Efficacy and Safety of Apremilast in Patients With Moderate to Severe Plaque Psoriasis of the Scalp: Results of a Phase 3, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study

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INTRODUCTION

- Plaque psoriasis is a chronic, systemic inflammatory disease[1] that requires long-term treatment and routine evaluations to monitor improvement.[1,2]
- Many patients with psoriasis report that they are most bothered by symptoms in difficult-to-treat, highly visible, and pruritic areas, such as the scalp.[3]
- Topical therapies can be difficult to apply to the scalp area and may feel greasy on the hair.[3,4]
- STYLE (ClinicalTrials.gov: NCT03123471) is the first prospective, randomized, placebo (PBO)-controlled trial to evaluate the clinical efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor indicated for the treatment of moderate to severe plaque psoriasis, in patients with moderate to severe psoriasis of the scalp.

METHODS

Primary Objective

- To evaluate the efficacy of apremilast 30 mg twice daily (APR) vs. PBO in patients with moderate to severe plaque psoriasis of the scalp

Secondary Objectives

- To evaluate the efficacy of APR vs. PBO on whole body itch and scalp itch
- To evaluate the safety and tolerability of APR in patients with moderate to severe plaque psoriasis of the scalp

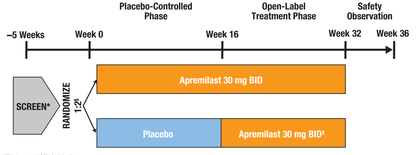
Key Inclusion Criteria

- Males or females ≥18 years of age
- Moderate to severe plaque psoriasis (Psoriasis Area and Severity Index [PASI] ≥12, psoriasis-involved body surface area [BSA] ≥10%, and static Physician Global Assessment [sPGA] ≥3 [moderate or greater])
- Moderate to severe plaque psoriasis of the scalp (scalp PGA [ScPGA] ≥3 [moderate or greater]; psoriasis-involved scalp surface area [SSA] ≥20%)
- Inadequate response or intolerance to ≥1 topical therapy for plaque psoriasis of the scalp

Study Design

- STYLE was a phase 3, multicenter, randomized, double-blind, PBO-controlled study (**Figure 1**).
- Patients were randomized (2:1) to APR or PBO for the double-blind PBO-controlled phase through Week 16 and then continued or switched to APR for open-label treatment through Week 32.
  - Treatment groups were stratified by baseline ScPGA score (3 [moderate] or 4 [severe]).

Figure 1. Study Design



ClinicalTrials.gov: NCT03123471
*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 32.
BID=twice daily.

METHODS (cont'd)

- The primary endpoint was the proportion of patients achieving ScPGA response (score of 0 [clear] or 1 [almost clear] with a ≥2-point reduction from baseline) at Week 16 with APR vs. PBO.
- Secondary endpoints included the proportion of patients with ≥4-point improvement from baseline in Whole Body Itch Numeric Rating Scale (NRS) and Scalp Itch NRS scores at Week 16 and at earlier visits (i.e., 12, 8, 4, and 2 weeks) and change from baseline in Dermatology Life Quality Index (DLQI) total score at Week 16.

Statistical Analyses

- Primary and secondary endpoints were analyzed in the intent-to-treat (ITT) population, defined as all randomized patients.
- Analyses of the proportions of patients achieving the primary endpoint, Whole Body Itch NRS response, and Scalp Itch NRS response were performed using the Cochran-Mantel-Haenszel test with missing values imputed using the multiple imputation (MI) method; change from baseline in DLQI total score was analyzed using an analysis of covariance with missing values at Week 16 imputed using the MI method.
- The primary and secondary efficacy endpoints were hierarchically ranked for testing using the following sequence: primary endpoint; ≥4-point improvement from baseline in Whole Body Itch NRS and Scalp Itch NRS, respectively, at Week 16, Week 12, Week 8, Week 4, and Week 2; and change from baseline in DLQI total score at Week 16.
- For the primary and secondary endpoints, sensitivity analyses were also performed using the last-observation-carried-forward (LOCF) and nonresponder imputation (NRI) methods.
- Safety assessments were analyzed in the safety population, defined as all randomized patients who received ≥1 dose of study drug.

RESULTS

Patients

- A total of 303 patients were randomized, including 102 patients in the PBO group and 201 patients in the APR group.
- In all, 252 patients completed the PBO-controlled phase (PBO, 84/102 [82.4%]; APR, 168/201 [83.6%]).
- The most frequently cited reasons for discontinuation included withdrawal by patient (7.3%), adverse events (AEs; 3.6%), and lack of efficacy (2.3%).
- Demographic and baseline clinical characteristics were generally comparable between the PBO and APR treatment groups (**Table 1**).

Table 1. Demographic and Baseline Clinical Characteristics

	PBO n=102*	APR n=201*
Age, mean (SD), years	46.7 (15.2)	47.0 (15.0)
Male, n (%)	62 (60.8)	125 (62.2)
White, n (%)	75 (73.5)	154 (76.6)
BMI, mean (SD), kg/m^2†	31.7 (7.2)	30.7 (7.1)
Psoriasis duration, mean (SD), years	14.8 (11.3)	15.7 (12.4)
Psoriasis-involved SSA, mean (SD), %	58.2 (26.4)	61.9 (27.2)
ScPGA, n (%)		
Moderate (3)	78 (76.5)	155 (77.1)
Severe (4)	24 (23.5)	46 (22.9)
sPGA, n (%)		
Moderate (3)	76 (74.5)	153 (76.1)
Severe (4)	26 (25.5)	48 (23.9)
Scalp Itch NRS score, mean (SD)	6.7 (2.4)	6.6 (2.5)
Whole Body Itch NRS score, mean (SD)	7.2 (2.0)	7.2 (2.3)
Psoriasis-involved BSA, mean (SD), %	21.2 (14.8)	19.0 (10.8)
DLQI total score, mean (SD)	12.6 (7.2)	12.6 (7.0)
Prior use of psoriasis medications		
Phototherapy, n (%)	3 (2.9)	10 (5.0)
Conventional systemic therapy, n (%)	27 (26.5)	61 (30.3)
Biologic therapy, n (%)	31 (30.4)	53 (26.4)

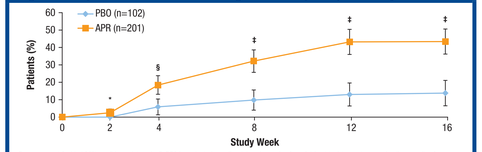
*The n reflects the number of patients as initially treated at Week 0; actual number of patients available for each parameter may vary.
†BMI is based on the last weight and height measurements taken before the randomization date.
SD=standard deviation; sPGA=static PGA.

RESULTS (cont'd)

ScPGA Response

- At Week 16, significantly more patients treated with APR (43.4%) vs. PBO (13.8%; *P*<0.0001) achieved the primary endpoint, ScPGA response (score of 0 [clear] or 1 [almost clear] with a ≥2-point reduction from baseline) (**Figure 2**).
- Results from sensitivity analyses comparing APR vs. PBO using LOCF and NRI were consistent with the MI results for the primary endpoint (LOCF: 40.3% vs. 13.7%, *P*<0.0001; NRI: 38.8% vs. 10.8%, *P*<0.0001).

Figure 2. Proportion of Patients Achieving ScPGA Response,* MI Analysis

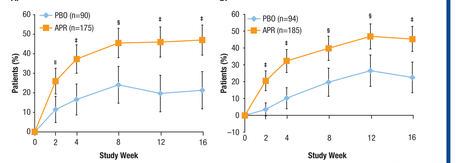


Bars represent 2-sided 95% confidence intervals. ScPGA is evaluated on a 5-point scale ranging from 0 (clear) to 4 (severe), assessing the severity of erythema, scaling, and plaque elevation.
*ScPGA response was defined as the proportion of patients achieving ScPGA score of 0 (clear) or 1 (almost clear) with ≥2-point reduction from baseline.
*P<0.05. §P<0.001. ‡P<0.0001.

Scalp and Whole Body Itch NRS

- In patients treated with APR, the proportions who achieved ≥4-point improvement from baseline at Week 16 in Scalp Itch NRS and Whole Body Itch NRS scores were significantly greater vs. patients treated with PBO (**Figure 3**).
  - A ≥4-point improvement from baseline on the Scalp Itch NRS was achieved in 47.0% of patients treated with APR vs. 21.3% receiving PBO (*P*<0.0001).
  - A ≥4-point improvement from baseline on the Whole Body Itch NRS was achieved in 45.3% of patients treated with APR vs. 22.5% receiving PBO (*P*=0.0001).
  - Statistically significant improvements with APR vs. PBO were observed on both itch NRS measures as early as Week 2 (scalp: 26.0% vs. 11.5%, *P*=0.0025; whole body: 20.5% vs. 3.5%, *P*<0.0001).
- Similar results were obtained from sensitivity analyses comparing APR vs. PBO at Week 16 using LOCF and NRI for Scalp Itch NRS response (LOCF: 46.3% vs. 18.9%, *P*<0.0001; NRI: 40.0% vs. 15.6%, *P*<0.0001) and Whole Body Itch NRS response (LOCF: 44.3% vs. 20.2%, *P*<0.0001; NRI: 40.0% vs. 19.1%, *P*=0.0005).

Figure 3. Proportion of Patients Achieving ≥4-Point Improvement in A) Scalp Itch NRS Score and B) Whole Body Itch NRS Score, MI Analysis



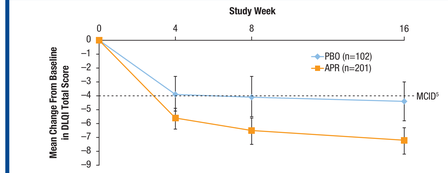
Patients rated their scalp itch or whole body itch on a scale of 0 (no itch) to 10 (worst imaginable itch). Analyses were based on patients in the ITT population with baseline Scalp Itch NRS score ≥4 or Whole Body Itch NRS score ≥4, as appropriate. Error bars represent 95% confidence interval.
‡P<0.01. §P<0.001. ‡P≤0.0001.

RESULTS (cont'd)

Quality of Life

- Mean change from baseline in DLQI total score over 16 weeks is presented in **Figure 4**.
- At Week 16, least-squares mean improvement from baseline in DLQI total score was significantly greater with APR vs. PBO (–6.7 vs. –3.8, *P*<0.0001).

Figure 4. Mean Change in DLQI Total Score, Data as Observed



PBO, n	102	97	92	83
APR, n	201	192	184	169

The DLQI total score has a possible range from 0 to 30, with higher scores corresponding to poorer health-related quality of life.
Error bars represent 95% confidence interval.

Safety

- The most common AEs reported with APR treatment from Weeks 0 to 16 included diarrhea, nausea, headache, and vomiting (**Table 2**).
- The proportion of patients with serious AEs during the PBO-controlled period was comparable between treatment groups (**Table 2**).
  - One patient in the PBO group reported a serious AE of noncardiac chest pain, and 2 patients in the APR group reported serious AEs (asthma [n=1] and chronic kidney disease [n=1]). The serious AEs were not considered treatment related.
- During the PBO-controlled period, 11 patients had ≥1 AE leading to drug withdrawal in the APR group (diarrhea [n=6], nausea [n=3], vomiting [n=3], agitation [n=1], anxiety [n=1], arthralgia [n=1], depression [n=1], dizziness [n=1], dysesthesia [n=1], headache [n=1], and joint effusion [n=1]) and 3 patients had ≥1 AE leading to drug withdrawal in the PBO group (depressive symptoms [n=1], nausea [n=1], and psoriasis [n=1]).

Table 2. Overview of Adverse Events

	Weeks 0 to 16	
	PBO n=102	APR n=200
Patients	**n (%)**	**n (%)**
≥1 AE	49 (48.0)	133 (66.5)
≥1 Serious AE	1 (1.0)	2 (1.0)
≥1 Severe AE	2 (2.0)	5 (2.5)
AE leading to drug withdrawal	3 (2.9)	11 (5.5)
Most common adverse events,§ n (%)		
Diarrhea	11 (10.8)	61 (30.5)
Nausea	6 (5.9)	43 (21.5)
Headache	5 (4.9)	23 (11.5)
Vomiting	2 (2.0)	11 (5.5)

CONCLUSIONS

- Efficacy was demonstrated in this first prospective, randomized, PBO-controlled trial of APR in patients with moderate to severe plaque psoriasis of the scalp.
- Significantly greater improvements in scalp and whole body itch and quality of life were reported in patients treated with APR vs. PBO.
- AEs were consistent with the known safety profile of APR.[6,7]

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