PO16

Cytokine Effects of Apremilast as a Mechanism of Efficacy in Systemic-Naive Patients With Moderate Plaque Psoriasis: Results From the UNVEIL Trial

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INTRODUCTION

- Apremilast, an oral phosphodiesterase 4 inhibitor, regulates the expression of proinflammatory cytokines involved in the pathology of psoriasis, including tumor necrosis factor (TNF)-α, interleukin (IL)-23, IL-17, and IL-22.[1-5]
- A previous pharmacodynamics (PD) subanalysis of clinical trials in patients with moderate to severe psoriasis demonstrated that the effects of apremilast on IL-17A, IL-17F, IL-22, and TNF play a role in determining clinical efficacy.[6]
- Evaluating Apremilast in a Phase IV Trial of Efficacy and Safety in Patients With Moderate Plaque Psoriasis (UNVEIL; NCT02425826) was the first prospective, randomized, controlled trial to demonstrate the clinical efficacy and safety of a systemic treatment, oral apremilast 30 mg twice daily (APR), exclusively in patients with moderate plaque psoriasis (5% to 10% psoriasis-involved body surface area [BSA]) who were naive to systemic and biologic therapy.[7]
- To characterize the PD relationship between cytokine changes and clinical response to APR treatment in patients with moderate psoriasis, a PD subanalysis was performed in UNVEIL patients, focusing on the Th17 pathway cytokines IL-17A, IL-17F, IL-22, and IL-23.

METHODS

Patients

Key Inclusion Criteria

- Males or females ≥18 years of age
- Chronic plaque psoriasis for ≥6 months before signing the informed consent form
- Moderate plaque psoriasis at screening and baseline as defined by BSA of 5% to 10% and static Physician's Global Assessment (sPGA) score 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 indication 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

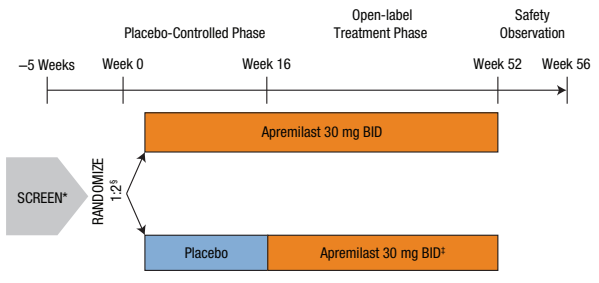
Study Design

- UNVEIL is a phase IV multicenter, randomized, double-blind, placebo (PBO)-controlled 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.
- During the open-label APR treatment phase (Weeks 16 to 52), all patients continued taking APR.

Pharmacodynamics Assessments

- Blood samples were collected from a subset of UNVEIL patients who consented to participate in the PD subanalysis.
- Samples obtained at Weeks 0 (baseline), 4, and 16 were analyzed for interleukins (IL)-17A, -17F, -22, and -23; leptin; adiponectin; apolipoproteins A-I, A-II, B, and E; and numbers of circulating T-helper 17 (Th17) cells, regulatory T cells, and total T-cell numbers.
- Randomized patients who received ≥1 dose of study medication and had a baseline value and ≥1 post-baseline value on or before Week 16 for any biomarker were included in the PD subanalysis.

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).

Statistical Analysis

- Change from baseline for each biomarker was summarized by time point and treatment group using descriptive statistics.
- The PBO and APR treatment groups were compared using the Wilcoxon rank sum test to determine any significant differences in the change from baseline and the percentage change from baseline for each biomarker at Week 4 and Week 16; data are presented as observed, with no imputation for missing values.
- Histograms were developed to depict the frequency distribution of percentage change from baseline for each biomarker at Week 4 and Week 16.
- Spearman correlations were used to describe the relationship between the percentage change from baseline to Week 16 for each biomarker and the percentage change from baseline to Week 16 in the product of the sPGA and BSA (PGAxBSA).
- Scatterplots of percentage change from baseline to Week 16 in PGAxBSA vs. percentage change from baseline to Week 16 in each biomarker were generated and include the sample size, correlation coefficient, and *P* value.

RESULTS

Pharmacodynamics Subpopulation

- Of 221 patients randomized into UNVEIL, the PD subpopulation included 38 patients (PBO, n=12; APR, n=26).
- During Weeks 0 to 16 (PBO-controlled period), 4 patients from the PD subpopulation discontinued the trial (PBO, n=1 due to adverse event; APR, n=3 due to adverse event, withdrawal by patient, and other [n=1 each]).
- Biomarkers were measured at Week 4 in 11 and 22 patients and at Week 16 in 11 and 21 patients treated with PBO and APR, respectively.
- Baseline demographics and disease characteristics were generally similar between the treatment groups (**Table 1**).

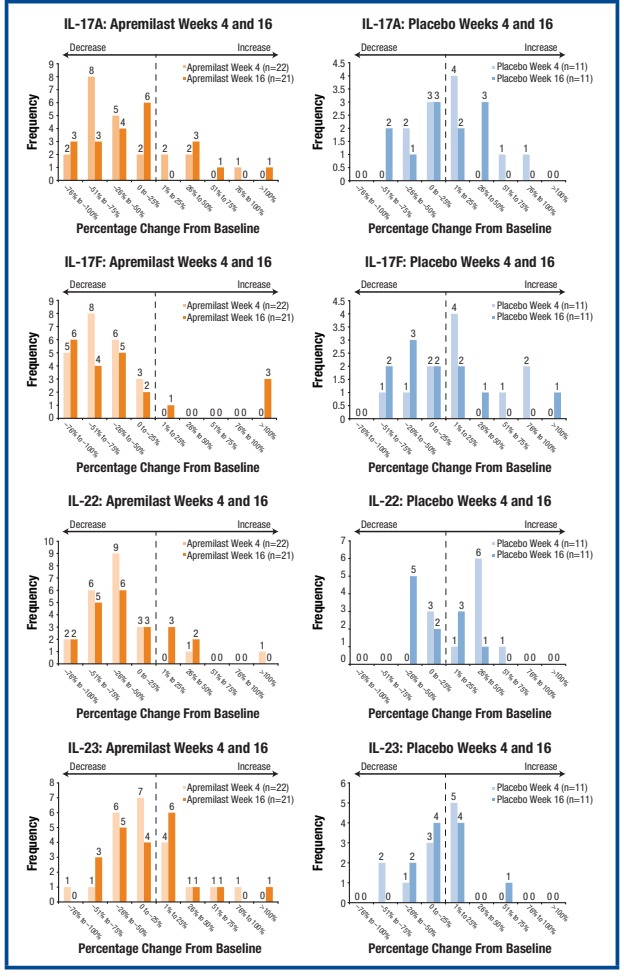
Table 1. PD Subpopulation Baseline Demographics and Disease Characteristics

	PBO n=12	APR n=26
Age, mean (SD), years	49.3 (18.7)	52.3 (14.7)
Male, n (%)	9 (75.0)	15 (57.7)
Body mass index, mean (SD), kg/m²	30.3 (7.0)	29.3 (5.4)
BSA, mean (SD), %	6.7 (1.3)	7.2 (1.7)
PASI (0–72), mean (SD)	7.2 (1.4)	8.5 (6.8)
PGAxBSA, mean (SD)	20.0 (3.9)	22.3 (6.2)

Change in Cytokine Levels With APR Treatment

- At Week 4, treatment with APR vs. PBO was associated with significant median percentage reductions in IL-17A ($P<0.05$), IL-17F ($P<0.001$), and IL-22 ($P<0.01$).
- Cytokine reductions with APR treatment persisted at Week 16 but were smaller in magnitude and achieved a statistically significant difference vs. PBO for IL-22 only ($P<0.05$).
- At Week 4 and Week 16, numerically more patients treated with APR had decreases in IL-17A, IL-17F, IL-22, and IL-23 compared with PBO (**Figure 2**).

Figure 2. Percentage Change From Baseline in Cytokine Levels at Weeks 4 and 16



Change in Levels of Leptin, Adiponectin, and Apolipoproteins With APR Treatment

- At Weeks 4 and 16, levels of leptin, adiponectin, and apolipoproteins A-I, A-II, B, and E were largely unchanged from baseline in the PBO and APR treatment groups (**Table 2**).

Table 2. Change From Baseline in Leptin, Adiponectin, and Apolipoprotein Levels at Weeks 4 and 16

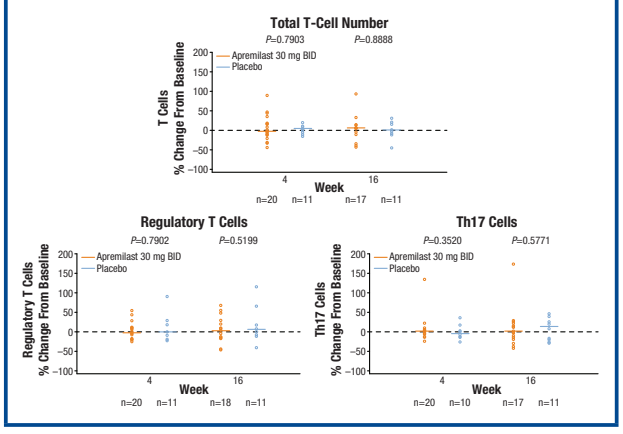
	PBO		APR	
Median % change	Week 4 n=11	Week 16 n=11	Week 4 n=22	Week 16 n=21
Leptin	–19.7	–6.1	–5.5	9.5
Adiponectin	–6.7	–6.4	–5.1	3.9
Apolipoprotein A-I	–14.3	–5.0	–4.6	0.0
Apolipoprotein A-II	–10.7	–3.8	–3.4	–4.3
Apolipoprotein B	3.4	–9.5	2.7	–8.9
Apolipoprotein E	0.0	15.4	–5.7	–4.7

RESULTS (cont'd)

Change in T-cell Populations With APR Treatment

- At Weeks 4 and 16, numbers of Th17 cells, regulatory T cells, and total numbers of T cells were largely unchanged from baseline in the PBO and APR treatment groups (**Figure 3**).

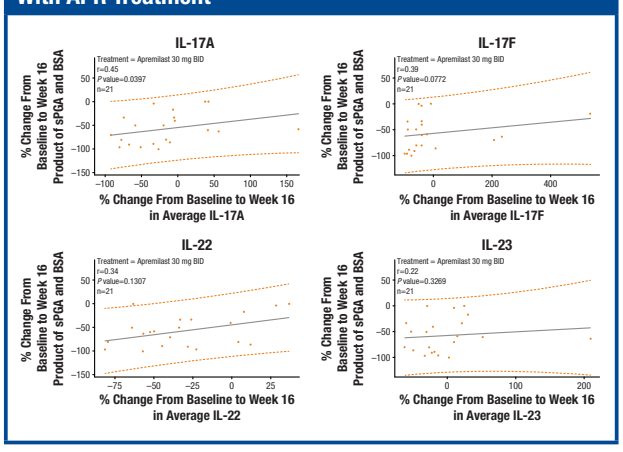
Figure 3. Median Percentage Change From Baseline in T-Cell Numbers at Weeks 4 and 16



Correlation Between Percentage Change in Cytokine Levels and Improvement in PGAxBSA at Week 16

- At Week 16 in the PD subpopulation of patients receiving APR, improvement from baseline in PGAxBSA significantly correlated with change from baseline in IL-17A ($r=0.45$; $P=0.0397$) (**Figure 4**).
- Correlations between changes from baseline in PGAxBSA and IL-17F, IL-22, and IL-23 at Week 16 in patients receiving APR showed trends but were not statistically significant (**Figure 4**).
- Changes from baseline in PGAxBSA at Week 16 did not significantly correlate with any of the other biomarkers examined (data not shown).

Figure 4. Correlations Between Median Percentage Change From Baseline in PGAxBSA and Cytokine Levels at Week 16 With APR Treatment



CONCLUSIONS

- APR significantly reduced IL-17A, IL-17F, and IL-22 plasma levels after 4 weeks of treatment. IL-23 plasma levels trended downward, but the decrease did not reach statistical significance within the 16-week timeframe.
- Apremilast had no effect on adipokines, apolipoproteins, or the number of peripheral blood Th17 cells, regulatory T cells, or total T cells within the 16-week timeframe.
- The significant association between percentage change from baseline in IL-17A and PGAxBSA at Week 16 suggests that IL-17A may be an important mechanism through which APR exerts its clinical efficacy in moderate psoriasis.

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DISCLOSURES

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