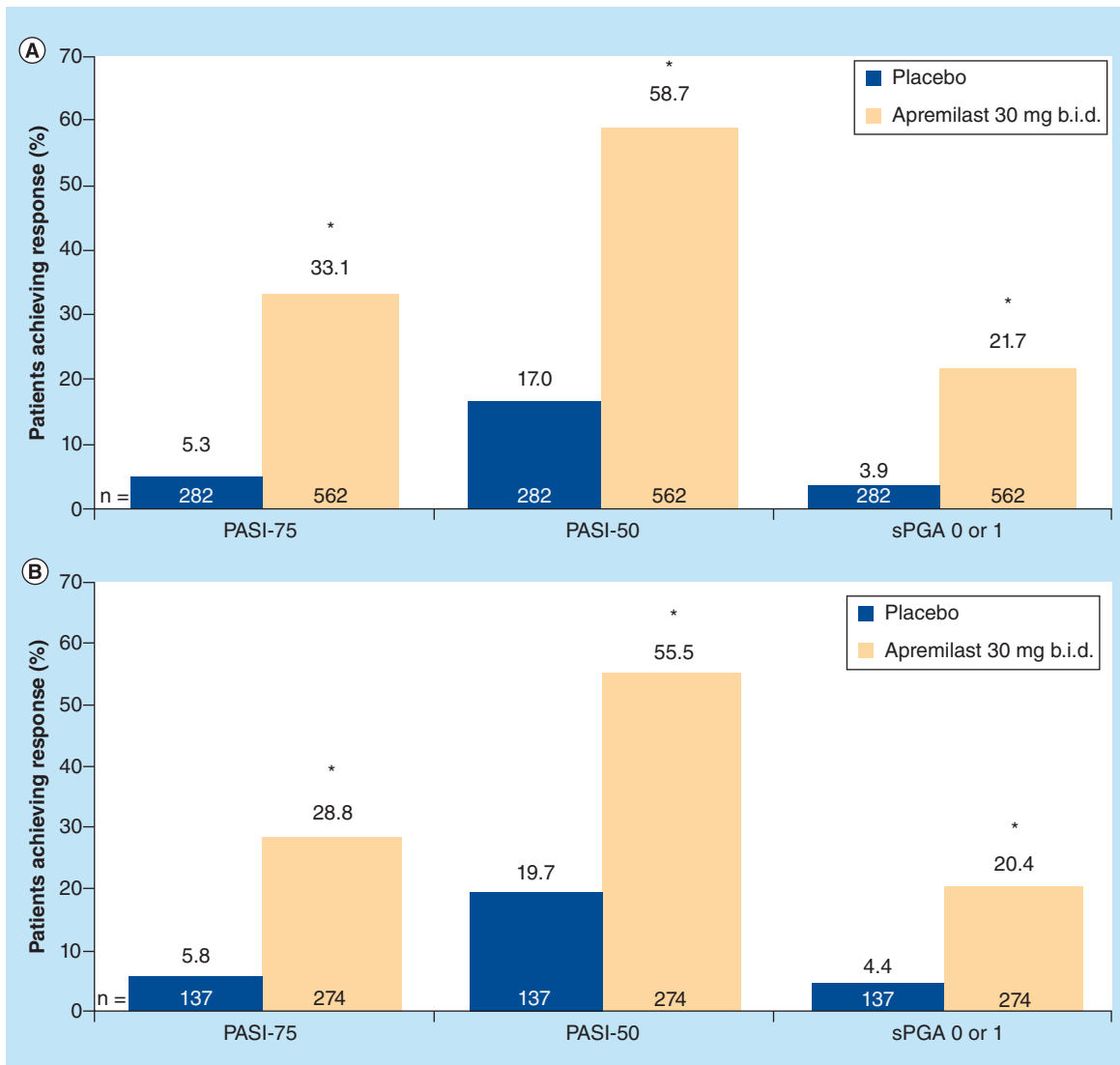
reduction from baseline; major secondary efficacy end point), as well as achievement of a 50% decrease from baseline PASI score (PASI-50) (Figure 3).

Among patient-reported outcomes, pruritus severity, as measured using a 100-mm visual analog scale, was significantly decreased from baseline in patients receiving apremilast 30 mg twice daily compared with patients receiving placebo (-31.5 vs -7.3 mm in ESTEEM 1; -33.5 vs -12.2 mm in ESTEEM 2;  $p < 0.0001$  for both studies); at week 16 these changes represent a decrease of approximately 50% in the severity of pruritus in both studies. Significant improvement in pruritus was observed as early as week 2 with apremilast 30 mg twice daily in both ESTEEM 1 and ESTEEM 2 ( $p < 0.001$  vs placebo [*post hoc* analysis]) [54]. The benefit of apremilast was also noted across patient subgroups with psoriasis in especially difficult-to-treat

Table 1. Baseline patient demographics and disease characteristics in ESTEEM 1 and ESTEEM 2 (full analysis set).

Characteristic	ESTEEM 1 (n = 844)		ESTEEM 2 (n = 411)	
	Placebo (n = 282)	Apremilast 30 mg twice daily (n = 562)	Placebo (n = 137)	Apremilast 30 mg twice daily (n = 274)
Age, mean (SD); years	46.5 (12.7)	45.8 (13.1)	45.7 (13.4)	45.3 (13.1)
Male, n (%)	194 (68.8)	379 (67.4)	100 (73.0)	176 (64.2)
BMI, mean (SD); kg/m <sup>2</sup>	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)
White, n (%)	250 (88.7)	507 (90.2)	128 (93.4)	250 (91.2)
Duration of plaque psoriasis, mean (SD); years	18.7 (12.4)	19.8 (13.0)	18.7 (12.1)	17.9 (11.4)
PASI, mean (SD)	19.4 (7.4)	18.7 (7.2)	20.0 (8.0)	18.9 (7.1)
PASI >20, n (%)	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%, n (%)	149 (52.8)	266 (47.3)	80 (58.4)	143 (52.2)
sPGA = 4 (severe); n (%)	89 (31.6)	161 (28.6)	49 (35.8)	75 (27.4)
NAPSI ≥1; n (%)	195 (69.1)	363 (64.6)	91 (66.4)	175 (63.9)
ScPGA ≥3 (moderate to very severe); n (%)	189 (67.0)	374 (66.5)	93 (67.9)	176 (64.2)
PPPGA ≥3 (moderate to severe); n (%)	26 (9.2)	57 (10.1)	16 (11.7)	26 (9.5)
Pruritus VAS score, mean (SD); mm	65.2 (24.8)	66.2 (25.5)	65.0 (26.0)	67.8 (25.2)
DLQI score, mean (SD)	12.1 (6.7)	12.7 (7.1)	12.8 (7.1)	12.5 (7.1)
Systemic (conventional and/or biologics); n (%)	150 (53.2)	301 (53.6)	73 (53.3)	157 (57.3)
Conventional systemic, n (%)	102 (36.2)	212 (37.7)	53 (38.7)	106 (38.7)
Biologic, n (%)	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; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; ScPGA: Scalp Physician Global Assessment; sPGA: Static Physician Global Assessment; SD: Standard deviation; VAS: Visual analog scale.



**Figure 3. PASI-75, PASI-50 and sPGA responses at week 16, last observation carried forward. (A)** ESTEEM 1 and **(B)** ESTEEM 2. The mean baseline PASI score was 19.4 (ESTEEM 1) and 20.0 (ESTEEM 2) for placebo and 18.7 (ESTEEM 1) and 18.9 (ESTEEM 2) for apremilast 30 mg twice daily.

\* $p < 0.0001$  vs placebo.

b.i.d.: twice daily; LOCF: Last observation carried forward; PASI-75: 75% reduction from baseline Psoriasis Area and Severity Index score; PASI-50: 50% reduction from baseline Psoriasis Area and Severity Index score; sPGA response: sPGA score of 0 (clear) or 1 (almost clear) with at least a two-point reduction from baseline.

areas, including patients with nail and scalp psoriasis, in both studies at week 16. Achievement of Nail Psoriasis Severity Index (NAPSI)-50 response (e.g.,  $\geq 50\%$  improvement from baseline in target nail NAPSI score) or Scalp Physician Global Assessment score of 0 (clear) or 1 (minimal) was significantly greater with apremilast versus placebo (Table 2). At week 16, 33 and 45% of patients with nail psoriasis at baseline treated with apremilast in ESTEEM 1 and 2, respectively, had achieved a NAPSI-50 response. In addition, patients in the apremilast group had a significant improvement in patient-reported health-related quality of life compared with those in the placebo group ( $p < 0.0001$ ), based on

improvements from baseline at week 16 in the Dermatology Life Quality Index (DLQI) (Table 2) [51,52]. In ESTEEM 2, the achievement of Palmoplantar Psoriasis Physician Global Assessment score of 0 (clear) or 1 (almost clear) at week 16 in the subgroup of patients in ESTEEM 2 who had palmoplantar psoriasis at baseline was significantly greater in patients treated with apremilast versus placebo (Table 2).

During the maintenance phase of ESTEEM 1 and ESTEEM 2 (weeks 16–32, period B), the PASI-75 response was sustained among patients initially randomized to apremilast 30 mg twice daily at baseline, as were improvements in pruritus VAS. Patients ini-

Table 2. Efficacy outcomes at week 16 in ESTEEM 1 and ESTEEM 2: pruritus, NAPS I score, ScPGA response, PPPGA response and DLQI response

End point	ESTEEM 1 (n = 844)		ESTEEM 2 (n = 411)	
	Placebo (n = 282)	Apremilast 30 mg twice daily (n = 562)	Placebo (n = 137)	Apremilast 30 mg twice daily (n = 274)
Pruritus:				
– Mean change in pruritus VAS score (mm)	-7.3	-31.5 <sup>†</sup>	-12.2	-33.5 <sup>†</sup>
Patients with target nail psoriasis, NAPS I ≥1:				
– Mean percentage change in NAPS I	6.5	-22.5 <sup>‡</sup>	-7.1	-29.0 <sup>§</sup>
– NAPS I-50 (%)	14.9	33.3 <sup>§</sup>	18.7	44.6 <sup>§</sup>
Patients with scalp psoriasis, ScPGA ≥3:				
– ScPGA score 0 (clear) or 1 (minimal), %	17.5	46.5 <sup>‡</sup>	17.2	40.9 <sup>‡</sup>
Patients with palmoplantar psoriasis, PPPGA ≥3:				
– PPPGA 0 (clear) or 1 (almost clear), %	30.8	38.6	31.5	65.4 <sup>¶</sup>
Quality of life:				
– Mean change in DLQI score	-2.1	-6.6 <sup>‡</sup>	-2.8	-6.7 <sup>‡</sup>
Patients with baseline DLQI >5:				
– DLQI response <sup>#</sup> (%)	29.7	65.8 <sup>‡</sup>	38.7	67.7 <sup>‡</sup>
– DLQI response + PASI-50 response (%)	11.0	48.1 <sup>‡</sup>	13.4	49.1 <sup>‡</sup>

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

<sup>†</sup>Represents an approximately 50% decrease from baseline in pruritus severity.

<sup>‡</sup>p < 0.0001 vs placebo.

<sup>§</sup>p = 0.0052 vs placebo.

<sup>¶</sup>p = 0.0315 vs placebo.

<sup>#</sup>DLQI response = ≥5-point decrease from baseline [55].

DLQI: Dermatology Life Quality Index; NAPS I: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; PPPGA: Palmoplantar Psoriasis Physician Global Assessment; ScPGA: Scalp Physician Global Assessment; VAS: Visual analog scale.

tially randomized to placebo in period A who were switched to apremilast at week 16 also demonstrated improvements in PASI-75 response (Figure 4), mean percentage change from baseline in PASI, and pruritus VAS. During the randomized treatment withdrawal phase (weeks 32–52, period C), the mean percentage improvement in the PASI score was maintained over 52 weeks in patients who were PASI responders (ESTEEM 1: PASI-75; ESTEEM 2: PASI-50) at week 32 [51,52]. Specifically, the mean percentage change from baseline in PASI score was -88 to -81% from weeks 32 to 52 in ESTEEM 1; in ESTEEM 2, the mean percentage change from baseline in PASI score was -77 to -74% from weeks 32 to 52.

### Apremilast safety in the ESTEEM studies (pooled analysis)

Apremilast 30 mg twice daily demonstrated acceptable safety and tolerability with long-term treatment in the ESTEEM 1 and ESTEEM 2 pivotal trials. In both studies, most adverse events were mild to moderate in severity for both the 16-week placebo-controlled and the 52-week apremilast-exposure periods. The most common adverse events reported for apremilast 30 mg twice daily during the placebo-controlled period included diarrhea (17.8%), nausea (16.6%) and upper respiratory tract infection (8.4%) (Table 3). Diarrhea

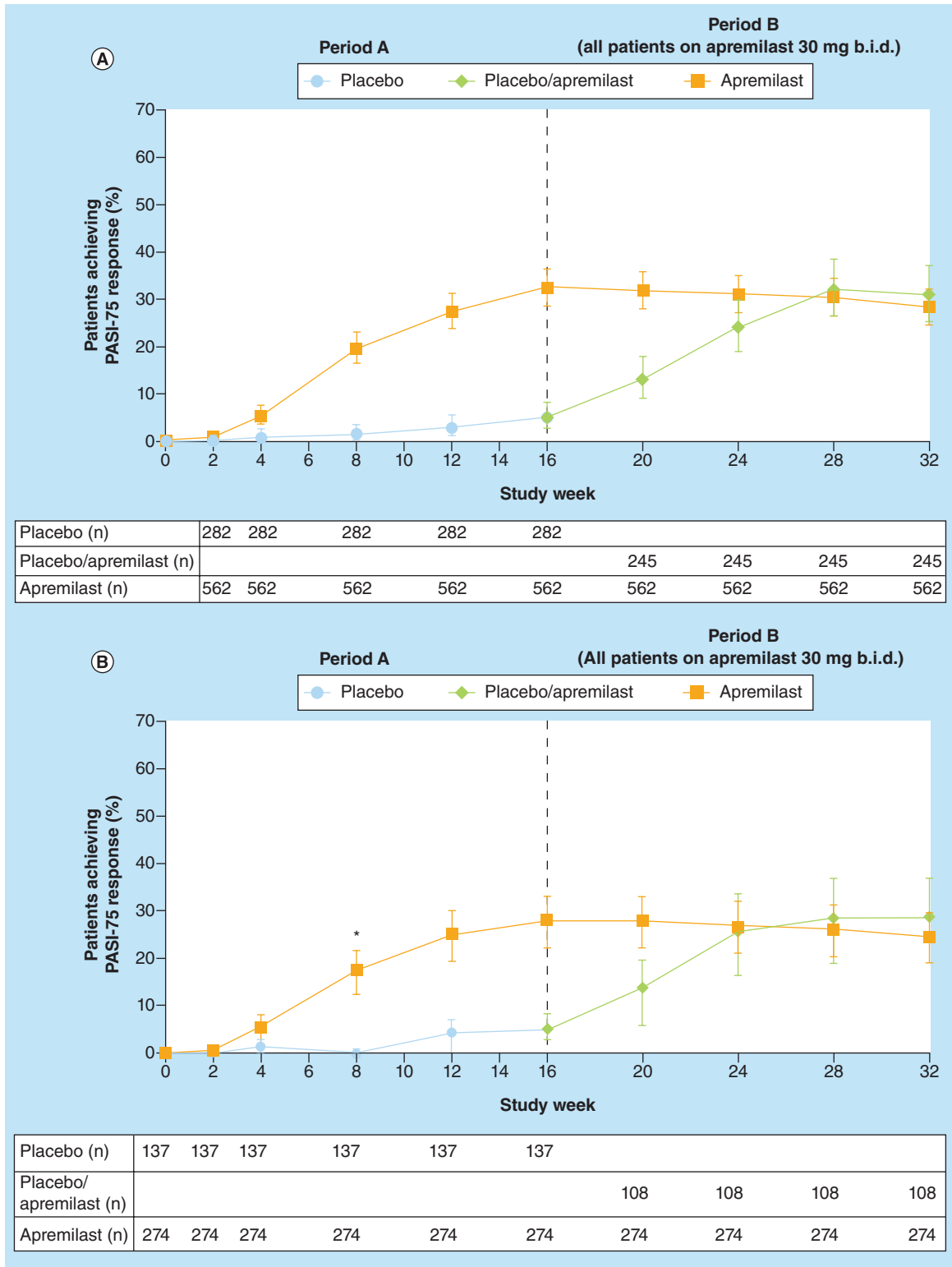
and nausea were predominantly mild and occurred with the highest incidence in the first 2 weeks of treatment, then at a reduced incidence after the first month of dosing [56,57].

Long-term (uncontrolled) data (≥52 weeks of exposure) did not indicate an increase in adverse events (including serious adverse events) based on exposure-adjusted incidence rates (EAIR) per 100 patient-years. During the ESTEEM clinical studies, one death occurred with placebo treatment (completed suicide) and two deaths occurred with apremilast 30 mg twice daily treatment (on day 111 [cardiac failure] and day 666 [cerebrovascular accident] of apremilast exposure). Discontinuations due to adverse events were low during weeks 0–16 and did not increase with longer apremilast exposure, based on the EAIR per 100 patient-years among patients exposed to apremilast for ≥52 weeks (weeks 0–16, placebo EAIR: 13.8, apremilast 30 mg twice daily EAIR: 19.2; weeks 0 to ≥52: apremilast 30 mg twice daily EAIR: 8.8).

Exposure-adjusted incidence rates of major cardiac events, serious infections including systemic opportunistic infection or malignancies in ESTEEM 1 and ESTEEM 2 (pooled analysis) were comparable to placebo [52]. Although eight patients (ESTEEM 1: n = 5; ESTEEM 2: n = 3) in the apremilast group had a medical history of tuberculosis, there were no cases of reac-



tivated tuberculosis reported in patients treated with apremilast in either study. Markedly abnormal laboratory test results among apremilast-treated patients were infrequent, transient and not clinically meaningful.



**Figure 4. PASI-75 responses over 32 weeks. (A) ESTEEM 1 and (B) ESTEEM 2.**

\*First time point measuring nonoverlapping confidence intervals between placebo and apremilast 30 mg b.i.d.  
b.i.d.: twice daily; PASI-75: 75% reduction from baseline Psoriasis Area and Severity Index score.

Table 3. Adverse events occurring in ≥5% of patients regardless of treatment in ESTEEM 1 and ESTEEM 2 (pooled analysis).

Patients	Placebo-controlled period <sup>†</sup> weeks 0–16				Apremilast-exposure period weeks 0 to ≥52	
	Placebo (n = 418); patient-years = 116.5		Apremilast 30 mg twice daily (n = 832); patient-years = 236.8		Apremilast 30 mg twice daily (n = 1184); patient-years = 1127.9	
	n (%)	EAIR/100 patient-years <sup>‡</sup>	n (%)	EAIR/100 patient-years <sup>‡</sup>	n (%)	EAIR/100 patient-years <sup>‡</sup>
Diarrhea	28 (6.7)	25.5	148 (17.8)	74.2	208 (17.6)	22.1
Nausea	28 (6.7)	25.3	138 (16.6)	68.2	188 (15.9)	19.6
URTI	27 (6.5)	23.9	70 (8.4)	30.9	200 (16.9)	20.7
Nasopharyngitis	29 (6.9)	25.9	61 (7.3)	26.8	178 (15.0)	17.8
Tension headache	14 (3.3)	12.4	61 (7.3)	27.5	109 (9.2)	10.7
Headache	14 (3.3)	12.4	48 (5.8)	21.2	76 (6.4)	7.1

<sup>†</sup>As originally treated at week 0.

<sup>‡</sup>EAIR per 100 patient-years is defined as 100-times the number (n) of patients reporting the event divided by patient-years (up to the first event start date for patients reporting the event).

EAIR: Exposure-adjusted incidence rate; URTI: Upper respiratory tract infection.

Data taken from [58].

Weight loss was associated with apremilast treatment in the ESTEEM studies. During the weeks 0–16 placebo-controlled period, weight loss of more than 5%, considered potentially clinically relevant [59], was experienced by 13.7% of patients receiving apremilast 30 mg twice daily and 5.5% of patients receiving placebo; this was experienced in 20.0% of patients during long-term exposure (weeks 0 to ≥52). At week 52, the mean (median) change from baseline weight was -1.99 (-1.40) kg with apremilast 30 mg twice daily. Weight loss with apremilast did not lead to any overt medical sequelae or manifestations through the apremilast-exposure period [58], and no association between weight loss and diarrhea or nausea/vomiting has been identified.

Apremilast in psoriatic arthritis: the PALACE 1 Phase III study

The effectiveness of apremilast in the treatment of adults with active psoriatic arthritis has been evaluated in the PALACE Phase III clinical trial program. The PALACE 1 study compared the efficacy and safety of apremilast 20 mg twice daily and 30 mg twice daily with placebo in 504 patients with active psoriatic arthritis despite treatment with prior conventional and/or biologic therapies or concurrent conventional therapies [60,61]. At baseline, 65% of patients were taking conventional systemic therapies (the majority of whom were taking methotrexate, with a mean dose of 16.6 mg/week; other baseline conventional therapies were leflunomide [mean dose: 17.2 mg/day] and sulfasalazine [mean dose: 2.3 g/day]).

In PALACE 1 (n = 489, per-protocol population), a significantly greater proportion of patients receiving

apremilast 20 mg twice daily (31.3%; p = 0.0140) or 30 mg twice daily (39.8%; p = 0.0001) achieved a 20% improvement in baseline modified ACR20 response compared with placebo (19.4%) at week 16 (primary end point) [60]. Apremilast demonstrated efficacy regardless of prior biologic experience or concomitant use of conventional systemic therapy, although patients who were biologic-naïve showed a higher absolute rate of ACR20 response. Statistically significant and clinically meaningful improvements in various measures of psoriatic arthritis disease activity, including ACR20, ACR50, ACR70, Patient Global Assessment (0 to 100 mm VAS), Physician Global Assessment (0 to 100 mm VAS) and 28-joint count Disease Activity Score (DAS-28), were observed through week 24 [60].

Analysis of efficacy with longer-term treatment suggested sustained response among patients who continued receiving treatment with apremilast through week 52. Figure 5 illustrates the rates of ACR20 response over 52 weeks among patients initially randomized to apremilast and patients initially randomized to placebo and later switched to apremilast. At week 52, 63.0% of patients receiving apremilast 20 mg twice daily and 54.6% receiving apremilast 30 mg twice daily from baseline achieved an ACR20 response [61]. Likewise, patients initially randomized to placebo who were rerandomized to apremilast at weeks 16 or 24 demonstrated ACR20 response rates at week 52 that were consistent with patients randomized to apremilast at baseline (placebo/apremilast 20 mg twice daily: 53.1%; placebo/apremilast 30 mg twice daily: 50.0%) [61].

The safety and tolerability profile of apremilast in PALACE 1 was consistent with that observed in the

ESTEEM studies. In PALACE 1, the majority of adverse events occurred during the first 24 weeks, in which about 50% of placebo patients and about 60% of patients treated with apremilast reported one or more adverse events. The most common adverse events reported for apremilast 30 mg twice daily during the placebo-controlled period were diarrhea (19.0%), nausea (18.5%) and headache (10.7%) [60].

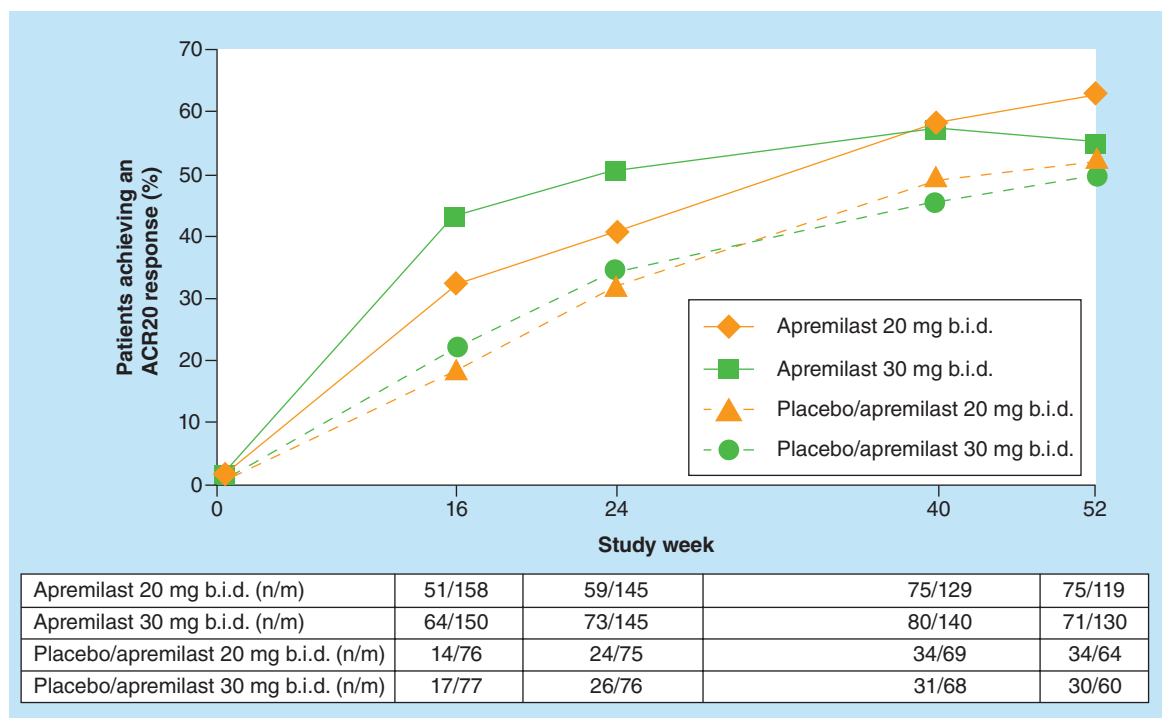
The nature, incidence and severity of adverse events were comparable over the 24-week and 52-week apremilast-exposure periods. Most adverse events (>90%) were mild to moderate in severity, and discontinuation rates due to an adverse event (weeks 0 to  $\geq 52$ ) were less than 10% [61]. One woman receiving apremilast 20 mg twice daily plus methotrexate died during the placebo-controlled phase due to multiorgan failure secondary to preexisting vitamin B<sub>12</sub> deficiency; this was considered unrelated to study medication by the investigator. Marked laboratory abnormalities were infrequent. Between weeks 24 and 52, new reports of diarrhea and nausea were infrequent with either apremilast dose (20 mg twice daily: diarrhea n = 2, nausea n = 5; 30 mg twice daily: diarrhea n = 3, nausea n = 2) [61]. Serious adverse events, including serious infections and possible major cardiac events, were infrequent during

both treatment periods, and incidence was comparable between the treatment groups [61]. No cases of lymphoma, *de novo* tuberculosis or tuberculosis reactivation were reported for the 52-week period. As in the ESTEEM studies, weight loss was associated with apremilast treatment. In PALACE 1, weight loss greater than 5% was observed in 15.8% of patients receiving apremilast 20 mg twice daily and 17.2% of patients receiving apremilast 30 mg twice daily at week 52 [61].

### Clinical implications

A new oral agent for psoriasis and psoriatic arthritis is a welcome addition to the clinic. The clinical utility of apremilast is vast, and in our clinic, we have treated >200 psoriasis patients with apremilast since its approval in 2014. In our experience, patients who are not ready to commit to lifelong maintenance dosing with a biologic or have needle phobia find apremilast an appealing option. In addition, apremilast may be an appropriate treatment option for patients with concomitant psoriatic arthritis. The pivotal clinical trial data support the combination of methotrexate and apremilast as a safe option in patients with psoriatic arthritis.

In our clinic, we have also prescribed apremilast in combination with traditional systemic and biologic



**Figure 5. Patients achieving an ACR20 response in the PALACE 1 study.** Data included are from patients initially randomized to apremilast 20 mg twice daily or apremilast 30 mg twice daily at baseline and from patients initially randomized to placebo and switched to apremilast at week 16 or week 24 (placebo/apremilast). Data are as observed.

ACR20: 20% improvement in baseline modified American College of Rheumatology response; b.i.d.: twice daily; n/m: Number of responders/number of patients with sufficient data for evaluation.

Figure reproduced with permission from [61].

agents for patients with refractory psoriasis. Our goal with these combinations is to improve function and quality of life, and this approach has been successful with many patients. We have used this strategy with success in refractory patients; however, this strategy is not currently in the approved label and warrants further study and scrutiny. To date, no safety or efficacy trials have used apremilast in combination with a biologic to increase therapeutic efficacy. It would be of interest to know whether the combination of apremilast with a biologic has better efficacy than either alone. It remains to be seen whether apremilast decreases the immunogenicity of biologics; however, there are no data, theoretical or otherwise, that we know of to date. Also off label, we have been prescribing apremilast for women of childbearing potential who intend to become pregnant in the near future and intend to abandon therapy during pregnancy. This population of patients may benefit from waiting to start chronic maintenance dosing with a biologic because interruption of therapy may lead to decreased efficacy of the biologic.

Finally, in addition to improving psoriasis and psoriatic arthritis, our goal is to impact our psoriasis patients' lives and improve their comorbidities. As many of our psoriasis patients are obese, it is of interest to us that there was a trend for weight loss in both the psoriasis and psoriatic arthritis clinical trials, as approximately 20% of patients experienced a weight decrease of >5% during long-term exposure to apremilast 30 mg twice daily [62,63]. Discussions among patients and through social media have led to patients coming to our clinic requesting a prescription for the pill that could lead to weight loss and improve their psoriasis and/or psoriatic arthritis symptoms. In addition to treating their psoriasis, apremilast may make an impact on their weight, one of the risk factors contributing to cardiovascular morbidity, and improve their lives – physically, functionally and metabolically – although this remains to be investigated in clinical studies.

In summary, apremilast is an appropriate option, in our opinion, for entry into systemics for the risk adverse, for refractory patients in combination with other therapies and for women of childbearing potential desiring intermittent therapy. Naturally, clinicians should weigh the risks and benefits of treatment with apremilast versus other appropriate treatments, such as biologics, on an individual basis for their patients with psoriasis and/or psoriatic arthritis. The long-term safety and efficacy of apremilast outside of clinical trials remain to be elucidated, and clearly more data are needed to guide clinicians, especially in combining apremilast with other therapies.

## Future perspective

Psoriasis is a serious, chronic disease with significant comorbidities [2,7] that often has profound effects on patients' social functioning, psychological well-being, quality of life and longevity [3,64–65]. Because psoriasis is a heterogeneous condition, impacted by genetic and environmental factors, treatment for plaque psoriasis must be individualized to the patient's needs, with the goal of providing optimal care and improving quality of life.

Apremilast is a novel oral PDE4 inhibitor that has been shown to be well tolerated and efficacious in the treatment of moderate-to-severe plaque psoriasis, as well as in psoriatic arthritis. A number of new biologics (including inhibitors of IL-17 or IL-23) and oral small molecules (with various mechanisms, e.g., Janus kinase inhibitors, anti-IL-23 receptor, IL-12/IL-23 expression inhibitor, calcineurin inhibitor) are currently in Phase II or Phase III trials for the treatment of psoriasis [17,35,66].

Despite substantial advances in the treatment of plaque psoriasis, a number of unmet needs remain. Dermatologists are challenged to engage in more in-depth patient education, better understand patient needs, and remain vigilant for emergent joint disease and possible psoriatic arthritis. Because psoriasis is a complex disease, but many of the currently available treatment options have limitations with respect to efficacy and/or safety, there is a need for other options. Research aimed at improving and streamlining treatment selection for individual patients is ongoing. Elucidation of the exact etiology of psoriatic disease, which requires continued research in the pathophysiology of plaque psoriasis and identification of biomarkers, could aid in predicting optimal therapeutic strategies.

## Disclosure

The opinions and recommendations for clinical use expressed in this article are those of the authors. The authors are fully responsible for the content of this article; no honoraria were provided to the authors for the development of this article. Authors directed all content and editorial decisions.

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## Executive summary

### Background

- Psoriasis is a chronic, immune-mediated, systemic inflammatory disease that is associated with multiple comorbidities and reduced quality of life.

### Apremilast clinical studies

- Apremilast, an oral PDE4 inhibitor, was approved by the US FDA in 2014 and by the European Commission in 2015 for the treatment of psoriasis and psoriatic arthritis.
- Apremilast has been shown to be efficacious and well tolerated in the treatment of moderate-to-severe psoriasis, including difficult-to-treat nail and scalp psoriasis.
- Apremilast also demonstrated significant improvements in pruritus severity and Dermatology Life Quality Index score.

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