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REVIEW ARTICLE

Selective Phosphodiesterase Inhibitors for Psoriasis: Focus on Apremilast

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Abstract Phosphodiesterase (PDE) 4 participates in regulating the inflammatory response by degrading cyclic adenosine 3′,5′-monophosphate (cAMP), a key second messenger. Inhibition of PDE4 increases the intracellular cAMP level, which in turn results in a reduction in inflammatory mediators and an increase in anti-inflammatory mediators. Immune-modulating effects of PDE4 inhibitors have been investigated in a number of inflammatory conditions, such as asthma, atopic dermatitis, chronic obstructive pulmonary disease, Behçet's disease, psoriasis, and psoriatic arthritis. Apremilast, a selective PDE4 inhibitor, has been shown to block the production of pro-inflammatory cytokines (interferon-γ, tumor necrosis factor-α, interleukin [IL]-12, IL-17, and IL-23), which are the key players in the pathogenesis of psoriasis. Increased intracellular cAMP levels result in a range of anti-inflammatory effects on numerous cell lines. A decrease in pro-inflammatory activity has been shown to result in a reduced psoriasiform response in preclinical in vivo models of psoriasis, and reduction of biologic activity in a pilot study in humans. The efficacy and safety of apremilast in the treatment of psoriasis have been demonstrated in phase II and III clinical trials. Apremilast demonstrated efficacy in reducing the severity of moderate to severe plaque psoriasis. Treatment with apremilast was well tolerated, with generally mild gastrointestinal complaints, which occurred early in the course of the treatment and resolved over time, and there was no requirement for laboratory test monitoring. These results make apremilast an attractive therapeutic option for plaque psoriasis.

Key Points

Apremilast, a selective phosphodiesterase 4 inhibitor, has been shown to reduce the production of pro-inflammatory cytokines and promote the production of anti-inflammatory cytokines.

Apremilast has proven efficacy and safety in the treatment of psoriasis and psoriatic arthritis in phase II and III studies.

Apremilast treatment is generally well tolerated and is a promising new treatment for psoriatic disease.

1 Introduction

Phosphodiesterase (PDE) 4 is involved in regulating the inflammatory response by degrading cyclic adenosine 3′,5′-monophosphate (cAMP), a key second messenger [1, 2]. Degradation of cAMP to adenosine monophosphate (AMP) reduces protein kinase A activity, leading to production of pro-inflammatory mediators (e.g., tumor necrosis factor [TNF]-α and interleukin [IL]-23) and inhibition of anti-inflammatory cytokines (e.g., IL-10) [1, 2].

Selective expression of PDE4 in cells of the immune system leads to their activation and upregulation in chronic plaque psoriasis and other inflammatory conditions [2]. In

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addition to its expression in immune cells, PDE4 is also expressed in structural cell types, such as keratinocytes, vascular endothelium, and synovium [2]. Psoriasis is a complex disease, manifested in the skin, joints, and possibly the bowel. Each of these manifestations is expressed through an inflammatory, immune-mediated process [3].

PDE4 inhibitors block the cAMP-degrading action of PDE4 by competitive binding to the cAMP catalytic site, which results in a reduction in T helper (T_h) 1, T_h2, and T_h17 immune responses [4]. As a result of PDE4 inhibition, there is an increase in the intracellular cAMP level, which leads to a reduction in inflammatory mediators and increase in anti-inflammatory mediators [1, 5]. The immune-modulating effects of PDE4 inhibitors have been investigated in a number of inflammatory conditions, such as asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis, Behçet's disease, psoriasis, and psoriatic arthritis (PsA) [1, 2, 4, 6].

Apremilast (CC-10004, Otezla™; Celgene Corporation) is a selective PDE4 inhibitor, which has been shown to block the production of the pro-inflammatory cytokines interferon (IFN)-γ, TNF-α, IL-12, IL-17, and IL-23—all major players in the pathogenesis of psoriasis. Apremilast was shown, through early-phase trials, to result in (1) a range of anti-inflammatory effects on a variety of cell lines in vitro; (2) a reduction in the psoriasiform response in a preclinical model of psoriasis in vivo; [7] and (3) a reduction of biologic activity in a pilot study in humans [8].

Apremilast binds to the catalytic site of the PDE4 enzyme and blocks degradation of cAMP [9]. Elevating intracellular cAMP, apremilast induces phosphorylation of the protein kinase A substrates cAMP responsive element binding protein (CREB), activates activating transcription factor (ATF)-1, and inhibits the transcriptional activity of nuclear factor (NF)-κB. Activation of ATF-1 and inhibition of NF-kB result in up- and downregulation of several different genes induced via toll-like receptor (TLR) 4 in monocytes and T cells [2, 10].

Apremilast has been evaluated in the treatment of psoriasis and PsA. The efficacy and safety of apremilast in the treatment of psoriasis have been demonstrated in phase II [11–14] and phase III clinical trials (ESTEEM [Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis] 1 and 2 [15, 16] and LIBERATE [Evaluation in a Placebo-Controlled Study of Oral Apremilast and Etanercept in Plaque Psoriasis]) [17]. In addition to psoriasis, the efficacy and safety of apremilast were also evaluated in the phase III PALACE (Psoriatic Arthritis Long-Term Assessment of Clinical Efficacy) clinical trial program in patients with PsA, which is discussed briefly in this review [18–22].

2 Apremilast in Plaque Psoriasis: Phase II Trials

The efficacy of apremilast has been evaluated in phase II, double-blind, randomized, placebo-controlled clinical trials [11–14].

In a 12-week trial ($n = 259$), the Psoriasis Area and Severity Index (PASI) was reduced by 75 % (PASI-75) in 24.4 % of patients treated with apremilast 20 mg twice daily (BID) versus 10.3 % of patients treated with placebo. A dose–response relationship was observed, with mean percentage PASI reductions from baseline of 52.1 % with apremilast 20 mg BID, 30.3 % with apremilast 20 mg once daily (OD), and 17.4 % with placebo [11].

In a phase IIb crossover trial ($n = 352$), Papp et al. [12] compared apremilast 10 mg BID, apremilast 20 mg BID, apremilast 30 mg BID, and placebo BID for 16 weeks. After 16 weeks, patients randomized to receive placebo were assigned to receive apremilast 20 mg BID or 30 mg BID up to 24 weeks. At 16 weeks, the primary end point of PASI-75 was observed in 11 % of the apremilast 10 mg BID group, 29 % of the apremilast 20 mg BID group, 41 % of the apremilast 30 mg BID group, and 6 % of the placebo group. At week 16, the difference between apremilast 10 mg BID and placebo was not significant.

In addition, patients treated with apremilast reported significant improvements in patient-reported quality-of-life outcomes, which included the Dermatology Life Quality Index (DLQI), the pruritus Visual Analog Scale (VAS), and the Physical Component Summary (PCS), Mental Component Summary (MCS), and individual domain scores of the Short-Form (SF)-36 and SF-6D health utilities. Patients receiving apremilast 30 mg BID seemed to have the most benefit [13].

Apremilast demonstrated a favorable safety profile, with mild to moderate adverse events (AEs), which included headache, nausea, upper respiratory tract infection, and diarrhea. None of the phase II trials reported significant changes in laboratory test values [12].

In an open-label, phase II study ($n = 30$), 46.7 % of patients treated with apremilast 20 mg BID achieved PASI-50, 30.0 % achieved PASI-75, and 13.3 % achieved PASI-90 (a mean improvement of 59.0 %) at week 12. Patients who remained on apremilast 20 mg BID during the 12-week extension phase ($n = 4$) maintained PASI-75 or greater through week 24. In addition, the pharmacodynamic analysis results supported the biologic activity of apremilast in psoriasis. A median reduction of 23 % ($p = 0.080$) in epidermal thickness was reported at week 4 compared with baseline. Epidermal hyperplasia and/or keratin 16 (K16; a marker of keratinocyte proliferation) was seen in 10 patients. A median reduction in epidermal thickness of 34 % ($p = 0.083$) was seen at week 12

compared with baseline. Histologic disease improvement was seen in nine patients, including five with no detectable K16 [14].

3 Apremilast in Plaque Psoriasis: Phase III Trials

The safety and efficacy of apremilast in patients with moderate to severe plaque psoriasis have been evaluated in three phase III clinical trials. Apremilast was compared with placebo in ESTEEM 1 and 2 [15, 16] and with etanercept and placebo in LIBERATE [17].

3.1 ESTEEM 1 and 2: 16-Week and 32-Week Efficacy Data

Two phase III, randomized, placebo-controlled trials, ESTEEM 1 ($n = 844$) [15] and ESTEEM 2 ($n = 413$) [16], evaluated the efficacy and safety of apremilast 30 mg BID in patients with moderate to severe plaque psoriasis (a PASI score ≥12), body surface area involvement (BSA) ≥10 %, and a Static Physician's Global Assessment (sPGA) score ≥3.

In ESTEEM 1 and 2, patients were randomized 2:1 to receive apremilast 30 mg BID ($n = 562$ and $n = 282$, respectively) or placebo ($n = 274$ and $n = 137$, respectively). At week 16, all patients in the placebo group were switched to apremilast 30 mg BID through week 32 [15, 16].

At week 32, all patients who had been randomized to receive apremilast 30 mg BID at baseline and subsequently achieved PASI-75 (in ESTEEM 1) or PASI-50 (in ESTEEM 2) were randomized (1:1, blinded) to continue receiving apremilast 30 mg BID or to receive placebo. All subject resumed treatment with apremilast at week 52, regardless of response [15, 16].

Treatment with apremilast was re-introduced to patients at the time of loss of effect—defined as the time of loss of 75 % (in ESTEEM 1) and loss of 50 % (in ESTEEM 2) of the PASI improvement obtained at week 32 relative to baseline—but no later than week 52. Patients who were initially receiving placebo or were randomized to receive apremilast 30 mg BID who did not attain PASI-75 (in ESTEEM 1) or PASI-50 (in ESTEEM 2) were permitted to add topicals and/or ultraviolet B phototherapy (UVB) at week 32, at the investigator's discretion [15, 16]. The study design of the ESTEEM clinical trial program is shown in Fig. 1.

3.1.1 PASI and sPGA

At week 16, significant improvements in achievement of PASI-75 and PASI-50 and in sPGA scores were seen with apremilast 30 mg BID in both ESTEEM 1 and ESTEEM 2 ($p < 0.0001$ for all). The results for PASI-75 (the primary end point), PASI-50, and sPGA responses at week 16 are shown in Fig. 2 [15, 16].

3.1.2 NAPSI-50, ScPGA, and PPPGA

Improvements with apremilast 30 mg BID were also seen in the Nail Psoriasis Severity Index (NAPSI), with greater proportions of patients achieving a NAPSI improvement ≥50 % (NAPSI-50) from baseline, a Scalp Physician's Global Assessment (ScPGA) score of 0–1, and a Palmoplantar Psoriasis Physician's Global Assessment (PPPGA) score of 0–1.

At week 16, significantly greater proportions of patients achieved NAPSI-50 with apremilast 30 mg BID than with placebo (33.3 % versus 14.9 % in ESTEEM 1 and 44.6 % versus 18.7 % in ESTEEM 2; $p < 0.0001$ for both) [16, 23]. At week 32, there was a continued improvement in those patients who remained on apremilast 30 mg BID, with 45.2 % (in ESTEEM 1) and 55.4 % (in ESTEEM 2) achieving a NAPSI-50 response [23]. In those patients who switched from placebo to apremilast 30 mg BID at week 16, the week-32 NAPSI-50 rates were reported as 34.9 % (in ESTEEM 1) and 52.0 % (in ESTEEM 2). At week 52, NAPSI-50 was maintained with apremilast in 70.7 % (in ESTEEM 1) and 68.6 % (in ESTEEM 2) of patients initially randomized to receive apremilast 30 mg BID and in 64.1 % (in ESTEEM 1) and 69.0 % (in ESTEEM 2) of those initially randomized to receive placebo (Table 1) [23].

In patients with an ScPGA score ≥3 at baseline, the percentages of patients reaching a score of 0–1 (clear or minimal scalp involvement) at week 16 were 46.5 % with apremilast 30 mg BID versus 17.5 % with placebo in ESTEEM 1, and 40.9 versus 17.2 %, respectively, in ESTEEM 2 ($p < 0.0001$) [16, 23].

In those patients who remained on apremilast 30 mg BID up to week 32, the percentages reaching an ScPGA score of 0–1 remained stable at 37.4 % in ESTEEM 1 and 32.4 % in ESTEEM 2 [23]. Those patients who switched from placebo to apremilast 30 mg BID showed improvements, with 43.6 % in ESTEEM 1 and 50.7 % in ESTEEM 2 achieving an ScPGA score of 0–1 at week 32. At week 52, achievement of an ScPGA score of 0–1 was maintained with apremilast in 83.3 % (in ESTEEM 1) and 62.5 % (in ESTEEM 2) of patients initially randomized to receive apremilast 30 mg BID and in 64.1 % (in ESTEEM 1) and 53.5 % (in ESTEEM 2) of those initially randomized to receive placebo (Table 1) [23].

The proportion of patients achieving a PPPGA score of 0–1 at week 16 has not yet been reported from ESTEEM 1; however, in ESTEEM 2, 65.4 % of patients treated with

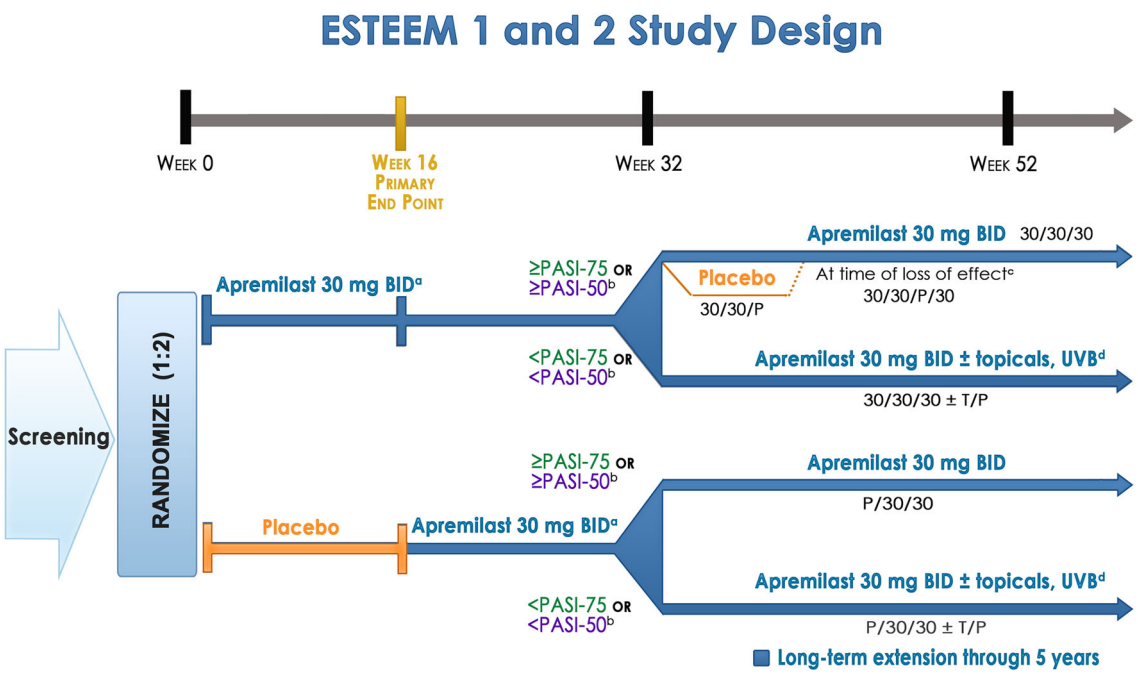

Fig. 1 ESTEEM [Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis] 1 and 2 study design [15, 16]. [a]Doses of apremilast were titrated during the first week of administration. [b]A responder was defined as a patient achieving a ≥75 % reduction from their baseline Psoriasis Area and Severity Index (PASI) score (≥PASI-75) in ESTEEM 1 or ≥PASI-50 in ESTEEM 2 at week 32. [c]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. [d]At week 32, patients had the option of adding topical therapy and/or ultraviolet B (UVB) phototherapy (T/P). The decision could made only at week 32 but did not need to be initiated at that visit. *30* apremilast 30 mg BID, *BID* twice daily, *P* placebo

apremilast 30 mg BID achieved a PPPGA score of 0–1 (clear or almost clear), versus 31.3 % of patients treated with placebo ($p = 0.0315$) [16].

In those patients who remained on apremilast 30 mg BID up to week 32, the percentage reaching a PPPGA score of 0–1 remained stable at 53.8 % in ESTEEM 2 [24]. Those patients who switched from placebo to apremilast 30 mg BID showed improvements, with 69.3 % achieving a PPPGA score of 0–1 at week 32 in ESTEEM 2 (Table 1) [24]. The proportions of patients achieving a PPPGA score of 0–1 at week 32 in ESTEEM 1 have not yet been published.

3.1.3 DLQI and VAS

In ESTEEM 1 and 2, apremilast 30 mg BID was also associated with a significantly greater proportion of patients achieving a minimum clinically important difference (MCID) in DLQI and pruritus VAS scores at week 16 compared with baseline ($p < 0.0001$ versus placebo) [15, 16, 25]. Over 90 % of patients receiving apremilast 30 mg BID who were PASI-75 responders at week 16 achieved an MCID in DLQI and pruritus VAS (Table 1) [16].

Of the patients who received apremilast 30 mg BID for 16 weeks in ESTEEM 1, 70.2 % achieved a ≥5-point improvement in DLQI, versus 33.5 % of those receiving placebo ($p < 0.0001$) [15]. In ESTEEM 2, 70.8 % of patients receiving apremilast 30 mg BID achieved a ≥5-point improvement in DLQI at 16 weeks, versus 42.9 % of those receiving placebo ($p < 0.0001$) [16]. At week 16, the decrease in the DLQI score was significantly greater with apremilast 30 mg BID than with placebo (ESTEEM 1 DLQI score: −6.6 versus −2.1; ESTEEM 2 DLQI score: −6.7 versus −2.8; both $p < 0.0001$) [16]. A significant and consistent decrease in pruritus with apremilast 30 mg BID compared with placebo was reported as early as week 2 in both ESTEEM 1 and 2. Pruritus, as measured by a VAS score (in millimeters), improved in severity by almost 50 % at week 16 compared with baseline ($p < 0.0001$) [16].

Treatment with apremilast 30 mg BID also had a significant impact on work productivity in patients with moderate to severe plaque psoriasis. Patients reaching PASI-75 had a significant improvement in work productivity, compared with those receiving placebo (−0.816 versus −0.403, respectively; $p = 0.006$) [26].

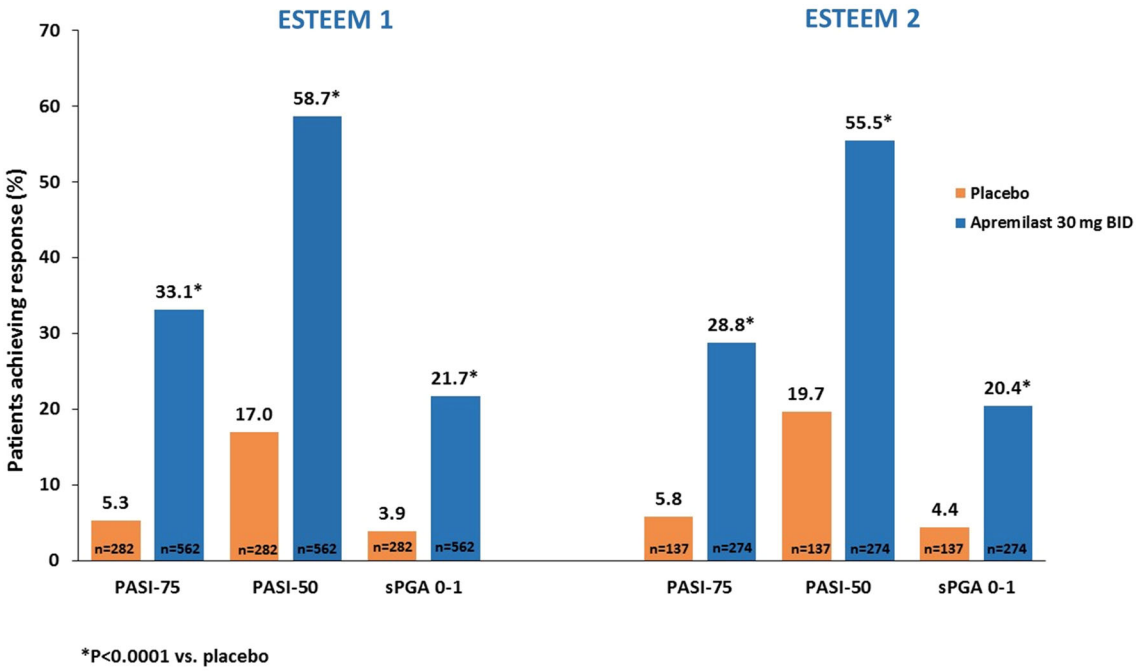

Fig. 2 ESTEEM [Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis] 1 and 2: patients achieving a 75 % reduction from their baseline Psoriasis Area and Severity Index score (PASI-75; the primary end point), PASI-50, and Static Physician's Global Assessment (sPGA) response (a score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline) with apremilast 30 mg twice daily (BID) versus placebo at week 16 [15, 16]. Full analysis set, last observation carried forward: $n = 844$ in ESTEEM 1 and $n = 411$ in ESTEEM 2

3.2 ESTEEM 1 and 2: 52-Week Efficacy Data

In ESTEEM 1, the time to loss of PASI improvement and loss of PASI-75 response were evaluated at 52 weeks. PASI-75 response was regained by 70.3 % of patients who were re-randomized to placebo and then re-initiated on apremilast 30 mg BID. The re-treatment period ranged from 3.4 to 22.1 weeks. The median times to loss of PASI-75 response were 5.1 and 17.7 weeks for patients re-randomized to placebo and apremilast 30 mg BID, respectively. In patients who were continuously treated with apremilast 30 mg BID from day 0 and were PASI-75 responders at week 32, a mean change in the PASI score of −81 % from baseline was observed at week 52 [15].

In ESTEEM 2 week-32 PASI-50 responders, the NAPSI-50, ScPGA score 0–1 and PPPGA score 0–1 achievements were sustained up to week 52 (NAPSI-50: 68.6 versus 64.3 % in the apremilast versus placebo groups; ScPGA score 0–1: 62.5 versus 53.5 %; PPPGA score 0–1: 100 versus 75 %) [27].

3.3 ESTEEM 1 and 2: Safety Data

Apremilast 30 mg BID had an acceptable safety and tolerability profile for up to 104 weeks, with most AEs being mild or moderate in severity [28, 29]. During the placebo-controlled and apremilast-exposure period, the most frequently reported AEs were diarrhea, upper respiratory tract infection, nausea, nasopharyngitis, tension headache, and headache (Table 2). The discontinuation rates for diarrhea and nausea were <2 % each in the apremilast 30 mg BID group through week 52, and few patients discontinued apremilast because of AEs during 52–104 weeks [28, 29].

In ESTEEM 1, apremilast 30 mg BID had a generally well-tolerated profile for up to 104 weeks, without increases in the incidence of AEs over time, with most AEs being of mild or moderate severity, which did not lead to discontinuation [15, 29].

The majority of AEs in ESTEEM 2 were also mild or moderate in severity. The discontinuation rates due to AEs were low during weeks 0–16 (apremilast: 5.5 %; placebo: 5.1 %). Some patients treated with apremilast had diarrhea and nausea, which were mostly mild in severity. The highest incidence of diarrhea and nausea was observed during the first week of apremilast administration and generally resolved within 1 month, with few patients reporting use of concomitant medications to control symptoms [16].

In ESTEEM 1 and 2, serious AEs (serious infections, malignancies, and cardiovascular events) and laboratory test value changes were consistent with those reported in previous apremilast studies. Overall, serious AE rates were low across treatment groups and laboratory test values

Table 1 ESTEEM [Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis] 1 and 2: Nail Psoriasis Severity Index (NAPSI), Scalp Physician's Global Assessment (ScPGA), Palmoplantar Psoriasis Physician's Global Assessment (PPPGA), Dermatology Life Quality Index (DLQI) and pruritus Visual Analog Scale (VAS) scores at weeks 16, 32 and 52 [16, 23–25, 27]

Scores	ESTEEM 1		ESTEEM 2		ESTEEM 1 and 2			
	PBO-controlled period, weeks 0–16 [23]		PBO-controlled period, weeks 0–16 [16, 23]		APR-exposure period, weeks 16–32 [23]		APR-exposure period, weeks 32–52 [23, 24, 27]	
	PBO, $n = 282$	APR 30, $n = 562$	PBO, $n = 137$	ARP 30, $n = 274$	APR 30/APR 30	PBO/APR 30	APR 30/APR 30	PBO/APR 30
NAPSI [% achieving NAPSI-50]	14.9	33.3*	18.7	44.6*	45.2 (ESTEEM 1)	34.9 (ESTEEM 1)	70.7 (ESTEEM 1)	64.1 (ESTEEM 1)
					55.4 (ESTEEM 2)	52.0 (ESTEEM 2)	68.6 (ESTEEM 2)	69.0 (ESTEEM 2)
ScPGA [% achieving score 0–1][a]	17.5	46.5*	17.2	40.9*	37.4 (ESTEEM 1)	43.6 (ESTEEM 1)	83.3 (ESTEEM 1)	64.1 (ESTEEM 1)
					32.4 (ESTEEM 2)	50.7 (ESTEEM 2)	62.5 (ESTEEM 2)	53.5 (ESTEEM 2)
PPPGA [% achieving clear or almost clear score]	NR	NR	31.3	65.4†	53.8	69.3	100	75
DLQI [% achieving ≥5-point improvement]	33.5	70.2*	42.9	70.8*	–	–	–	–
Pruritus VAS score [% achieving MCID][25]	33.7	70.6*	40.9	67.5*	–	–	–	–

APR apremilast, *APR 30* apremilast 30 mg twice daily, *MCID* minimum clinically important difference, *NAPSI-50* ≥50 % improvement from baseline NAPSI, *NR* not reported, *PBO* placebo

* $p < 0.0001$

† $p = 0.0315$

[a] In patients with baseline scores ≥3 [16, 23]

Table 2 ESTEEM [Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis] 1 and 2: adverse events reported in ≥5 % of any treatment group [15, 16, 29]

Adverse event	ESTEEM 1				ESTEEM 2	
	PBO-controlled period, weeks 0–16 [15]		APR-exposure period, weeks 0–52 [29][a]	APR-exposure period, weeks 52–104 [29][a]	PBO-controlled period, weeks 0–16 [16]	
	PBO, $n = 282$	APR 30, $n = 560$	APR 30, $n = 804$	APR 30, $n = 444$	PBO, $n = 136$	APR 30, $n = 272$
Diarrhea [%]	7.1	18.8	18.7	1.8	5.9	15.8
Nausea [%]	6.7	15.7	15.2	0.7	6.6	18.4
Upper respiratory tract infection [%]	7.4	10.2	18.2	9.7		
Nasopharyngitis [%]	8.2	7.3	13.7	6.8	4.4	7.4
Tension headache [%]	4.3	7.3	9.6	1.6	1.5	7.4
Headache [%]	4.6	5.5	6.5	0.7	0.7	6.3
Vomiting [%]	–	–	–	–	3.7	5.1
Psoriasis [%]	–	–	–	–	5.1	1.5

APR apremilast; *APR 30* apremilast 30 mg twice daily, *PBO* placebo

[a] The apremilast-exposure period (weeks 0–52 and 52–104) included all patients who received apremilast 30 mg twice daily, regardless of when treatment was initiated [15, 29]

were not significantly affected. No increase in incidence rates was noted with longer-term exposure to apremilast between 52 and 104 weeks [15, 16, 29].

No new safety signals for apremilast were identified in the second year of exposure as compared with the first [29].

Table 3 summarizes AEs reported in ≥5 % of patients during weeks 0–16 and over the entire period of exposure (weeks 0–104) to either placebo or apremilast 30 mg BID in ESTEEM 1 and 2 [15, 16, 29].

3.4 LIBERATE: 16-Week and 32-Week Efficacy Data

The phase IIIb LIBERATE clinical trial evaluated the efficacy and safety of apremilast 30 mg BID compared with placebo (the primary end point), and etanercept 50 mg once weekly (QW) compared with placebo (the secondary end point), at week 16 in patients with moderate to severe plaque psoriasis. The safety of switching from etanercept 50 mg QW to apremilast 30 mg BID at week 16 was compared with apremilast 30 mg BID from baseline [17].

During the 16-week placebo-controlled phase, patients were randomized 1:1:1 to receive apremilast 30 mg BID ($n = 83$), etanercept 50 mg QW ($n = 83$), or placebo ($n = 84$). At week 16, all patients in the placebo and etanercept groups were switched to apremilast 30 mg BID through week 32 [17]. The study design of the LIBERATE clinical trial is shown in Fig. 3.

Table 3 LIBERATE [Evaluation in a Placebo-Controlled Study of Oral Apremilast and Etanercept in Plaque Psoriasis]: adverse events reported in ≥5 % of any treatment group [17]

Adverse event[a]	PBO-controlled phase, weeks 0–16[b]			Extension phase, weeks 16–32[b]		
	PBO, $n = 84$	APR 30, $n = 83$	ETN 50, $n = 83$	PBO/APR, $n = 73$	APR/APR, $n = 74$	ETN/APR, $n = 79$
Nausea [*n* (%)]	2 (2.4)	9 (10.8)	4 (4.8)	3 (4.1)	2 (2.7)	5 (6.3)
Diarrhea [*n* (%)]	7 (8.3)	9 (10.8)	1 (1.2)	12 (16.4)	3 (4.1)	6 (7.6)
Vomiting [*n* (%)]	2 (2.4)	4 (4.8)	2 (2.4)	2 (2.7)	0 (0.0)	2 (2.5)
Headache [*n* (%)]	5 (6.0)	11 (13.3)	5 (6.0)	2 (2.7)	0 (0.0)	1 (1.3)
Tension headache [*n* (%)]	4 (4.8)	5 (6.0)	3 (3.6)	3 (4.1)	0 (0.0)	0 (0.0)

APR apremilast, *APR 30* apremilast 30 mg twice daily, *ETN* etanercept, *ETN* etanercept 50 mg once weekly, *PBO* placebo

[a] Each patient is counted only once for each applicable category

[b] Safety population

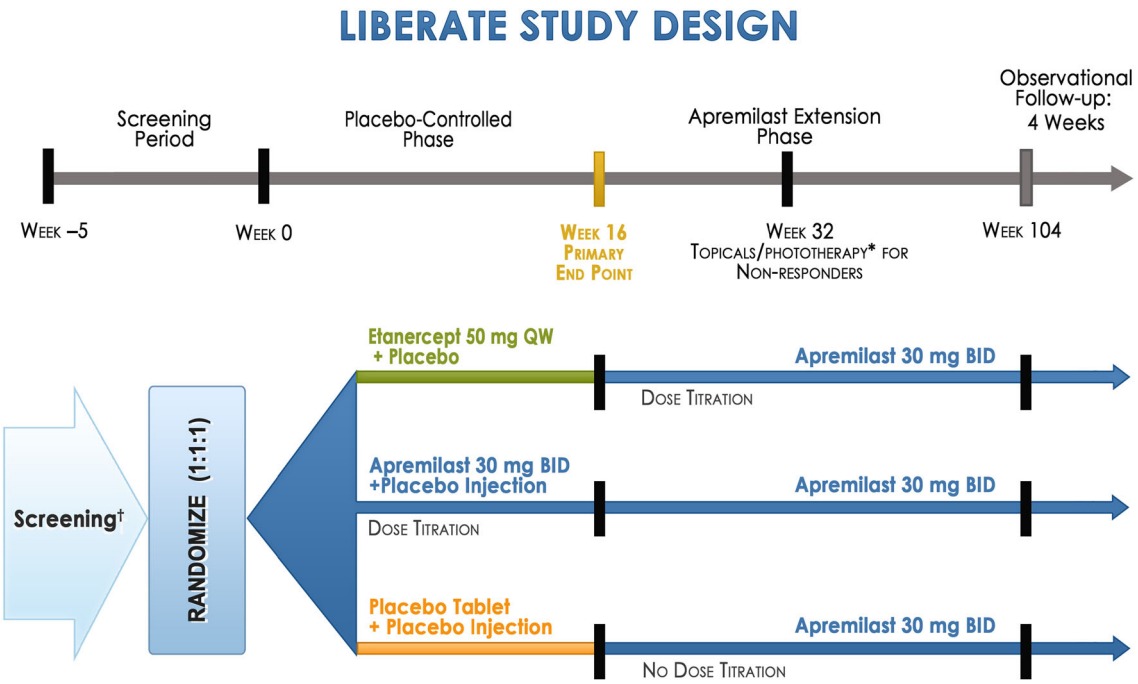

Fig. 3 LIBERATE [Evaluation in a Placebo-Controlled Study of Oral Apremilast and Etanercept in Plaque Psoriasis] study design [17]. *Starting at week 32, all non-responders (patients achieving a <50 % reduction from their baseline Psoriasis Area and Severity Index score) had the option of adding topical therapy and/or phototherapy (excluding oral psoralen and ultraviolet A) to their treatment regimen. †Patients were stratified according to their calculated body mass index (BMI) categories at screening (BMI ≥30 kg/m^2 or BMI 30 kg/m^2). *LOCF* last observation carried forward, *BID* twice daily, *QW* once weekly

3.4.1 *PASI and sPGA*

Apremilast 30 mg BID and etanercept 50 mg QW demonstrated statistically significant improvements in the PASI-75 response at week 16, compared with placebo ($p < 0.0001$). The PASI-75 response achieved at week 16 was sustained through week 32 with apremilast 30 mg BID in the active treatment arms. Improvements in the mean PASI score were observed as early as week 2. Post hoc analyses revealed non-significant differences ($p = 0.2565$) between apremilast 30 mg BID and etanercept 50 mg QW. More patients achieved PASI-75 at week 32 than at week 16 with apremilast treatment. The percentages of patients achieving a PASI-75 response at weeks 16 and 32 are shown in Fig. 4 [17].

Higher percentages of patients in the apremilast 30 mg BID and etanercept 50 mg QW groups achieved an sPGA score of 0–1 at week 16, compared with the placebo group ($p = 0.0005$ for placebo versus apremilast; $p < 0.0001$ for placebo versus etanercept). The response to active treatment was sustained with apremilast at week 32 (Fig. 5) [17].

3.4.2 *DLQI*

The mean change from baseline in the DLQI total score at week 16 was greater in patients treated with apremilast 30 mg BID (−8.3) or etanercept 50 mg QW (−7.8) than in those treated with placebo (−3.8). The improvement in the DLQI total score was sustained with apremilast 30 mg BID through week 32 [17].

3.5 LIBERATE: Safety Data

The safety profile of apremilast was acceptable and similar among patients who switched from etanercept to apremilast and those who received apremilast in the placebo-controlled phase [17]. No new safety signals were reported in comparison with the ESTEEM program and phase II data. Table 3 summarizes AEs reported in ≥5 % of patients during the placebo-controlled phase (weeks 0–16) and the extension phase (weeks 0–52) of either placebo, apremilast 30 mg BID, or etanercept 50 mg QW [17].

3.6 PALACE: 24-Week Efficacy Data in Psoriatic Arthritis

In patients with PsA, the efficacy and safety of apremilast were evaluated in the phase III PALACE clinical trial program [18–22]. To date, only the results of a 24-week placebo-controlled phase and the 52-week results of PALACE 1 have been published [20, 21]. In this trial, patients with active PsA ($n = 504$) were randomized

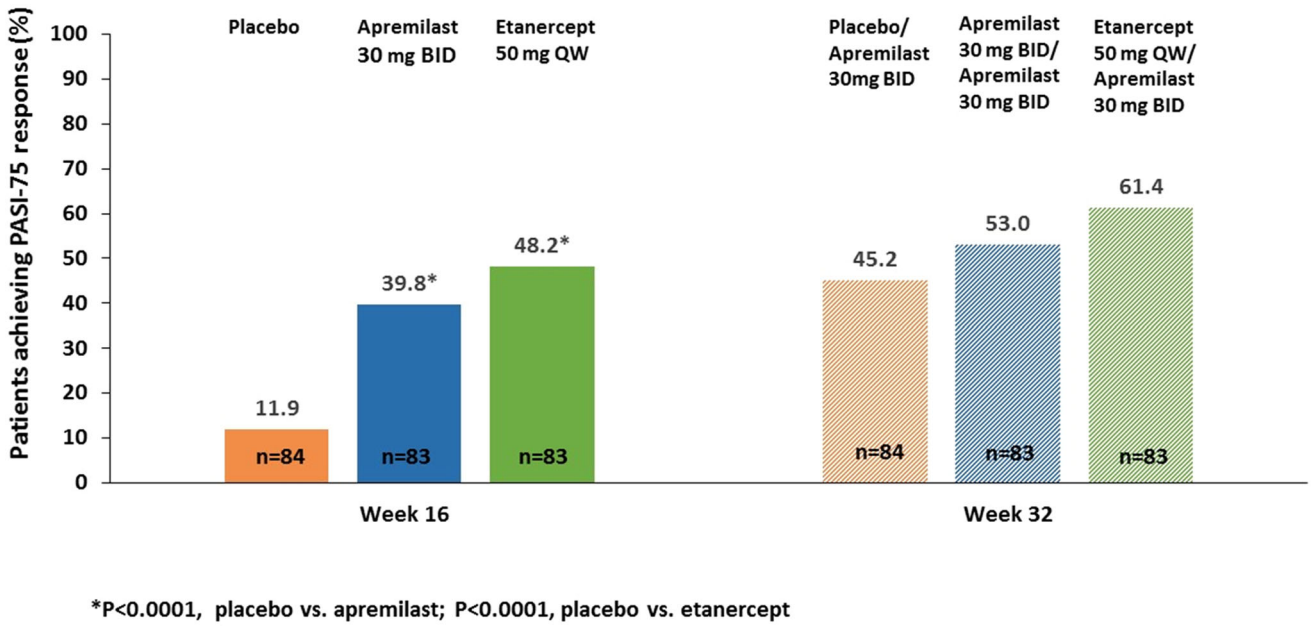

Fig. 4 LIBERATE [Evaluation in a Placebo-Controlled Study of Oral Apremilast and Etanercept in Plaque Psoriasis]: percentages of patients achieving a 75 % reduction from their baseline Psoriasis Area and Severity Index score (PASI-75) response at weeks 16 and 32 [17]. Modified intent-to-treat population, last observation carried forward. *BID* twice daily, *QW* once weekly

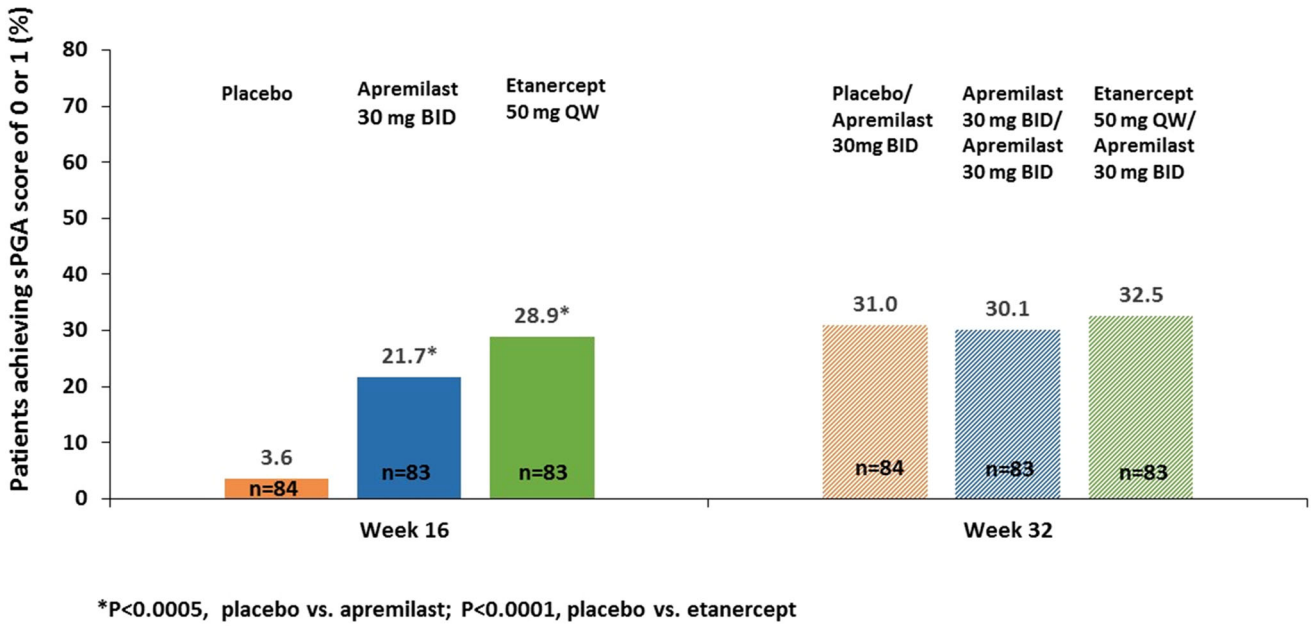

Fig. 5 LIBERATE [Evaluation in a Placebo-Controlled Study of Oral Apremilast and Etanercept in Plaque Psoriasis]: percentages of patients with a Static Physician's Global Assessment (sPGA) score ≥3 (moderate to very severe) at baseline who achieved a score of 0–1 at weeks 16 and 32 [17]. Modified intent-to-treat population, last observation carried forward. *BID* twice daily, *QW* once weekly

(1:1:1) to receive apremilast 20 mg BID, apremilast 30 mg BID, or placebo. At week 16, patients who did not have a ≥20 % reduction in swollen and tender joint counts were re-randomized equally to receive either apremilast dose if they were initially randomized to placebo, or they remained on their initial apremilast dose. Patients on background concomitant disease-modifying antirheumatic drugs (DMARDs) continued to receive stable doses. The primary end point was the proportion of patients achieving a 20 % improvement in the modified American College of Rheumatology (ACR) response criteria (ACR20) at week 16 [18, 19].

More patients receiving apremilast 20 mg BID (30.4 %; $p = 0.0166$) or apremilast 30 mg BID (38.1 %; $p = 0.0001$) achieved an ACR20 response than patients receiving placebo (19.0 %) at week 16 [19]. At week 24, an ACR20 response rate of 45.3 % was observed in patients treated with apremilast 30 mg BID, independent of their responses at week 16 [19]. In patients receiving apremilast continuously for 52 weeks ($n = 254$), an ACR20 response was observed at week 52 in 63.0 % of those receiving 20 mg BID and in 54.6 % of those receiving 30 mg BID [19]. Sustained rates of ACR20 response was seen in patients who continued receiving apremilast over 52 weeks; at week 52, 63.0 % of patients who had received apremilast 20 mg BID from baseline and 54.6 % of those who had received 30 mg BID achieved ACR20 [19]. The presentation of in-depth results for PsA is beyond the scope of this review.

4 Warnings and Precautions: Additional Data from Studies in Psoriasis

4.1 Weight Loss

Decreases of 5–10 % of body weight were reported in 12 % of patients with psoriasis treated with apremilast 30 mg BID versus 5 % of those treated with placebo during the controlled period of the trials. Weight loss ≥10 % of body weight occurred in 2 % of patients treated with apremilast 30 mg BID versus 1 % of the placebo group [30].

In a pooled analysis, weight loss was reported as an AE event in 1.4 % of patients treated with apremilast 30 mg BID (weeks 0–52) versus 0.2 % of patients treated with placebo (weeks 0–16). However, there were no reports of a serious AE of weight loss in any patients (weeks 0–52). Two patients (0.2 %) receiving apremilast 30 mg BID discontinued treatment because of weight loss (weeks 0–52). There was no link between weight loss and diarrhea or nausea/vomiting [31]. On the basis of these data, it is recommended that patients treated with apremilast have their weight monitored [30].

In ESTEEM 1, weight loss was reported as an AE in 1.0 % of patients (weeks 0–52) and in 0.5 % (weeks 52–104); none were serious AEs. The majority of patients receiving apremilast 30 mg BID maintained their body weight within ±5 % of baseline, regardless of the duration of exposure (76.1 %, 0–52 weeks; 65.1 %, 52–104 weeks). There was no increase in the number of patients with weight loss >5 % from 52 to 104 weeks [29].

In a pooled analysis of ESTEEM 1 and 2, the long-term mean (median) change in weight from baseline was −1.99 kg (−1.40 kg) for apremilast 30 mg BID at week 52 [31].

4.2 Depression

Patients with psoriasis are known to have increased risks of anxiety, depression and suicidality [32].

While treatment with another PDE4 inhibitor, roflumilast, has been associated with a risk of depression in patients with COPD [33], data from clinical trials assessing apremilast do not suggest an increase in depression nor in suicidal ideation in subjects treated with apremilast versus those treated with placebo [34].

In a pooled analysis, treatment-emergent depression, as self-reported by patients, was seen as an AE in 1.9 % of patients treated with apremilast 30 mg BID (weeks 0–52). Most depression AEs were mild or moderate in severity in patients treated with apremilast 30 mg BID, while one patient (0.1 %) had a severe depression AE during long-term treatment with apremilast 30 mg BID. One patient (0.1 %) discontinued treatment because of depression during long-term apremilast 30 mg BID exposure (weeks 0–52). A review of the medical history at baseline revealed that 13.6 % of patients had a history of depression at study entry [35].

The rate of depression reported as a treatment-emergent AE with apremilast was lower than the background rate in the psoriasis population (≥10 %). While numerical imbalances of depression were observed in the 16-week controlled data, the long-term, uncontrolled data did not suggest an increased risk of psychiatric disorders, including depression. Further, there was no increase in suicidality with apremilast 30 mg BID compared with placebo (one patient receiving placebo committed suicide, and one patient receiving apremilast 30 mg BID attempted suicide). On the basis of a comprehensive analysis of clinical trials of apremilast and the published literature on psoriasis, there is no evidence of an increased risk of psychiatric events, including suicidality, with the use of apremilast [34].

4.3 Renal Impairment

The dose of apremilast should be reduced to 30 mg OD in patients with severe renal impairment (creatinine clearance <30 mL/min) [30].

4.4 Drug Interactions

The use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, or phenytoin) with apremilast is not recommended. It has been shown that co-administration of the strong cytochrome P450 enzyme inducer rifampin results in a reduction in systemic exposure of apremilast, which may result in a loss of its efficacy [30].

5 Expert Opinion

Presently approved in the USA, Canada and the EU, apremilast provides a welcome addition to the basket of therapeutic options. Traditional treatments for psoriasis—phototherapy, methotrexate, cyclosporine and acitretin—are burdened by unpredictable AEs and predictable end-organ toxicity. And compared with the traditional agents, treatment with apremilast is relatively easy: there is no need to screen for hepatitis B or tuberculosis, no laboratory test monitoring, no apparent risk of end-organ toxicity and, for the most part, only minor issues surrounding tolerability. Few patients discontinue apremilast because of gastrointestinal intolerance. On the basis of its safety alone, apremilast is likely to be accepted by patients and prescribers.

With efficacy comparable to that of methotrexate (which has a PASI-75 achievement rate of approximately 40 % [36–38]), apremilast (which has a PASI-75 achievement rate of 30–42 %) should be seen as a viable alternative to methotrexate. What is missing is a higher dose of apremilast, acceptable for some patients with more severe disease and, on the basis of safety, a preferred treatment for psoriasis in the moderate range of severity. The results from the phase II and phase III studies suggest that higher doses will achieve higher levels of response with minimal or incremental increases in tolerability concerns. We anticipate that the rates of all levels of response will increase with greater exposure to apremilast.

Our clinical impression is that the arthritic component responds somewhat better than cutaneous psoriasis. The clinical impression is contrary to measures of response used in PsA and Ps studies—ACR and PASI scores, respectively. It should be pointed out that apremilast does not suppress production of acute-phase reactants. Since either the erythrocyte sedimentation rate (ESR) or the C-reactive protein (CRP) level is incorporated into the ACR assessment, the full impact of apremilast on joint disease assessed by the ACR response is blunted.

Missing from the literature are statements regarding long-term efficacy and maintenance of response, but, with ongoing research, these gaps should be filled. The near-term 16-week response and mid-term response are insufficient to establish clinical expectations of the long-term response. We do not know if efficacy is sustained over more than 1 year of continuous treatment; nor do we know the impact of interruptions in treatment. We can anticipate that lack of adherence may a produce a loss of response, as is observed with other chronic treatments. The long-term results from clinical studies of psoriasis and PsA are eagerly anticipated.

6 Conclusion

Apremilast has been demonstrated to reduce the severity of moderate to severe plaque psoriasis [15–17]. In addition to its efficacy, apremilast has demonstrated an acceptable safety and tolerability profile [15–17, 25, 28, 29]. Treatment with apremilast has been shown to result in generally mild gastrointestinal complaints, which occurred early in the course of the treatment and resolved with time, and there was no requirement for laboratory test monitoring [15–17, 25, 28, 29]. These results make apremilast an attractive therapeutic option for plaque psoriasis.

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Compliance with Ethical Standards

Dr. Kim Papp was an investigator in the apremilast psoriasis program. He has also received honoraria and been an advisor, consultant, speaker, and investigator for AbbVie, Active Biotech, Allergan, Amgen, Anacor, Astellas, Astra-Zeneca, Basilea, Bayer, Baxter, Biogen-Idec, Boehringer-Ingelheim, Celgene, Centocor, Forward Pharma, Genentech, Janssen, Kyowa, Kythera, Lilly, Leo Pharma, Merck (MSD), Merck-Serono, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Rigel, Roche, Takeda, and UBC.
Dr. Melinda Gooderham was an investigator for ESTEEM 2 and LIBERATE, sponsored by Celgene Corporation. She has also received honoraria and been a consultant, speaker, and investigator for AbbVie, Amgen, Astellas, Boehringer-Ingelheim, Celgene, Galderma, Genentech, Janssen, Kyowa, Eli Lilly, Leo Pharma, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc.; and has been an investigator for Allergan, Kythera, Medimmune, Roche, Takeda, and UBC.

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