Efficacy and Safety of Apremilast in Patients With Moderate Plaque Psoriasis With Lower BSA (UNVEIL Phase IV Study)

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INTRODUCTION

- Patients with moderate plaque psoriasis (i.e., 5% to 10% psoriasis-involved body surface area [BSA][1]) often receive no treatment or are undertreated with topical monotherapy.[2,3]
- Apremilast, an oral, small-molecule phosphodiesterase 4 inhibitor,[4] was shown to be effective and demonstrated acceptable tolerability in patients with moderate to severe psoriasis (BSA ≥10%) in the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) phase III clinical trial program.[5,6]
- Evaluating Apremilast in a Phase IV Trial of Efficacy and Safety in Patients With Moderate Plaque Psoriasis (UNVEIL) (ClinicalTrials.gov: NCT02425826) is the first prospective randomized, placebo (PBO)-controlled trial to demonstrate the clinical efficacy and safety of a systemic treatment (apremilast) in systemic- and biologic-naive patients with moderate plaque psoriasis. Apremilast 30 mg twice daily (APR) was clinically effective and well tolerated during the 16-week, double-blind, PBO-controlled phase.
- The efficacy and safety results of the open-label APR treatment phase up to Week 52 are presented.

METHODS

Patients

Key Inclusion Criteria

- Males or females ≥18 years of age
- Chronic plaque psoriasis for ≥6 months before screening
- Moderate plaque psoriasis at screening and baseline as defined by BSA of 5% to 10% and static Physician's Global Assessment (sPGA) of 3 (moderate) based on a scale ranging from 0 (clear) to 5 (very severe)
- No prior exposure to systemic or biologic treatments for psoriasis, psoriatic arthritis, or any other condition that could affect the assessment of psoriasis

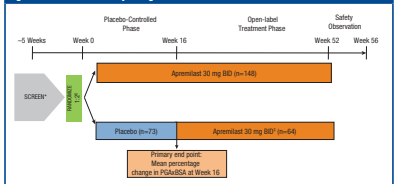
Key Exclusion Criteria

- Inflammatory or dermatologic condition, including forms of psoriasis other than plaque psoriasis
- Topical therapy within 2 weeks or phototherapy within 4 weeks of randomization

Study Design

- UNVEIL is a phase IV, multicenter, randomized, PBO-controlled, double-blind study (**Figure 1**).
- Patients were randomized (2:1) to receive APR or PBO during Weeks 0 to 16; patients in the PBO group were switched to APR at Week 16.
- All patients continued taking APR through Week 52.

Figure 1. The UNVEIL Study Design



ClinicalTrials.gov: NCT02425826
*Screening up to 35 days before randomization.
†All doses were titrated over the first week of treatment.
‡At Week 16, all placebo patients were switched to open-label apremilast 30 mg BID (with dose titration) through Week 52.
BID=twice daily; PGAxBSA=product of the static Physician's Global Assessment and body surface area involvement.

METHODS (cont'd)

Efficacy Assessments

Primary Efficacy

- The primary efficacy end point was the mean percentage change from baseline at Week 16 in PGAxBSA, which represents the product of sPGA and BSA scores.
- Overall BSA affected by psoriasis is estimated based on the patient's palm area, which equates to approximately 1% of total BSA.
- For the 6-point sPGA, for plaques in all involved areas, the severity of erythema, scaling, and plaque elevation each were scored; scores were averaged and rounded to the nearest whole number.[7]

Secondary Efficacy

- Proportions of patients achieving:
  - ≥75% reduction from baseline in PGAxBSA score (PGAxBSA-75)
  - sPGA response, defined as a score of 0 (clear) or 1 (almost clear)

QOL

- Quality of life (QOL) was assessed with the Dermatology Life Quality Index (DLQI).[8]

Safety Assessments

- Safety was evaluated based on adverse events (AEs), vital signs, clinical laboratory testing, and complete physical examinations.

Statistical Analysis

- Efficacy and QOL assessments were conducted for the intent-to-treat (ITT) population, which included all randomized patients; safety assessments were conducted in all randomized patients who received ≥1 dose of study medication.
- Mean percentage change from baseline in PGAxBSA and change from baseline in DLQI total score at Week 16 were compared between APR and PBO using a 2-sided analysis of covariance model with treatment and site as factors and baseline value as covariate.
- PGAxBSA-75 and sPGA responses at Week 16 were evaluated with 2-sided Cochran-Mantel-Haenszel tests stratified by site.
- Efficacy and QOL parameters at Week 52 were evaluated descriptively.
  - Week 16 and Week 52 APR/APR analyses were performed with the ITT population.
  - Week 52 PBO/APR analyses were performed with the modified ITT population (all patients who entered the APR extension phase).
- The last-observation-carried-forward methodology was used to impute missing values.
- Safety assessments were summarized using frequencies and percentages.

RESULTS

Patients

- A total of 221 patients were randomized to study treatment and constitute the ITT population; 185 patients (84%) completed the PBO-controlled phase (Weeks 0 to 16) and 136/185 patients (74%) completed the APR treatment phase (Weeks 16 to 52).
- Demographics and baseline disease characteristics were generally similar between treatment groups (**Table 1**).
  - At baseline, mean DLQI total scores were comparable between treatment groups, and the mean pruritus visual analog scale score was slightly higher in the PBO group.

Table 1. Patient Demographics and Baseline Disease Characteristics

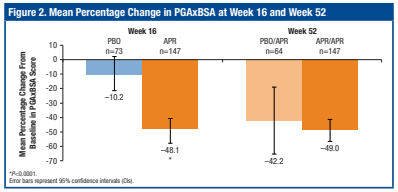
Characteristic	PBO n=73	APR n=148
Age, mean (SD), years	51.1 (13.7)	48.6 (15.4)
Male, n (%)	41 (56.2)	74 (50.0)
Body mass index, mean (SD), kg/m^2	30.8 (6.5)	30.5 (7.4)
Duration of psoriasis, mean (SD), years	13.9 (12.6)	17.5 (13.9)
PGAxBSA score, mean (SD)	21.6 (5.9)	21.8 (5.3)
BSA, mean (SD), %	7.1 (1.8)	7.2 (1.6)
PASI score (0–72), mean (SD)	8.0 (3.2)	8.2 (4.0)
DLQI total score, mean (SD)	11.1 (6.5)	11.0 (6.5)
Prior topical therapy, n (%)	59 (80.8)	122 (82.4)

PASI=Psoriasis Area and Severity Index.

RESULTS (cont'd)

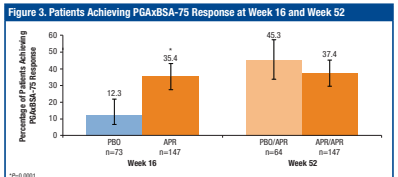
- At Week 16, significantly greater improvement in PGAxBSA occurred in patients receiving APR vs. PBO (**Figure 2**).
- At Week 52, improvement was maintained in the APR/APR group and emerged in the PBO/APR group after switching to APR.

Figure 2. Mean Percentage Change in PGAxBSA at Week 16 and Week 52



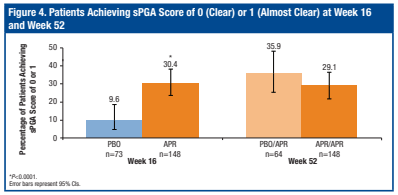
- Significantly more patients treated with APR achieved PGAxBSA-75 response at Week 16 vs. PBO (**Figure 3**).
- PGAxBSA-75 response was maintained in the open-label APR treatment phase.

Figure 3. Patients Achieving PGAxBSA-75 Response at Week 16 and Week 52



- Significantly more patients treated with APR achieved an sPGA score of 0 or 1 at Week 16 vs. PBO (**Figure 4**).
- Long-term sPGA response was maintained with APR treatment in the open-label treatment phase.

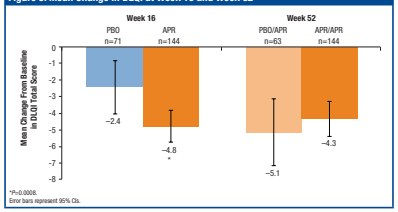
Figure 4. Patients Achieving sPGA Score of 0 (Clear) or 1 (Almost Clear) at Week 16 and Week 52



RESULTS (cont'd)

- Improvement in DLQI was significantly greater with APR than PBO at Week 16 (**Figure 5**).
- DLQI improvement was maintained in patients continuing on APR for up to 52 weeks, and developed after patients were switched from PBO to APR.

Figure 5. Mean Change in DLQI at Week 16 and Week 52



- Most AEs were mild or moderate (**Table 2**).
- The most common AEs (reported in ≥5% patients in either treatment group during the PBO-controlled period) included diarrhea, headache, nausea, upper respiratory tract infection, decreased appetite, and vomiting.

Table 2. Overview of Adverse Events

	Weeks 0 to 16				Weeks 0 to 52	
	PBO n=73		APR n=147		APR* n=211	
Patients, n (%)	n (%)	EAIR/100 Pt-Yrs	n (%)	EAIR/100 Pt-Yrs	n (%)	EAIR/100 Pt-Yrs
≥1 AE	35 (47.9)	262.3	92 (62.6)	459.8	142 (67.3)	242.7
≥1 Serious AE	0 (0)	0.0	3 (2.0)	7.4	10 (4.7)	6.8
≥1 Severe AE	1 (1.4)	4.9	3 (2.0)	7.5	5 (2.4)	3.4
AE leading to drug withdrawal	3 (4.1)	14.5	5 (3.4)	12.4	14 (6.6)	9.6
Most common AEs†, n (%)						
Diarrhea	12 (16.4)	63.7	43 (29.3)	139.8	59 (28.0)	53.8
Nausea	7 (9.6)	35.4	26 (17.7)	73.7	40 (19.0)	31.8
Headache	8 (11.0)	42.4	30 (20.4)	89.2	32 (15.2)	24.9
Nasopharyngitis	2 (2.7)	9.8	5 (3.4)	12.5	22 (10.4)	16.2
Upper respiratory tract infection	3 (4.1)	14.8	10 (6.8)	25.2	15 (7.1)	10.7
Vomiting	2 (2.7)	9.7	9 (6.1)	22.9	12 (5.7)	8.4
Decreased appetite	4 (5.5)	19.6	6 (4.1)	15.3	11 (5.2)	7.7

*Includes all patients exposed to APR, including those initially randomized to PBO and switched at Week 16 to APR. †Reported by ≥5% of patients in any treatment group; listed in order of incidence over 52-week period. Pt-yrs=patient-years. EAIR/100 pt-yrs=exposure-adjusted incidence rate per 100 patient-years, calculated as (number of events*100)/(total exposure time [in years] of safety population). The exposure time for a patient without a specific event is the treatment duration, whereas the exposure time for a patient with the specific event is the treatment duration up to the start date (inclusive) of the first occurrence of the specific event.

CONCLUSIONS

- APR was clinically effective in systemic- and biologic-naive patients with moderate plaque psoriasis (BSA of 5% to 10%).
- APR significantly improved PGAxBSA score, PGAxBSA-75 response rate, sPGA 0 or 1 response rate, and DLQI total score at Week 16 compared with PBO.
- Clinical responses were maintained with continued APR treatment through Week 52 and emerged in patients who switched from PBO to APR at Week 16.
- The incidence of AEs, based on EAIR per 100 patient-years, did not increase with longer exposure to APR.
- Safety and tolerability were consistent with previous studies[5,6]; no new safety or tolerability issues were observed up to 52 weeks.

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