

Efficacy and Safety of Apremilast in Systemic- and Biologic-Naive Patients With Moderate Plaque Psoriasis: 52-Week Results of UNVEIL

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ABSTRACT

Background: Many patients with moderate plaque psoriasis are undertreated despite broadening treatment options. In the phase IV UNVEIL study, oral apremilast demonstrated efficacy and safety in systemic-naive patients with chronic moderate plaque psoriasis with lower psoriasis-involved body surface area (BSA; 5%–10%) during the 16-week, double-blind, placebo-controlled phase. We describe efficacy and safety of apremilast in this population through week 52 in UNVEIL.

Methods: Patients with moderate plaque psoriasis (BSA 5%–10%; static Physician's Global Assessment [sPGA] score of 3 [moderate]) and naive to systemic therapies for psoriasis were randomized (2:1) to receive apremilast 30 mg twice daily or placebo for 16 weeks. At week 16, patients continued on apremilast (apremilast/apremilast) or were switched from placebo to apremilast (placebo/apremilast) through week 52 (open-label apremilast treatment phase). Efficacy assessments included the product of sPGA and BSA (PGAxBSA) (mean percentage change from baseline; ≥75% reduction from baseline [PGAxBSA-75]), sPGA response (achievement of score of 0 [clear] or 1 [almost clear]), and the Dermatology Life Quality Index (DLQI; mean change from baseline).

Results: A total of 136 patients completed the 52-week analysis period (placebo/apremilast, n=50/64; apremilast/apremilast, n=86/121). At week 52, improvements in all efficacy end points observed at week 16 were maintained in the apremilast/apremilast group (mean percentage change from baseline in PGAxBSA: –55.5%; PGAxBSA-75: 42.1%; sPGA response: 33.1%; mean change from baseline in DLQI score: –4.4); similar improvements emerged in the placebo/apremilast group after switching to apremilast. The most common adverse events (≥5% of patients) through week 52 were diarrhea (28.0%), nausea (19.0%), headache (15.2%), nasopharyngitis (10.4%), upper respiratory tract infection (7.1%), vomiting (5.7%), and decreased appetite (5.2%).

Conclusions: Apremilast was effective in systemic-naive patients with moderate plaque psoriasis with BSA 5%–10%; efficacy was sustained through week 52. No new safety signals emerged with continued apremilast exposure.

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INTRODUCTION

Recently, the treatment landscape in plaque psoriasis has broadened substantially, with the availability of new oral, topical, and biologic options.[1-3] However, many patients with moderate psoriasis (5% to 10% psoriasis-involved body surface area [BSA])[4] receive no treatment or are undertreated with topical monotherapy[5,6] because physicians may consider conventional systemic treatments or biologic agents inappropriate for management of moderate psoriasis, based on the risk-benefit profile.[7]

Apremilast is an oral, small-molecule phosphodiesterase 4 inhibitor that demonstrated efficacy and a favorable safety and tolerability profile in phase III studies in patients with moderate to severe psoriasis.[8,9] The Evaluating Apremilast in a Phase IV Trial of Efficacy and Safety in Patients With Moderate Plaque Psoriasis (UNVEIL) study investigated the effects of apremilast in patients with moderate plaque psoriasis, defined as 5% to 10% BSA involvement and static Physician's Global Assessment (sPGA) score of 3 (moderate) on a 6-point scale, who were naive to systemic and biologic therapy.[10] Week 16 results demonstrated apremilast was effective in this new population; the primary efficacy end point, mean percentage change in the product of sPGA and BSA score (PGAxBSA), was met.[10] Apremilast was well tolerated and significantly improved quality of life (QOL).[10] Patients treated with

apremilast reported significantly greater treatment satisfaction than patients receiving placebo.[10] We describe the efficacy and safety of apremilast in the open-label apremilast treatment phase (weeks 16 to 52) of UNVEIL.

MATERIALS AND METHODS

Patient Population

Adults aged ≥18 years with a diagnosis of chronic plaque psoriasis for ≥6 months were eligible.[10] Patients were required to have moderate plaque psoriasis, defined as BSA involvement of 5% to 10% and sPGA score of 3 (moderate) on a 6-point scale (0 [clear], 1 [almost clear], 2 [mild], 3 [moderate], 4 [severe], 5 [very severe]). Patients were ineligible if they had prior exposure to systemic or biologic treatment for psoriasis, psoriatic arthritis, or any indication that could affect assessment of psoriasis, or inflammatory or dermatologic conditions, including forms of psoriasis other than plaque psoriasis (eg, erythrodermic, guttate, or generalized, inverse, or pustular psoriasis).

Study Design and Treatment Regimen

UNVEIL was a phase IV, randomized, double-blind, placebo-controlled, multicenter investigation in the United States (NCT02425826). The study design and methods of the 16-week, placebo-controlled phase of UNVEIL have been reported.[10] Using a centralized interactive voice response system, eligible patients were randomized (2:1) to receive apremilast 30 mg twice daily (apremilast) or placebo. At week 16, patients randomized to placebo at baseline initiated open-label treatment with apremilast (placebo/apremilast) and patients randomized to apremilast at baseline continued active treatment (apremilast/apremilast) through week 52. The institutional review boards of participating investigation sites approved the protocol, and all patients provided written informed consent before the conduct of any study-related procedures.[10]

Assessments

The primary efficacy end point was mean percentage change from baseline in PGAxBSA score at week 16. The PGAxBSA is a validated tool[11] that is simpler to use than the Psoriasis Area and Severity Index (PASI) for calculating disease severity and may be more likely to differentiate among patients with lower disease severity than the PASI.[12] PGAxBSA was evaluated at scheduled time points throughout the open-label apremilast treatment phase, including week 52. Clinical assessments of psoriasis-involved BSA and sPGA were previously described.[10]

End points evaluated at week 52 using the sPGA and BSA assessments included mean percentage change from baseline in PGAxBSA, achievement of ≥75% reduction from baseline in PGAxBSA (PGAxBSA-75), and achievement of sPGA response, defined as a score of 0 (clear) or 1 (almost clear). Other efficacy end points at week 52 included mean percentage change from baseline in PASI score; percentage of patients achieving ≥75% reduction from baseline in PASI score (PASI-75); percentage of patients achieving score of 0 (clear) or 1 (very mild) on the Patient's Global Assessment (PtGA) scale (0 [clear] to 4 [severe]); mean change from baseline in pruritus visual analog scale (VAS) score (0 to 100 mm); percentage of patients achieving Scalp Physician's Global Assessment (ScPGA) score of 0 (clear) or 1 (minimal) with a ≥2-point reduction from baseline in patients with ScPGA ≥1 at baseline; among patients with nail psoriasis at baseline, mean percentage change from baseline in Nail Psoriasis Severity Index (NAPSI) score and percentage of patients achieving ≥50% reduction from baseline in NAPSI score (NAPSI-50) in the target nail. Quality of life was assessed with the Dermatology Life Quality Index (DLQI); end points included mean change from baseline in DLQI total score and percentage of patients with baseline DLQI score >5 who achieved a minimal clinically important difference (MCID) on the DLQI, defined as a decrease from baseline ≥5 points. Patient satisfaction was assessed using the 11-item, patient-completed Treatment Satisfaction Questionnaire for Medication (TSQM), version II.[13] Safety was evaluated based on adverse events (AEs) and other standard assessments previously described.[10]

Statistical Analysis

Statistical analyses performed for the placebo-controlled phase, including the primary end point, have been reported.[10] In the extension portion of the study reported here, efficacy was examined over 52 weeks using the intent-to-treat population established during the placebo-controlled phase and data from all patients who entered the open-label apremilast treatment phase (weeks 16 to 52). Data for 52-week analyses were summarized descriptively by treatment assignment from the randomized, double-blind phase (ie, placebo/apremilast and apremilast/apremilast groups). Last-observation-carried-forward methodology was used to impute missing efficacy measurements. Safety data were summarized descriptively for the 52-week apremilast-exposure period for patients who received ≥1 dose of apremilast, regardless of when apremilast was initiated (week 0 or week 16).

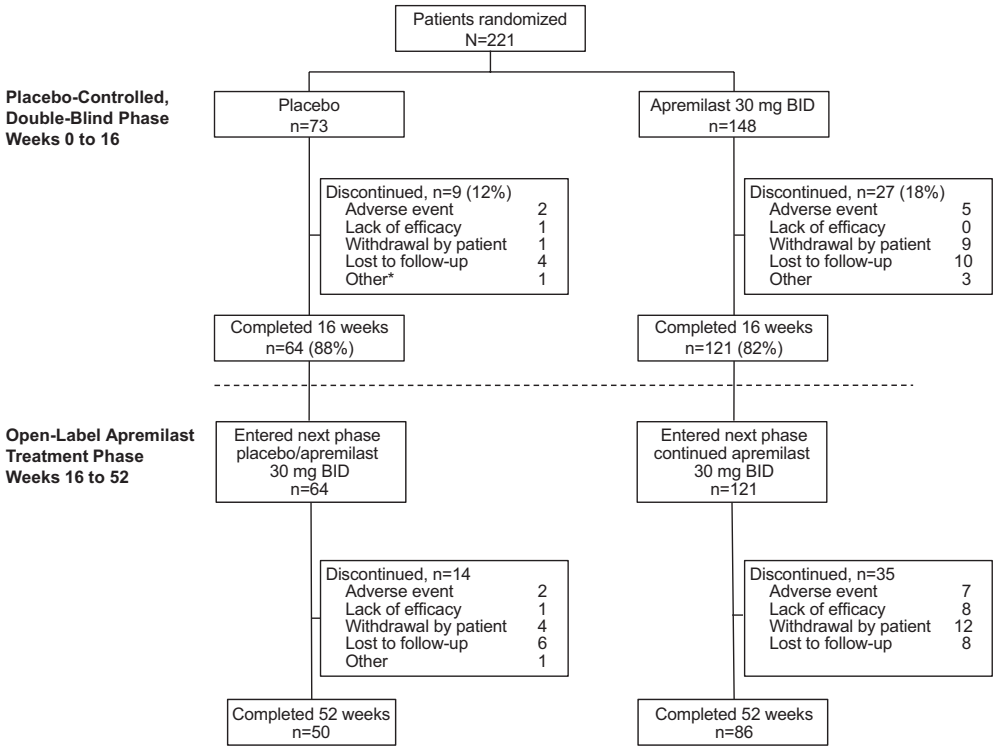
RESULTS

Disposition and Baseline Characteristics

A total of 221 patients were initially enrolled and randomized (placebo, n=73; apremilast, n=148)[10]; 185 (84%) completed the placebo-controlled phase (weeks 0 to 16) and entered the open-label apremilast treatment phase (Figure 1). There were 136 (74%) patients who completed the 52-week analysis period, including 50/64 (78%) patients initially randomized to placebo and 86/121 (71%) initially randomized to apremilast.

Baseline demographics and disease characteristics, based on the ITT population, were comparable between treatment groups, as previously reported.[10] At baseline, mean duration of psoriasis was 13.9 and 17.5 years in the placebo and apremilast

FIGURE 1. Patient disposition. One patient was randomized in error, discontinued prior to study treatment, and is included in "Other" (placebo).
BID=twice daily.



groups, respectively. Also at baseline, mean psoriasis-involved BSA was 7.2%, mean PASI score was 8.1, mean PGAxBSA score was 21.8, and mean DLQI score was 11.0. Most patients (82%) reported prior treatment with topical therapy. In addition, 167 (76%) patients had scalp disease and 83 (38%) patients had nail disease at baseline.[10]

Efficacy Assessments

At week 16, mean percentage change from baseline in PGAxBSA score (primary end point) was significantly greater with apremilast vs. placebo (–48.1% vs. –10.2%; $P<0.0001$).[10] At week 52, improvements in all efficacy end points were maintained among patients in the apremilast/apremilast group and emerged in patients in the placebo/apremilast group after switching to apremilast (Table 1). Mean percentage improvement in PGAxBSA score was sustained among patients who continued receiving apremilast through week 52 (Figure 2). In the apremilast/apremilast group, mean percentage change from baseline in PGAxBSA score at week 52 was –55.5% (Table 1); patients in the placebo/apremilast group demonstrated improvements at week 52 (–42.2%). Achievement of PGAxBSA-75 was maintained or improved during the open-label treatment phase (Figure 3). Specifically, 42.1% of patients initially randomized to apremilast and 45.3% initially randomized to placebo achieved PGAxBSA-75 at week 52 (Table 1). Similarly, proportions of patients with sPGA score of 0 (clear) or 1 (almost clear) were maintained or improved in the apremilast/apremilast and placebo/apremilast groups, respectively, during open-label apremilast treatment (Table 1).

At week 52, 37.5% of patients in the placebo/apremilast group and 26.4% in the apremilast/apremilast group achieved PASI-75 (Table 1). Improvements in pruritus VAS score and scalp and nail disease (ie, ScPGA and NAPSI scores) were maintained in the apremilast/apremilast group and emerged in the placebo/apremilast group during open-label treatment with apremilast (Figure 4; Table 1).

QOL Assessments

DLQI score improvements observed during the placebo-controlled period[10] were sustained over 52 weeks among patients in the apremilast/apremilast group (–4.4), and improvements emerged among patients in the placebo/apremilast group (–5.1; Table 1). Among patients with baseline DLQI score >5, the proportion of patients who achieved DLQI MCID was maintained in patients continuing apremilast for up to 52 weeks, and increased after patients were switched to apremilast (Figure 5).

Satisfaction scores at week 52 for apremilast based on the TSQM, version II, indicated high levels of satisfaction based on domain scores for effectiveness, convenience, side effects, and global satisfaction. At week 52, patients reported high satisfaction on the

TABLE 1.

Summary of Clinical Efficacy End Points at Week 52 (LOCF)		
	Placebo/Apremilast (n=64)	Apremilast/Apremilast (n=121)
PGAxBSA, mean % change	–42.2	–55.5
PGAxBSA-75 response, %	45.3	42.1
sPGA score 0 (clear) or 1 (almost clear), %	35.9	33.1
PASI, mean % change	–46.1	–47.9
PASI-75, %	37.5	26.4
PtGA score of 0 (clear) or 1 (very mild), %	42.2	37.2
Pruritus VAS, mean change, mm	–25.3	–20.8
ScPGA score 0 (clear) or 1 (minimal)*, %	46.9	47.7
NAPSI score in target nail[§] mean % change	–52.7	–51.9
NAPSI-50[‡], %	69.6	62.5
DLQI score, mean change	–5.1	–4.4
DLQI response (decrease of ≥5 points [MCID])[†], %	55.6	59.4
DLQI score of 0 or 1, %	34.4	27.3
TSQM score, mean		
Effectiveness	57.7	54.1
Side effects	77.3	75.5
Convenience	72.7	71.8
Global satisfaction	59.2	59.9

*Achievement of ScPGA 0 or 1 with ≥2-point reduction from baseline; examined in patients with ScPGA score ≥1 at baseline who entered and were treated in the open-label apremilast treatment phase (placebo, n=49; apremilast, n=88).
[§]Examined in patients with NAPSI score ≥1 at baseline who entered and were treated in the open-label apremilast treatment phase: placebo, n=23; apremilast, n=48).
[‡]Examined in patients with NAPSI score ≥1 at baseline; ≥50% reduction from baseline NAPSI score.
[†]Examined in patients with DLQI score >5 at baseline who entered and were treated in the open-label apremilast treatment phase: placebo, n=54; apremilast, n=96.
Data are from patients who entered and were treated with apremilast in the open-label apremilast treatment phase (weeks 16 to 52), with missing values imputed using LOCF methodology.
BID=twice daily;
DLQI=Dermatology Life Quality Index;
LOCF=last observation carried forward;
MCID=minimal clinically important difference;
NAPSI=Nail Psoriasis Severity Index;
NAPSI-50=≥50% reduction from baseline in NAPSI score;
PGAxBSA=product of the static Physician's Global Assessment and body surface area with psoriasis involvement;
PGAxBSA-75=≥75% reduction from baseline in PGAxBSA score;
PtGA=Patient's Global Assessment;
ScPGA, Scalp Physician's Global Assessment;
sPGA=static Physician's Global Assessment;
TSQM=Treatment Satisfaction Questionnaire for Medication, version II (higher scores indicate greater satisfaction);
VAS=visual analog scale.

side effects domain (mean score: placebo/apremilast, 77.3; apremilast/apremilast, 75.5) compared with other domain scores. Mean global satisfaction scores were 59.2 in the placebo/apremilast group and 59.9 in the apremilast/apremilast group (Table 1).

Safety

During the apremilast-exposure period (0 to 52 weeks), 211 patients received ≥1 dose of apremilast, and total exposure to apremilast was 149.7 patient-years. Similar to the placebo-controlled period (0 to 16 weeks),[10] most AEs were mild or moderate in severity, and AEs leading to treatment discontinuation up to 52 weeks occurred in 6.6% of patients receiving apremilast (Table 2). Eleven serious AEs occurred among 10 (4.7%) patients treated with apremilast; each serious AE occurred in 1 patient. There was 1 serious AE, diverticulitis, that was considered related to study treatment. The diverticulitis event occurred in 1 patient and lasted 13 days, did not cause any dose change, and resolved. One patient with a history of depression attempted suicide, which was considered a serious AE but not related to study treatment. During the apremilast-exposure period, nonserious AEs of depression were reported in 4 patients, of which 3 were considered treatment-related; 1 patient had a prior history of depression. A nonserious AE of suicidal ideation was reported in 1 patient, which was considered treatment-related.

The most common AEs (≥5% of patients) were diarrhea, nausea, headache, nasopharyngitis, upper respiratory tract infection, vomiting, and decreased appetite (Table 2). Among patients reporting an AE of diarrhea during apremilast treatment through week 52, protocol-defined diarrhea (≥2 loose watery stools in 1 day) was reported during follow-up questioning in 47/211 (22.3%) patients exposed to apremilast; 3 patients exposed to apremilast withdrew from the study due to diarrhea. At week 52, mean change from baseline in body weight was –1.94 kg (mean percentage change, –2.1%) in patients exposed to apremilast, and >5% weight loss from baseline occurred in 44/210 (21.0%) patients. Eight patients experienced weight loss >10%, and weight loss was reported as an AE in 2 patients during the apremilast-exposure period.

DISCUSSION

Current findings from UNVEIL demonstrate that systemic- and biologic-naive patients with moderate psoriasis (BSA 5%–10%) experienced sustained improvement in their signs and symptoms for up to 52 weeks of treatment with apremilast. At week 52, PGAxBSA scores were reduced from baseline by 55.5% in patients receiving apremilast throughout the study and by 42.2% in patients initially randomized to placebo who switched to apremilast at week 16. Lasting improvements in pruritus were observed; both treatment groups reported a reduction from baseline pruritus >20 mm. Patients experienced sustained improvements in scalp and nail involvement, considered difficult-to-treat manifestations of psoriasis,[14-16] with continued apremilast treatment to week 52. Improvements in QOL were sustained and treatment satisfaction remained high over 52 weeks. Safety and tolerability were consistent with the known safety profile of apremilast. The findings from this study in the moderate population are consistent with the sustained efficacy of apremilast demonstrated in 2 large phase III, randomized studies in patients with moderate to severe psoriasis (ESTEEM 1 and 2).[8,9]

As noted in the primary report of the 16-week UNVEIL findings,[10] among patients with moderate psoriasis and lower BSA, baseline DLQI scores were indicative of significant QOL impairments associated with psoriatic disease, similar to those reported in the ESTEEM 1 study in patients with more severe disease (~12.0).[8] In UNVEIL, the level of patient-reported QOL impairment at baseline, as assessed by DLQI (~11.0), highlights the potential for dermatologists to underestimate the impact of psoriasis on patients' QOL. This may be due to scalp and nail lesions that contribute to the limited BSA but may be embarrassing and respond poorly to treatment, in addition to non-observable symptoms such as pain and pruritus, which can limit normal function and interfere with sleep.[17-19] Non-observable symptoms such as pruritus may contribute to poor QOL in patients with mild disease and patients with severe disease.[19] Patients with less severe disease involvement based on standard measures of severity (eg, PASI, BSA) are often undertreated with topical monotherapy or receive no treatment.[5,6] Findings from the extension phase of this study demonstrate that apremilast may be a suitable long-term option for patients with lower BSA involvement.

FIGURE 2. PGAxBSA mean percentage change from baseline at week 16 and week 52 (LOCF).
*P<0.0001 vs. placebo.
Error bars indicate 95% confidence intervals. Based on the ITT population.
ITT=intent to treat;
LOCF=last observation carried forward;
PGAxBSA=product of the static Physician's Global Assessment and body surface area with psoriasis involvement.

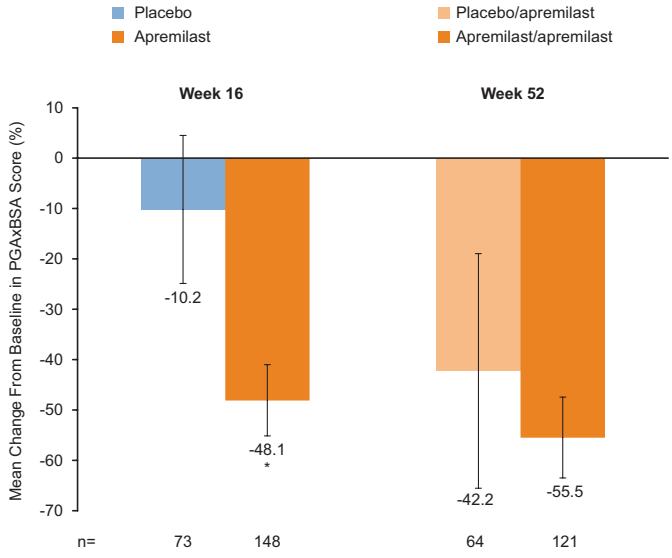


FIGURE 3. Proportion of patients achieving PGAxBSA-75 response at week 16 and week 52 (LOCF).
*P<0.0001 vs. placebo.
Error bars indicate 95% confidence intervals. Based on the ITT population.
ITT=intent to treat;
LOCF=last observation carried forward;
PGAxBSA-75=≥75% reduction from baseline in product of the static Physician's Global Assessment and body surface area with psoriasis involvement.

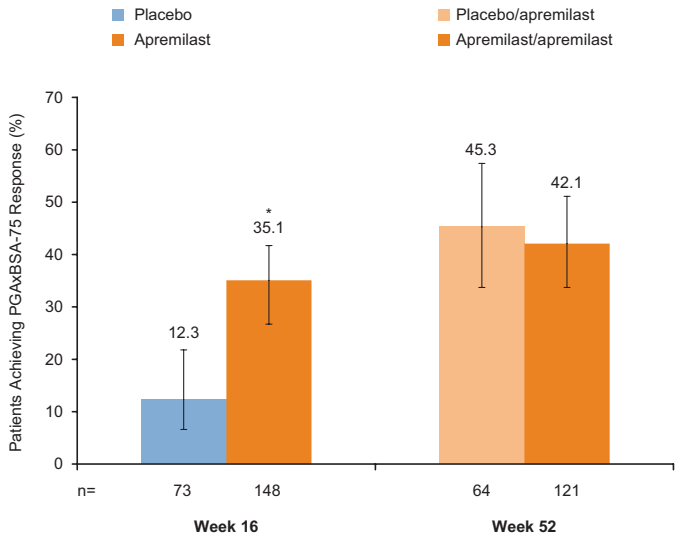


FIGURE 4. Proportion of patients achieving ScPGA 0 (clear) or 1 (minimal) response at week 16 and week 52 (LOCF).
*P=0.0178 vs. placebo. Includes patients with ScPGA ≥1 at baseline.
ScPGA response defined as a score of 0 (clear) or 1 (minimal) with a ≥2-point reduction from baseline.
Error bars indicate 95% confidence intervals.
LOCF=last observation carried forward;
ScPGA=Scalp Physician's Global Assessment.

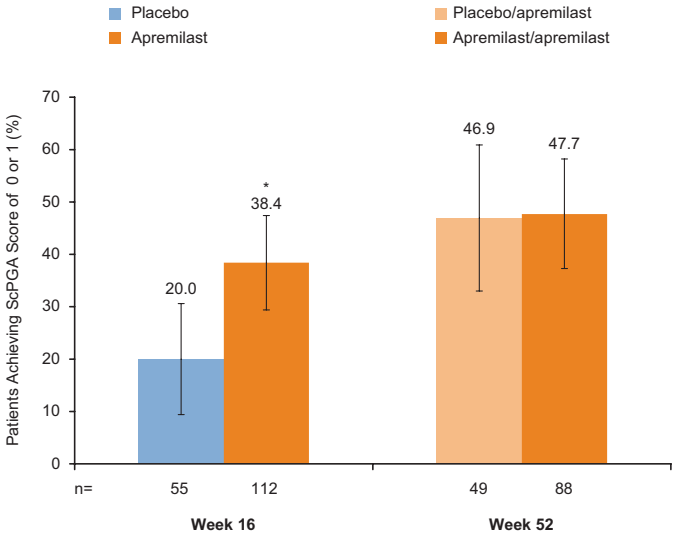
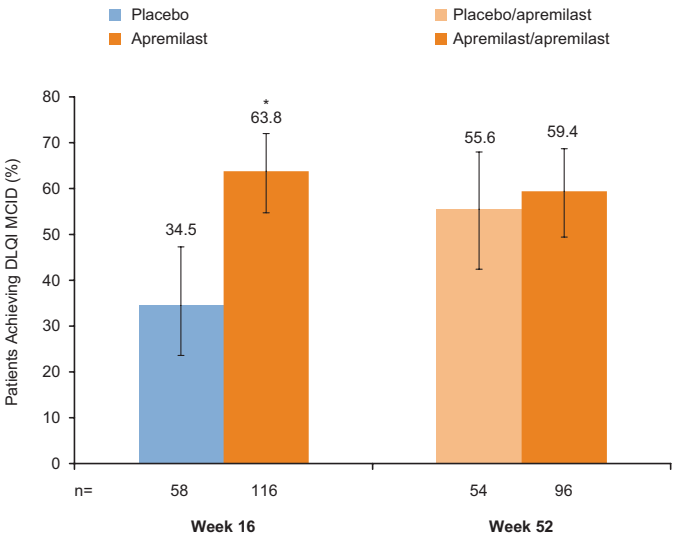


FIGURE 5. Proportion of patients achieving DLQI MCID at week 16 and week 52 (LOCF).
*P=0.0009 vs. placebo.
Includes patients with DLQI >5 at baseline.
DLQI MCID=≥5-point decrease from baseline.
Error bars indicate 95% confidence intervals.
BID=twice daily;
DLQI=Dermatology Life Quality Index;
LOCF=last observation carried forward;
MCID=minimal clinically important difference.



The safety profile of apremilast over 52 weeks in the UNVEIL patient population was generally similar to that observed in the placebo-controlled period[10] as well as with longer-term treatment in phase III studies, described previously.[8,9,20,21] Rates of severe AEs and serious AEs were low, as was the rate of treatment discontinuation due to an AE (6.6%). Of note, over the full 52-week apremilast-exposure period, rates of spontaneously reported diarrhea (28%) and protocol-defined diarrhea (22%) were higher than what has been reported in other apremilast studies (14.0% to 19.2%).[8,9,20,21] Awareness among physicians and patients that diarrhea is a recognized AE with apremilast may have increased the likelihood of patients reporting the event. Patients who are more susceptible to complications of diarrhea or vomiting should be monitored. Also of note, 1 patient (in the apremilast/apremilast group) reported suicidal ideation that was considered related to study treatment. All patients should be monitored for changes in mood or presence of depressive symptoms while receiving apremilast treatment.[3]

Study limitations of note were that during weeks 16 to 52, apremilast treatment was open-label, and therefore efficacy ratings may reflect some unknown degree of positive bias on the part of patients or dermatologists. However, symptom improvement was similar to that reported in other controlled studies of apremilast in patients with psoriasis.[8,9,22] In addition, study results are for 52 weeks, and efficacy and safety of longer-term apremilast

TABLE 2.

Adverse Events Through Week 52 in Patients Treated With Apremilast/Apremilast

Overview	Apremilast-Exposure Period 0 to 52 Weeks Apremilast 30 mg BID n=211
Patients, n (%)	
≥1 AE	142 (67.3)
≥1 Serious AE	10 (4.7)
≥1 Severe AE	5 (2.4)
AE leading to drug withdrawal	14 (6.6)
AEs in ≥5% of patients, n (%)	
Diarrhea	59 (28.0)
Nausea	40 (19.0)
Headache	32 (15.2)
Nasopharyngitis	22 (10.4)
URTI	15 (7.1)
Vomiting	12 (5.7)
Decreased appetite	11 (5.2)

Data are from patients who received ≥1 dose of apremilast, regardless of when apremilast dosing began (baseline for apremilast/apremilast patients, or week 16 for placebo/apremilast patients); the apremilast-exposure period started from the date of first dose of apremilast.
AE=adverse event;
BID=twice daily.

treatment have not yet been described exclusively in patients with moderate disease. However, results from other longer-term studies in patients with moderate to severe psoriasis are consistent with findings from the current 52-week study.[23,24]

CONCLUSION

In UNVEIL, improvements in signs and symptoms of moderate plaque psoriasis (BSA 5% to 10%) achieved with 16 weeks of apremilast treatment[10] were sustained or displayed continued improvement with treatment that extended up to 52 weeks in systemic- and biologic-naive patients. Apremilast had a significantly positive and sustained impact on QOL and treatment satisfaction, with few patients discontinuing longer-term treatment because of AEs. The open-label apremilast treatment phase further demonstrated that apremilast is a systemic treatment with a favorable risk-benefit profile that may be appropriate for patients with moderate plaque psoriasis.

DISCLOSURES

Linda Stein Gold: Celgene Corporation, LEO Pharma, Novartis, Pfizer, and Stiefel/GlaxoSmithKline–investigator and/or consultant.

Jerry Bagel: AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, and Valeant–advisory board member, speaker, consultant, and/or research support; Sun Pharma–consultant.

Mark Lebwohl: Boehringer Ingelheim, Celgene Corporation, Eli Lilly, Janssen/Johnson & Johnson, Kadmon, MedImmune/AstraZeneca, Novartis, Pfizer, and ViDac–research support through Icahn School of Medicine at Mount Sinai.

J. Mark Jackson: AbbVie, Amgen, Celgene Corporation, Dermira, Galderma, Genentech, Janssen, Lilly, Medimetriks, Merck, Novartis, Pfizer, Promius, and TopMD–research, honoraria, consulting, and/or other support.

Rongdean Chen: Celgene Corporation–employment at the time of study conduct.

Joana Goncalves: Celgene Corporation–employment.

Eugenia Levi: Celgene Corporation–employment.

Kristina Callis Duffin: AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corporation, Centocor/Janssen, Eli Lilly, Novartis, Pfizer, Regeneron, Stiefel, and XenoPort–consultant, steering committee member, advisory board member, has received grants, and/or has received honoraria.

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