Safety and Efficacy of Apremilast Through 104 Weeks in Patients With Moderate to Severe Psoriasis Who Continued on Apremilast or Switched From Etanercept Treatment in the LIBERATE Study

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INTRODUCTION

- Psoriasis is a chronic, systemic inflammatory disease affecting 1% to 4% of the world's population.[1-3]
- Currently available therapies are often compromised by adverse events (AEs), safety and tolerability issues, and route of administration (injection/infusion vs. oral).[4]
- Apremilast, an oral, small-molecule phosphodiesterase 4 inhibitor, works intracellularly within immune cells to regulate the production of inflammatory mediators.[5]
- Apremilast was approved by the US Food and Drug Administration and by the European Commission for treatment of psoriasis and psoriatic arthritis.
- Evaluation in a Placebo-Controlled Study of Oral Apremilast and Etanercept in Plaque Psoriasis (LIBERATE; NCT01690299) is a global phase 3b study of apremilast 30 mg twice daily (APR) or etanercept 50 mg once weekly (ETN), compared with placebo (PBO) for the treatment of biologic-naive patients with moderate to severe plaque psoriasis.
- The objective of the current analysis was to explore the efficacy of APR and ETN in patients for 16 weeks and through 104 weeks of the LIBERATE study.

METHODS

Patients

Key Inclusion Criteria

- Adults ≥18 years of age with chronic plaque psoriasis for ≥12 months who were candidates for phototherapy and had no prior exposure to biologics for the treatment of psoriatic arthritis or psoriasis
- Moderate to severe plaque psoriasis, as defined by Psoriasis Area and Severity Index (PASI) score ≥12, psoriasis-involved body surface area (BSA) ≥10%, and static Physician Global Assessment (sPGA) score ≥3
- Inadequate response, inability to tolerate, or contraindication to ≥1 conventional systemic agent for the treatment of psoriasis

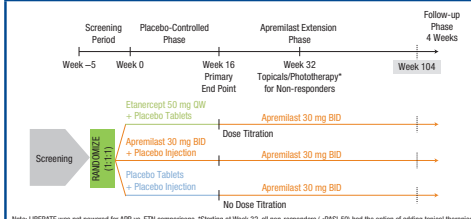
Key Exclusion Criteria

- Prior treatment with >3 systemic agents for the management of psoriasis
- Other clinically significant or major uncontrolled diseases; serious infections, including latent, active, or history of incompletely treated tuberculosis

Study Design

- There were 2 treatment phases: a 16-week randomized, double-blind, PBO-controlled phase and an 88-week APR extension phase (overall treatment duration, 104 weeks; **Figure 1**). At Week 16, patients in the PBO and ETN groups switched to APR, and patients in the APR group continued APR. APR was maintained from Weeks 16 to 104 (APR extension phase).

Figure 1. Study Design



Note: LIBERATE was not powered for APR vs. ETN comparisons. *Starting at Week 32, all non-responders (<PASI-50) had the option of adding topical therapies and/or ultraviolet B phototherapy (excluding oral psoralen combined with ultraviolet A) to their treatment regimen. Two patients in each group received topical therapy and/or phototherapy. BID=twice daily; PASI-50=≥50% reduction from baseline in Psoriasis Area and Severity Index score; QW=once weekly.

Statistical Analysis

- Efficacy assessments were conducted for the PBO-controlled phase in the modified intent-to-treat (mITT) population (all randomized patients who received ≥1 dose of study medication and had both baseline PASI and ≥1 post-treatment PASI evaluations); Week 104 analyses included patients who entered the APR extension phase and were treated in the phase.
- The safety population consisted of all patients who were randomized and received ≥1 dose of study medication.
- Continuous end points were evaluated using an analysis of covariance model with treatment and baseline body mass index (BMI; <30 and ≥30 kg/m²) as factors and baseline value as a covariate.
- Missing values were imputed using the last-observation-carried-forward (LOCF) methodology.

RESULTS

- Demographic and baseline characteristics were generally well balanced between treatment groups (**Table 1**).

Table 1. Baseline Patient Demographic and Disease Characteristics

	PBO n=84	APR n=83	ETN n=83
Age, mean, years	43.4	46.0	47.0
Male, n (%)	59 (70.2)	49 (59.0)	49 (59.0)
BMI, mean, kg/m²	29.54	29.15	29.86
Weight, mean, kg	89.51	88.52	88.08
Duration of psoriasis, mean, years	16.6	19.7	18.1
PASI score (0–72), mean	19.4	19.3	20.3
PASI score >20, n (%)	32 (38.1)	28 (33.7)	34 (41.0)
BSA, mean, %	27.3	27.1	28.4
BSA >20%, n (%)	42 (50.0)	45 (54.2)	47 (56.6)
NAPSI score ≥1, n (%)	46 (54.8)	52 (62.7)	50 (60.2)
NAPSI score*, mean (SD)	4.1 (1.9)	4.2 (2.0)	4.3 (2.2)
ScPGA ≥3, n (%)	58 (69.0)	54 (65.1)	54 (65.1)
Prior use of conventional systemic medications, n (%)[‡]	70 (83.3)	66 (79.5)	58 (69.9)

*In patients with NAPSI ≥1 for target nail, representing worst nail psoriasis at baseline. [‡]No prior exposure to biologic therapy for treatment of psoriatic arthritis or psoriasis. NAPSI=Nail Psoriasis Severity Index; ScPGA=Scalp Physician Global Assessment.

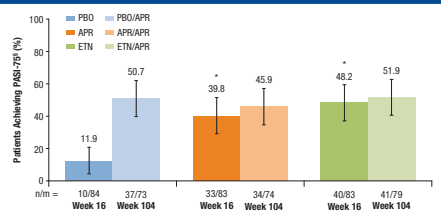
RESULTS (cont'd)

Efficacy

PASI-75 Response

- At Week 16, a ≥75% reduction from baseline in PASI score (PASI-75) was achieved by significantly more patients receiving APR vs. PBO (*P*<0.0001) (**Figure 2**).
- The PASI-75 response achieved at Week 16 was sustained through Week 104 in patients continuing APR or switching from ETN to APR at Week 16 (**Figure 2**).

Figure 2. Percentage of Patients Achieving PASI-75 Response (mITT, LOCF)

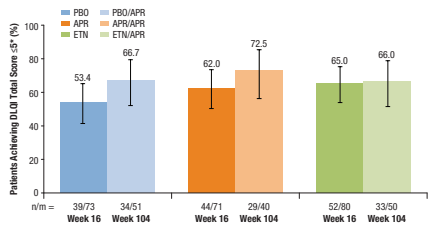


*P<0.0001 vs. PBO.
[§]Response at Week 16 and Week 104 was determined using the LOCF methodology. The analysis for Week 16 includes all patients in the modified intent-to-treat (mITT) group, while the Week 104 analysis includes patients who entered the apremilast extension phase and were treated in the phase. Error bars indicate 2-sided 95% confidence intervals.

DLQI Total Score ≤5 (minimal impairment)

- At Week 16, across treatment groups, 53.4% to 65.0% of patients achieved a DLQI score ≤5 (*P*=NS vs. PBO) (**Figure 3**).
- At Week 104, DLQI ≤5 was achieved by 66.0% to 72.5% of patients across treatment groups (**Figure 3**).

Figure 3. Percentage of Patients Achieving DLQI Total Score ≤5 (data as observed)

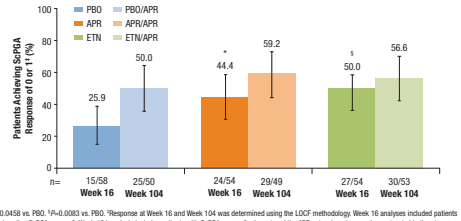


*Examined among all patients who had data at time of observation (i.e., completers, without imputation). Error bars indicate 2-sided 95% CIs.

Scalp and Nail Response

- Among patients with baseline ScPGA ≥3 (moderate or greater), ScPGA response of 0 (clear) or 1 (minimal) was achieved by significantly more patients receiving APR compared with patients receiving PBO at Week 16 (**Figure 4**).
- The ScPGA response achieved at Week 16 was sustained through Week 104 in APR/APR patients and ETN/APR patients. Responses at Week 104 among PBO/APR patients were generally similar to those in APR/APR patients (**Figure 4**).

Figure 4. Percentage of Patients Achieving ScPGA Response of 0 (Clear) or 1 (Minimal) (mITT, LOCF)

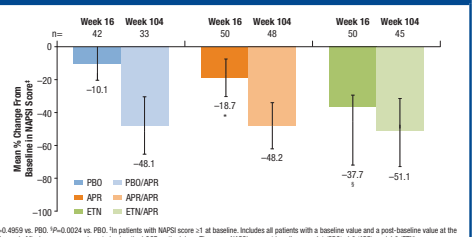


*P=0.0458 vs. PBO. [‡]P=0.0083 vs. PBO. [¶]Response at Week 16 and Week 104 was determined using the LOCF methodology. Week 16 analyses included patients with baseline ScPGA score ≥3. Week 104 analysis includes patients with ScPGA score ≥3 who entered the APR extension phase and were treated in the phase. Error bars indicate 2-sided 95% confidence intervals.

- The proportions of patients with nail psoriasis at baseline (NAPSI ≥1) who achieved NAPSI-50 at Week 16 were higher with APR (25.0%) or ETN (48.0%) than PBO (10.9%; *P*=0.0701 vs. APR and *P*<0.0001 vs. ETN).
- At Week 104, NAPSI-50 response was 60.4% (APR/APR), 65.2% (ETN/APR), and 48.6% (PBO/APR) (**Figure 5**).
- The mean percentage change from baseline in NAPSI score continued to improve in APR/APR patients and was sustained in ETN/APR patients through Week 104 (**Figure 5**).

RESULTS (cont'd)

Figure 5. Mean Percentage Change in NAPSI Score at Week 16 and Week 104 (mITT, LOCF)



*P=0.4959 vs. PBO. [‡]P=0.0024 vs. PBO. [‖]In patients with NAPSI score ≥1 at baseline. Includes all patients with a baseline value and a post-baseline value at the study week. Missing scores were imputed using the LOCF methodology. The mean NAPSI score at baseline was 4.1 (PBO), 4.2 (APR), and 4.3 (ETN).

- No increase in incidence of adverse events (AEs) occurring in ≥5% of patients in the PBO-controlled period was observed among patients in the APR/APR group with long-term exposure to APR.
- All cases of diarrhea and nausea occurring in the APR extension phase (**Table 2**) were mild or moderate in severity and generally resolved within 1 month.

Table 2. Adverse Events in ≥5% of Patients in Any Treatment Group

	APR Extension Phase (Weeks 16 to 104)		
	PBO/APR[‡]	APR/APR	ETN/APR[‡]
Patients, n (%)[*,§]	n=73; Pt-Yrs=95.6	n=74; Pt-Yrs=89.4	n=79; Pt-Yrs=102.3
	n (%)	n (%)	n (%)
Diarrhea	13 (17.8)	4 (5.4)	6 (7.6)
Nausea	5 (6.8)	3 (4.1)	5 (6.3)
URTI	5 (6.8)	5 (6.8)	1 (1.3)
Bronchitis	1 (1.4)	4 (5.4)	1 (1.3)
Nasopharyngitis	4 (5.5)	2 (2.7)	5 (6.3)
Headache	5 (6.8)	2 (2.7)	3 (3.8)
Sinusitis	0 (0.0)	1 (1.4)	5 (6.3)
Pain in extremity	1 (1.4)	3 (4.1)	4 (5.1)
Arthralgia	4 (5.5)	4 (5.4)	3 (3.8)
Rebound psoriasis	1 (1.4)	2 (2.7)	7 (8.9)
Psoriasis	2 (2.7)	4 (5.4)	0 (0.0)

*Each patient is counted once for each applicable category. [‡]Data are from patients who entered the APR extension phase and were treated in the phase. [§]No dose titration for APR. [‖]Dose titration for APR. URTI=upper respiratory tract infection.

CONCLUSIONS

- APR demonstrated significant efficacy vs. PBO at Week 16 that was sustained through Week 104 in biologic-naive patients with moderate to severe plaque psoriasis.
- APR and ETN each demonstrated statistically significant improvements in scalp psoriasis compared with PBO at Week 16 that were sustained through Week 104.
- Improvements in QOL achieved with APR and ETN at Week 16 (compared with PBO) were sustained through Week 104.
- Improvements in nail psoriasis were achieved with APR at Week 16, and continued APR treatment over 104 weeks resulted in further improvements in nail psoriasis.
- Efficacy was maintained in ETN patients who switched to APR.
- AE rates did not increase with prolonged APR exposure, and no new safety or tolerability issues were observed through Week 104 in patients with moderate to severe plaque psoriasis.

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DISCLOSURES

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