Efficacy of Apremilast on Quality-of-Life Measures in Patients With Moderate Plaque Psoriasis (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]
- Patients with moderate psoriasis often report substantial impairments in disease-related quality of life (QOL), despite having lower psoriasis-involved BSA.[3]
- Among the symptoms of psoriasis, pruritus is a key contributor to QOL impairments.[4]
- Apremilast, an oral, small-molecule phosphodiesterase 4 inhibitor,[5] improved QOL and disease severity, with acceptable tolerability, in phase III clinical studies of patients with moderate to severe psoriasis.[6-8]
- Evaluating Apremilast in a Phase IV Trial of Efficacy and Safety in Patients With Moderate Plaque Psoriasis (UNVEIL; ClinicalTrials.gov: NCT02425826), the first prospective, randomized, placebo (PBO)-controlled trial in systemic- and biologic-naive patients with moderate plaque psoriasis, demonstrated that apremilast 30 mg twice daily (APR) was effective, generally well tolerated, and had a positive impact on QOL during the 16-week, double-blind, PBO-controlled phase.
- The improvements in QOL and pruritus as well as treatment satisfaction are described for the open-label APR treatment phase (Weeks 16 to 52) of UNVEIL.

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

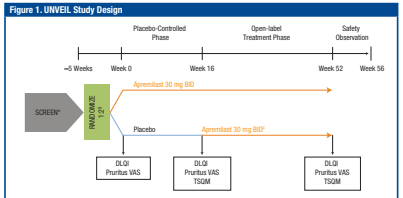
Key Exclusion Criteria

- 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.
- An unmedicated moisturizer was the only topical therapy permitted during the study.

Figure 1. 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.

METHODS (cont'd)

QOL, Pruritus, and Treatment Satisfaction Assessments

- Patients completed the Dermatology Life Quality Index (DLQI), pruritus visual analog scale (VAS), and Treatment Satisfaction Questionnaire for Medication (TSQM) version II.

QOL

- QOL was assessed with the DLQI, a validated instrument that consists of 10 items pertaining to the skin and designed to assess QOL in a dermatology clinical setting.[9]
- QOL end points:
  - Mean change from baseline in DLQI total score at Week 16 and Week 52
  - Proportion of patients with baseline DLQI >5 who achieved DLQI response (i.e., minimal clinically important difference [MCID], defined as ≥5-point improvement from baseline in DLQI total score among patients with baseline DLQI >5).

Pruritus

- Pruritus was assessed on a 100-mm VAS ranging from "no itch" (0) to "itch as severe as can be imagined" (100).
- Pruritus end points included mean change from baseline in pruritus VAS at Week 16 and Week 52.

Treatment Satisfaction

- Treatment satisfaction was assessed using the TSQM version II, a validated, self-administered, 11-question instrument designed to evaluate patient satisfaction with current treatment.[10]
  - An algorithm is used to transform scores to a 0 to 100 scale for effectiveness, side effects, convenience, and global satisfaction, with higher scores indicating greater satisfaction.
  - Mean TSQM scores for effectiveness, side effects, convenience, and global satisfaction were assessed at Week 16 and Week 52.

Safety Assessments

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

Statistical Analysis

- QOL, pruritus, and treatment satisfaction assessments were conducted for the intent-to-treat population, which included all randomized patients; safety assessments were conducted in all randomized patients who received ≥1 dose of study medication.
- Changes from baseline in DLQI total score and pruritus VAS score at Week 16 were compared between the APR and PBO groups using a 2-way analysis of covariance (ANCOVA) model with treatment and site as factors and baseline value as a covariate.
- The proportions of patients achieving a DLQI response at Week 16 were compared between groups using a 2-sided Cochran-Mantel-Haenszel test stratified by site.
- Mean TSQM scores at Week 16 were compared between treatment groups by 2-way analysis of variance (ANOVA) with treatment and site as factors.
- QOL, pruritus, and treatment satisfaction parameters at Week 52 were evaluated descriptively.
- The last-observation-carried-forward (LOCF) 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 intent-to-treat 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 mean pruritus VAS 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)	48.8 (15.4)
Male, n (%)	41 (56.2)	74 (50.0)
Body mass index, mean (SD), kg/m²	30.8 (6.5)	30.5 (7.4)
Duration of psoriasis, mean (SD), years	13.9 (12.6)	17.5 (13.9)
BSA, mean (SD), %	7.1 (1.8)	7.2 (1.6)
sPGA score=3 (moderate)*, n (%)	70 (95.9)	144 (97.3)
DLQI total score, mean (SD)	11.1 (6.5)	11.0 (6.5)
Pruritus VAS score, mean (SD), mm	60.0 (22.5)	55.0 (24.3)
PASI score (0–72), mean (SD)	8.0 (3.2)	8.2 (4.0)

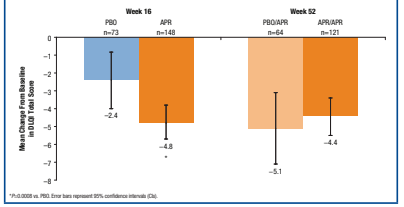
*Although the inclusion criterion was sPGA=3, patients with sPGA=4 were enrolled in error (n=4).
PASI=Psoriasis Area and Severity Index.

RESULTS (cont'd)

Effect of APR on QOL

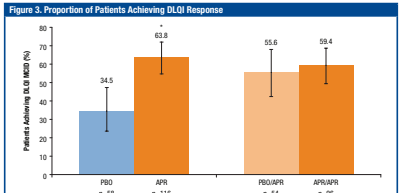
- At Week 16, improvement from baseline in DLQI total score was significantly greater with APR than with PBO (−4.8 vs. −2.4; P=0.0008) (**Figure 2**).
- Significantly more patients with a baseline DLQI total score >5 who received APR vs. PBO achieved the DLQI MCID at Week 16 (63.8% vs. 34.5%; P=0.0009) (**Figure 3**).
- At Week 52, improvement in the DLQI total score was maintained in patients who were randomized to APR and then continued on APR during the open-label APR treatment phase (mean change from baseline: −4.4).
- Patients who switched from PBO to APR at Week 16 achieved similar improvements in DLQI total score at Week 52 (mean change from baseline: −5.1) (**Figure 2**).
- Among patients who were initially randomized to APR at baseline, the percentage of patients who achieved DLQI MCID at Week 16 was maintained over 52 weeks (**Figure 3**).

Figure 2. Improvements in DLQI Total Score



*P<0.0008 vs. PBO. Error bars represent 95% confidence intervals (CIs).

Figure 3. Proportion of Patients Achieving DLQI Response



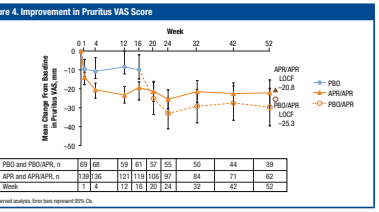
*P<0.0009 vs. PBO. Error bars represent 95% CIs.

Effect of APR on Pruritus VAS

- At Week 16, mean change from baseline in pruritus VAS score was −19.2 mm in the APR group and −10.2 mm in the PBO group (P=0.0016) (**Figure 4**).
- The improvement in pruritus VAS was maintained at Week 52 in patients who continued on APR, and mean VAS scores improved in those switched from PBO to APR (**Figure 4**).

RESULTS (cont'd)

Figure 4. Improvement in Pruritus VAS Score



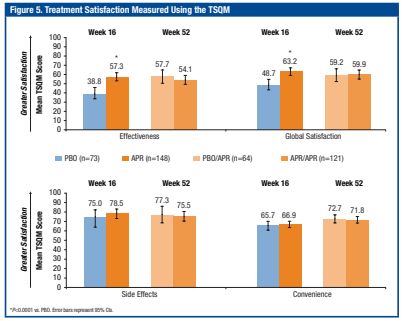
PBO and PBO/APR, n	69	68	59	61	57	55	50	44	39
APR and APR/APR, n	139	136	121	119	106	97	84	71	62
Week	1	4	12	16	20	24	32	42	52

As-observed analysis. Error bars represent 95% CIs.

Treatment Satisfaction

- At Week 16, treatment effectiveness, as measured by the TSQM, was significantly greater with APR than with PBO (P<0.0001). Global satisfaction also favored APR over PBO (P<0.0001), whereas satisfaction with side effects (P=0.34) and convenience (P=0.63) did not differ between treatment groups (**Figure 5**).
- At Week 52, levels of satisfaction were maintained on all domains (**Figure 5**).

Figure 5. Treatment Satisfaction Measured Using the TSQM



*P<0.0001 vs. PBO. Error bars represent 95% CIs.

Safety

- The most common AEs reported with APR treatment from 0 to 52 weeks included diarrhea, nausea, headache, and nasopharyngitis; most AEs were mild or moderate in severity (**Table 2**).
- Exposure-adjusted incidence rates (EAIR) per 100 patient-years did not increase with longer exposure up to 52 weeks.
- No new safety or tolerability signals were observed up to 52 weeks.

RESULTS (cont'd)

Table 2. Overview of Adverse Events

Overview	Weeks 0 to 16 PBO n=73 n (%)	Weeks 0 to 16 PBO n=73 EAIR/100 pt-yrs	Weeks 0 to 16 APR n=147 n (%)	Weeks 0 to 16 APR n=147 EAIR/100 pt-yrs	Weeks 0 to 52 APR* n=211 n (%)	Weeks 0 to 52 APR* n=211 EAIR/100 pt-yrs
≥1 AE	35 (47.9)	202.3	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†						
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
URTI	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	8 (5.4)	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; URTI=upper respiratory tract infection.
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 the specific event is the treatment duration; 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 improved QOL and reduced pruritus at Week 16 in systemic- and biologic-naive patients with moderate plaque psoriasis (BSA 5% to 10%); these improvements were maintained over 52 weeks with continued APR treatment.
- The beneficial effects of APR on QOL and pruritus were consistent with those previously reported in patients with moderate to severe plaque psoriasis in randomized phase III trials.[6,7]
- Global treatment satisfaction was greater with APR than with PBO at Week 16, and satisfaction remained high over 52 weeks of APR treatment.
- The safety and tolerability of APR were consistent with previous studies.[6,7] No new safety or tolerability issues were observed with APR treatment up to 52 weeks.

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