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Original Article

Apremilast mechanism of efficacy in systemic-naive patients with moderate plaque psoriasis: Pharmacodynamic results from the UNVEIL study

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ABSTRACT

Background: Pharmacodynamic (PD) subanalyses of clinical trials in patients with moderate to severe psoriasis demonstrated the efficacy of apremilast correlated with reductions in cytokines involved in the pathogenesis of psoriasis.
Objective: This PD subanalysis of a phase IV, randomized, controlled trial (UNVEIL) in systemic-naive patients with moderate plaque psoriasis (psoriasis-involved body surface area [BSA] 5%–10%; static Physician's Global Assessment [sPGA] = 3) evaluated the relationship between efficacy and changes in inflammatory biomarkers with apremilast 30 mg twice daily (BID) versus placebo.
Methods: Patients were randomized (2:1) to apremilast 30 mg BID or placebo for 16 weeks. Blood samples were analyzed for interleukins (IL)-17A, –17F, -22, and -23; cardiometabolic biomarkers (leptin; adiponectin; apolipoproteins A–I, A-II, B, and E); and the number of T-helper 17 (Th17) cells, regulatory T cells, and total T cells at Weeks 0, 4, and 16. Correlations were examined between percentage change in biomarkers and efficacy (based on PGAxBSA).
Results: Of 221 randomized patients, 38 were included in PD analyses (placebo, n = 12; apremilast, n = 26). Median percentage reductions in plasma cytokine levels were significantly greater with apremilast versus placebo for IL-17A ($P < 0.05$), IL -17F ($P < 0.001$), and IL-22 ($P < 0.01$) at Week 4 and IL-22 ($P < 0.05$) at Week 16. At Week 16, in patients receiving apremilast, improvement in PGAxBSA significantly correlated with change in IL-17A ($r = 0.45$, $P = 0.04$). Adipokines, apolipoproteins, and T-cell population levels were largely unchanged.
Conclusion: Clinical improvements in psoriasis correlated with apremilast-mediated decreases in IL-17A without significantly affecting systemic IL-23 levels, adipokines, or Th17 and regulatory T-cell numbers.

1. Introduction

Psoriasis is a systemic inflammatory disease characterized by overproliferation of keratinocytes and epidermal thickening resulting from dysregulated immune responses. [1,2] This chronic condition, which affects approximately 1% to 4% of the world's population, is often associated with comorbidities, including obesity, type 2 diabetes, hyperlipidemia, hypertension, and cardiovascular disease [3–7]. The pathogenesis of psoriasis involves keratinocyte recruitment of myeloid dendritic cells, which produce interleukin (IL)-23 to activate T helper 17 (Th17) cells [2,8,9]. Th17 cells, in turn, produce several cytokines that are

Abbreviations: AE, adverse event; BID, twice daily; BSA, psoriasis-involved body surface area; ELISA, enzyme-linked immunosorbent assay; IL, interleukin; LLoQ, lower limit of quantitation; PD, pharmacodynamics; sPGA, static Physician's Global Assessment; Th17, T helper 17; ULoQ, upper limit of quantitation; UNVEIL, Evaluating Apremilast in a Phase IV Trial of Efficacy and Safety in Patients With Moderate Plaque Psoriasis.

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known to be involved in the inflammatory disease process in psoriasis, including IL-17 and IL-22 [2,8]. It also has been suggested that dysfunction of other T-cell populations, such as regulatory T cells, may contribute to the pathogenesis of psoriasis [9–12].

Patients with plaque psoriasis, the most common form of the disease, experience bothersome symptoms such as itching, redness, flaking, and scaling, which can have substantial impacts on quality of life. [2,13,14] Despite the availability of treatment options for patients with moderate to severe plaque psoriasis, many patients with moderate psoriasis (i.e., psoriasis-involved body surface area [BSA] 3%–10% [15]) do not receive treatment or are undertreated with topical therapies [16] and report quality-of-life impairments similar to patients with more severe disease [17]. Currently available systemic therapies for psoriasis are associated with safety risks, and concerns about safety and tolerability may lead patients to discontinue systemic therapies [16,18,19].

Given that many patients with moderate psoriasis (BSA 3% to 10%) report being unsatisfied with their treatment,[20] there is a need for medications that offer sustained efficacy and manageable safety. Apremilast, an oral phosphodiesterase 4 inhibitor, is approved for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy or patients with active psoriatic arthritis. [21] In vitro analyses of T-cell cultures demonstrated that apremilast inhibits Th1 cytokines, Th2 cytokines, and Th17 cytokines, with half-maximal inhibitory concentration (IC_{50}) values ranging from 0.03 and 0.09 μM for IL-5 and IL-17, respectively, to 1.3 and 2.4 μM for IFN-γ and IL-2, respectively. [22] In pharmacodynamic (PD) analyses in patients with moderate to severe psoriasis, apremilast demonstrated partial inhibition of key cytokines that regulate inflammation in psoriasis, including IL-23, IL-17, and IL-22. [22–24] It also has been shown that reductions in plasma levels of IL-17A, IL−17 F, IL-22, and tumor necrosis factor alpha (TNF-α) with apremilast correlated with improvements in efficacy measures, suggesting that cytokine inhibition is a key mechanism by which apremilast exerts clinical efficacy in psoriasis. [23–26] Using predictive modeling algorithms, PD analyses in patients with moderate to severe psoriasis evaluated IL-17A, IL-17-F, IL-22, and TNF-α at Week 4 as predictors of PASI improvement at Week 16. The models identified synergistic and nonlinear effects among the cytokines in predicting the likelihood of PASI improvement with apremilast; IL−17 F was identified as the most important predictor of PASI improvement.[24]

Recently, Evaluating Apremilast in a Phase IV Trial of Efficacy and Safety in Patients With Moderate Plaque Psoriasis (UNVEIL; NCT02425826), the first prospective, randomized, controlled trial exclusively in patients with moderate plaque psoriasis (BSA 5%–10%) who were naive to systemic and biologic therapy, demonstrated the clinical efficacy and safety of systemic oral treatment with apremilast 30 mg twice daily (BID). [17,27] To characterize the PD relationship between cytokine changes and clinical response to apremilast treatment in systemic-naive patients with moderate psoriasis, a PD analysis was performed among a subset of patients enrolled in UNVEIL. The primary objective of this analysis was to explore the mechanism of action of apremilast by investigating its effects on the Th17 pathway cytokines IL-17A, IL−17 F, IL-22, and IL-23 and on T-cell populations, namely Th17 cells and regulatory T cells. A secondary objective assessed the effects of apremilast on cardiometabolic biomarkers such as adipocyte-derived hormones and cholesterol-binding proteins.

2. Materials and methods

2.1. Study design

This biomarker and correlative analysis is a substudy of UNVEIL, a phase IV, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of apremilast 30 mg BID versus placebo in patients with moderate plaque psoriasis (**Appendix**). Details of the study design have been previously described. [17] Briefly, patients were randomized (2:1) to receive apremilast 30 mg BID or placebo during Weeks 0–16, with dose titration over the first week of treatment. At Week 16, patients initially randomized to placebo were switched to apremilast 30 mg BID, with dose titration, and patients initially randomized to apremilast continued taking apremilast through Week 52. This study adhered to Good Clinical Practice according to the International Conference on Harmonisation and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The protocol was approved by the institutional review boards of participating medical centers, and all patients provided written informed consent before participating in the study. Patients completed written informed consent forms to provide blood samples for the cytokine and leukocyte assessments and for the cardiometabolic analysis separately.

2.2. Patients

Eligible patients were adults (aged ≥18 years) with a diagnosis of chronic plaque psoriasis for 6 months before signing the informed consent form. At the screening and baseline (Week 0) visits, patients had moderate plaque psoriasis, defined as psoriasis-involved 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). Patients included in the study had no prior exposure to systemic or biologic treatments for psoriasis, psoriatic arthritis, or any other indication that could affect the assessment of psoriasis. Patients were excluded from the study if they had an inflammatory or dermatologic condition, including forms of psoriasis other than plaque psoriasis, or if they had received topical therapy within 2 weeks or phototherapy within 4 weeks of randomization.

2.3. Pharmacodynamic assessments

Blood samples for biomarker analyses were collected at Weeks 0 (baseline), 4, and 16. The plasma concentrations of IL-17A, IL−17 F, IL-22, and IL-23 were assessed by immunoassay using ultra-sensitive single molecule counting (SMC™) Erenna® technology (EMD Millipore, Alameda, CA), a version enzyme-linked immunosorbent assay (ELISA) that enhances sensitivity and dynamic range by improving signal-to-noise ratios. The plasma concentrations of leptin, adiponectin, and apolipoproteins A–I, A-II, B, and E were assessed using the Myriad RBM Luminex assay LLoQ (Myriad RBM, Austin, TX). Numbers of circulating Th17 cells, regulatory T cells, and total T cells were quantified by Epiontis epigenetic assay, which enumerates cells based upon the demethylation status of the IL-17A, FOXP3, and CD3 genes, respectively (Epiontis, Berlin, Germany).

2.4. Statistical analysis

This PD analysis was performed in a subset of randomized patients who received ≥1 dose of study medication and had a baseline value and at least one postbaseline value on or before Week 16 for any biomarker. Baseline was defined as the last biomarker value measured at Week 0 before the first dose of study medication was administered (on or before the day of the first dose of study medication). Demographic and baseline disease characteristics were described using summary statistics for continuous variables and number and percentage for categorical variables. Observed values and change from baseline for each biomarker

Table 1
Baseline Demographics and Disease Characteristics for the Pharmacodynamics Subpopulation.

	Placebo n = 12	Apremilast 30 mg BID n = 26
Age, mean (SD), years	49.3 (18.7)	52.3 (14.7)
Male, n (%)	9 (75.0)	15 (57.7)
Race, n (%)		
Asian	2 (16.7)	1 (3.8)
White	9 (75.0)	23 (88.5)
Other	1 (8.3)	2 (7.7)
Ethnicity, n (%)		
Not Hispanic or Latino	12 (100.0)	24 (92.3)
Hispanic or Latino	0 (0)	2 (7.7)
Body mass index, mean (SD), kg/m^2	30.3 (7.0)	29.3 (5.4)
BSA, mean (SD), %	6.7 (1.3)	7.2 (1.7)
sPGA, n (%)		
1 (Almost Clear)	0 (0)	0 (0)
2 (Mild)	0 (0)	0 (0)
3 (Moderate)	12 (100.0)	24 (92.3)
4 (Severe)	0 (0)	2 (7.7)
5 (Very Severe)	0 (0)	0 (0)
PASI (0–72), mean (SD)	7.2 (1.4)	8.5 (6.8)
PGAxBSA, mean (SD)	20.0 (3.9)	22.3 (6.2)

BSA = psoriasis-involved body surface area; PASI = Psoriasis Area and Severity Index; PGAxBSA = product of the sPGA and BSA; SD = standard deviation; sPGA = static Physician's Global Assessment.

were summarized by time point and treatment group using descriptive statistics. At Week 4 and Week 16, between-group comparisons in change from baseline and percentage change from baseline for each biomarker were performed using the Wilcoxon rank sum test, and frequency distribution of percentage change from baseline for each biomarker at Week 4 and Week 16 was presented graphically using histograms. Data are presented as observed, with no imputation for missing values. However, to mediate the impact of extreme values, biomarker values that were below the lower limit of quantitation (<LLoQ) were imputed to be one-half of the LLoQ, and values above the upper limit of quantitation (>ULoQ) were imputed to be 2 times the ULoQ. 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 were generated to show the percentage change from baseline to Week 16 in PGAxBSA versus the percentage change from baseline to Week 16 in each biomarker.

3. Results

3.1. Patients

Of 221 randomized patients in UNVEIL, the PD subpopulation included 38 patients (12 patients who received placebo and 26 patients who received apremilast). During the placebo-controlled period (Weeks 0 to 16), 4 patients from the PD subpopulation discontinued the study. In the placebo group, 1 patient discontinued due to an adverse event (AE) of a sore shoulder that was considered a nonserious AE and was mild in severity. In the apremilast group, 1 patient discontinued due to an AE (the AE was a nonserious AE of intermittent nausea that was moderate in severity and resolved after treatment was withdrawn), 1 patient withdrew from the study, and 1 patient was withdrawn from the study because of a protocol violation (the patient did not meet the inclusion criteria of having a baseline sPGA score of 3). Patient demographics and baseline disease characteristics were similar between treatment groups for patients in the PD subpopulation (Table 1) and were generally comparable to patients in the full intent-to-treat population. Mean age, body mass index, and disease severity were similar between treatment groups, and most patients in the study were male.

3.2. Changes in plasma cytokine levels

At baseline, median plasma cytokine levels for the placebo and apremilast 30 mg BID treatment groups were generally similar for IL-17A, IL−17 F, IL-22, and IL-23. At Week 4, significantly greater median percentage reductions from baseline in plasma cytokine levels were observed with apremilast versus placebo for IL-17A, IL−17 F, and IL-22; changes from baseline in plasma levels of IL-23 were similar in the apremilast and placebo treatment groups (Table 2). Reductions in plasma cytokine levels observed with apremilast were sustained at Week 16 but were smaller in magnitude compared with Week 4; a statistically significant difference versus placebo was observed for IL-22 but not for the other cytokines assessed (Table 2). At Week 4 and Week 16, the proportions of patients who had decreases in IL-17A, IL−17 F, IL-22, and IL-23 were numerically greater among patients treated with apremilast versus placebo (Fig. 1a-h).

3.3. Changes in levels of adipokines and apolipoproteins

Baseline median plasma concentrations of leptin, adiponectin, and apolipoproteins A–I, A-II, B, and E were comparable between

Table 2
Change From Baseline in Plasma Levels of Cytokines and Cardiometabolic Biomarkers at Weeks 4 And 16.

	Placebo, n = 12			Apremilast 30 mg BID, n = 22				
	Baseline n = 12	Week 4 n = 11	Week 16 n = 11	Baseline, n = 22	Week 4 n = 22		Week 16 n = 21	
Cytokines	**Median (pg/mL)**	**Median % change**	**Median % change**	**Median (pg/mL)**	**Median % change**	***P* value***	**Median % change**	***P* value***
IL-17A	0.335	9.26	−1.57	0.475	−42.50	0.0193	−19.51	0.2001
IL−17 F	1.650	12.82	−1.86	2.495	−64.43	0.0005	−41.67	0.1227
IL-22	7.443	8.62	−16.31	9.780	−42.89	0.0021	−33.58	0.0368
IL-23	0.603	−6.63	−8.96	0.453	−15.17	0.6911	−19.17	0.6655
Cardiometabolic biomarkers	**Median (μg/mL)**	**Median % change**	**Median % change**	**Median (μg/mL)**	**Median % change**	***P* value***	**Median % change**	***P* value***
Leptin	0.008	−19.7	−6.1	0.010	−5.5	0.3662	9.5	0.8440
Adiponectin	3.30	−6.67	−6.35	3.45	−5.13	0.8945	3.85	0.7234
Apolipoprotein A-I	1950.0	−14.3	−5.0	2100.0	−4.6	0.3556	0.0	0.9686
Apolipoprotein A-II	0.319	−10.7	−3.8	0.328	−3.4	0.6635	−4.3	0.5050
Apolipoprotein B	1390.0	3.4	−9.5	1385.0	2.7	0.6911	−8.9	0.9060
Apolipoprotein E	41.0	0.0	15.4	49.5	−5.7	0.4392	−4.7	0.1227

* *P* value versus placebo based on Wilcoxon rank sum test. IL = interleukin.

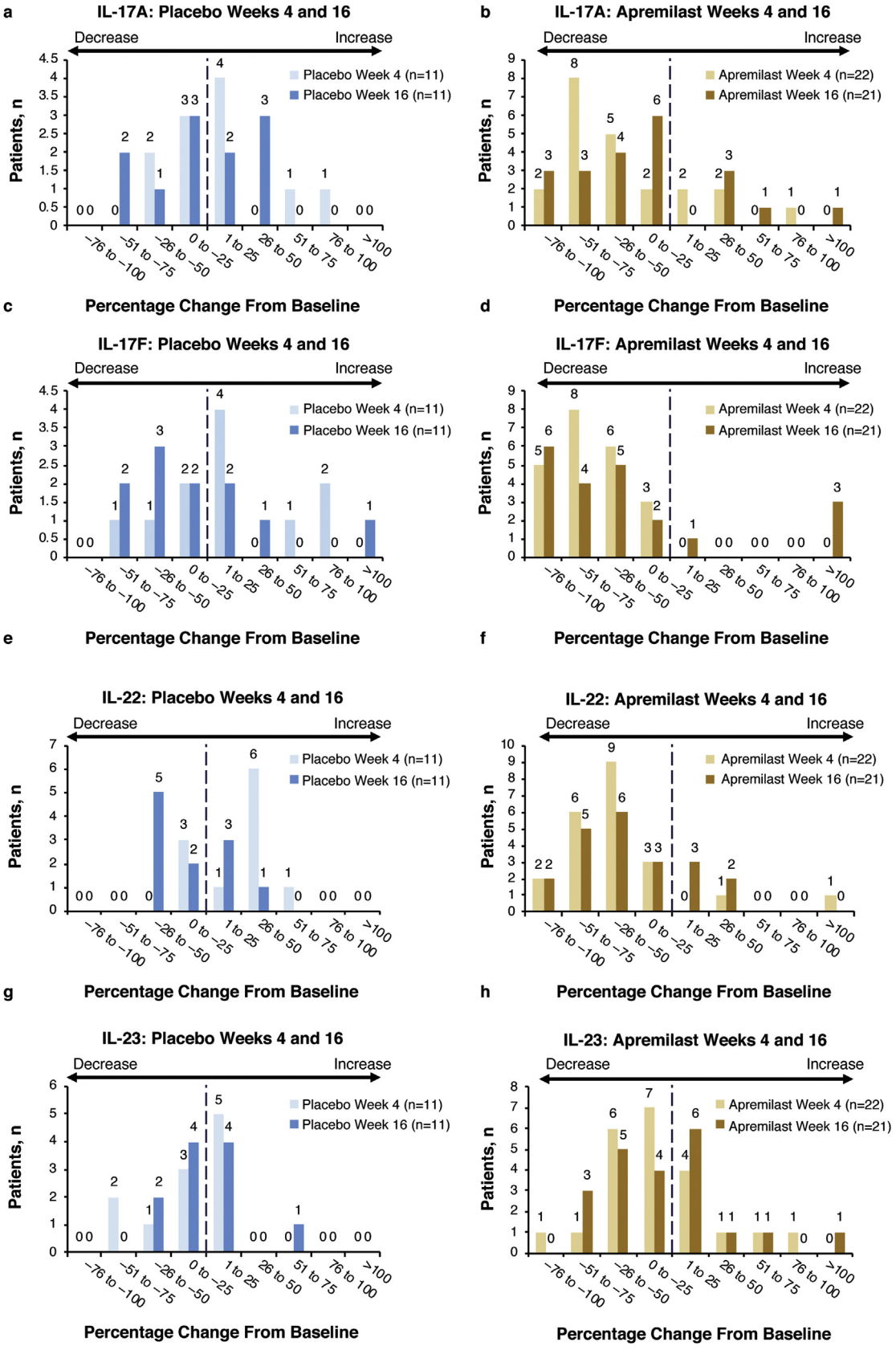

Fig. 1. a–h. Percentage Change From Baseline in Cytokine Levels at Week 4 and Week 16 IL = interleukin.

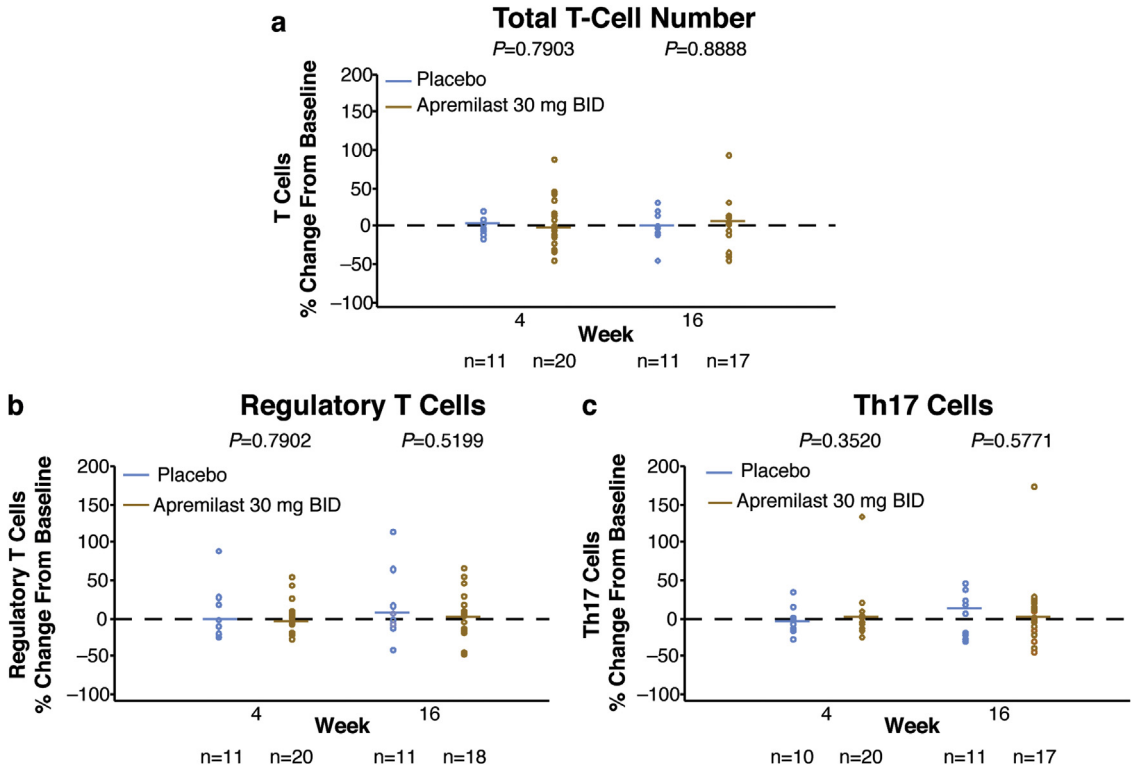

Fig. 2. Median Percentage Change From Baseline in Total T-Cell (a), Regulatory T-Cell (b), and Th17 Cell (c) Numbers at Week 4 and Week 16.

patients receiving placebo and apremilast 30 mg BID (Table 2). At Weeks 4 and 16, median percentage changes from baseline in plasma levels of leptin, adiponectin, and apolipoproteins A–I, A-II, B, and E were not significantly different between placebo and apremilast (Table 2).

3.4. Changes in T-cell populations

Median T-cell populations at baseline were similar between the placebo and apremilast 30 mg BID groups, respectively (Th17 cells: 0.8% vs. 0.7%; regulatory T cells: 1.5% vs. 1.8%; total T-cells: 30.2% vs. 30.9%). There were no statistically significant differences in median percentage change from baseline in T-cell populations between the placebo and apremilast groups, respectively, at Week 4 (Th17 cells: 2.7% vs. − 3.9%, $P = 0.3520$; regulatory T cells: −2.0% vs. 0%, $P = 0.7902$; total T cells: −2.3% vs. 4.1%, $P = 0.7903$) and Week 16 (Th17 cells: 1.9% vs. 14.6%, $P = 0.5771$; regulatory T cells: 3.5% vs. 7.3%, $P = 0.5199$; total T cells: 6.0% vs. 0.9%, $P = 0.888$). At Week 4 and Week 16, median percentage changes from baseline in the numbers of Th17 cells, regulatory T cells, and total T cells were similar in patients receiving placebo and apremilast (Fig. 2**a-c**).

3.5. Correlations between percentage change in biomarker levels and improvement in PGAxBSA at week 16

Spearman correlations were statistically significant and positive between percentage change from baseline in PGAxBSA and plasma levels of IL-17A at Week 16 in the apremilast 30 mg BID group (Fig. 3a and Table 3). Although correlations between changes from baseline in PGAxBSA and IL−17 F, IL-22, and IL-23 at Week 16 were not statistically significant, trends toward positive associations were observed in the apremilast group (Fig. 3b–d and Table 3). In the placebo group, statistically significant correlations were not observed between changes from baseline in PGAxBSA and any of the cytokines assessed at Week 16 (Fig. 3e–h and Table 3). Furthermore, there were no statistically significant correlations between changes from baseline in PGAxBSA at Week 16 and the cardiometabolic biomarkers or T-cell populations in the placebo group or the apremilast 30 mg BID group (Table 3).

3.6. Discussion

In this PD substudy of UNVEIL, a phase IV, randomized, controlled trial, treatment with apremilast 30 mg BID significantly reduced IL-17A, IL−17F, and IL-22 plasma levels after 4 weeks of treatment in systemic-naive patients with moderate plaque psoriasis, and significant associations were observed between the percentage changes from baseline in IL-17A and PGAxBSA at Week 16. These findings are consistent with prior studies conducted in patients with moderate to severe psoriasis and psoriatic arthritis, which found significant associations between reduction in plasma levels of relevant cytokines and measures of clinical efficacy with apremilast [23–26]. The current analysis expands on these previous findings and demonstrates that in systemic-naive patients with moderate psoriasis, partial inhibition of systemic Th17 cytokines with apremilast treatment occurred without affecting systemic levels of the upstream cytokine IL-23, T-cell populations, or any of the tested adipokines or apolipoprotein biomarkers assessed by Week 16. Taken together, these findings indicate that apremilast mediates clinical anti-inflammatory effects in psoriasis largely via inhibition of expression of the Th17 cytokine IL-17. This analysis further substantiates that IL-17 is a central cytokine in psoriatic pathophysiology, [28,29] with its inhibition necessary for the treatment of psoriasis and psoriatic arthritis [28].

In this PD substudy, among the apremilast-treated patients there was a significant correlation between percentage change from baseline at Week 16 in PGAxBSA and percentage change from baseline at Week 16 in IL-17A ($P = 0.0397$), and a trend for IL-17F

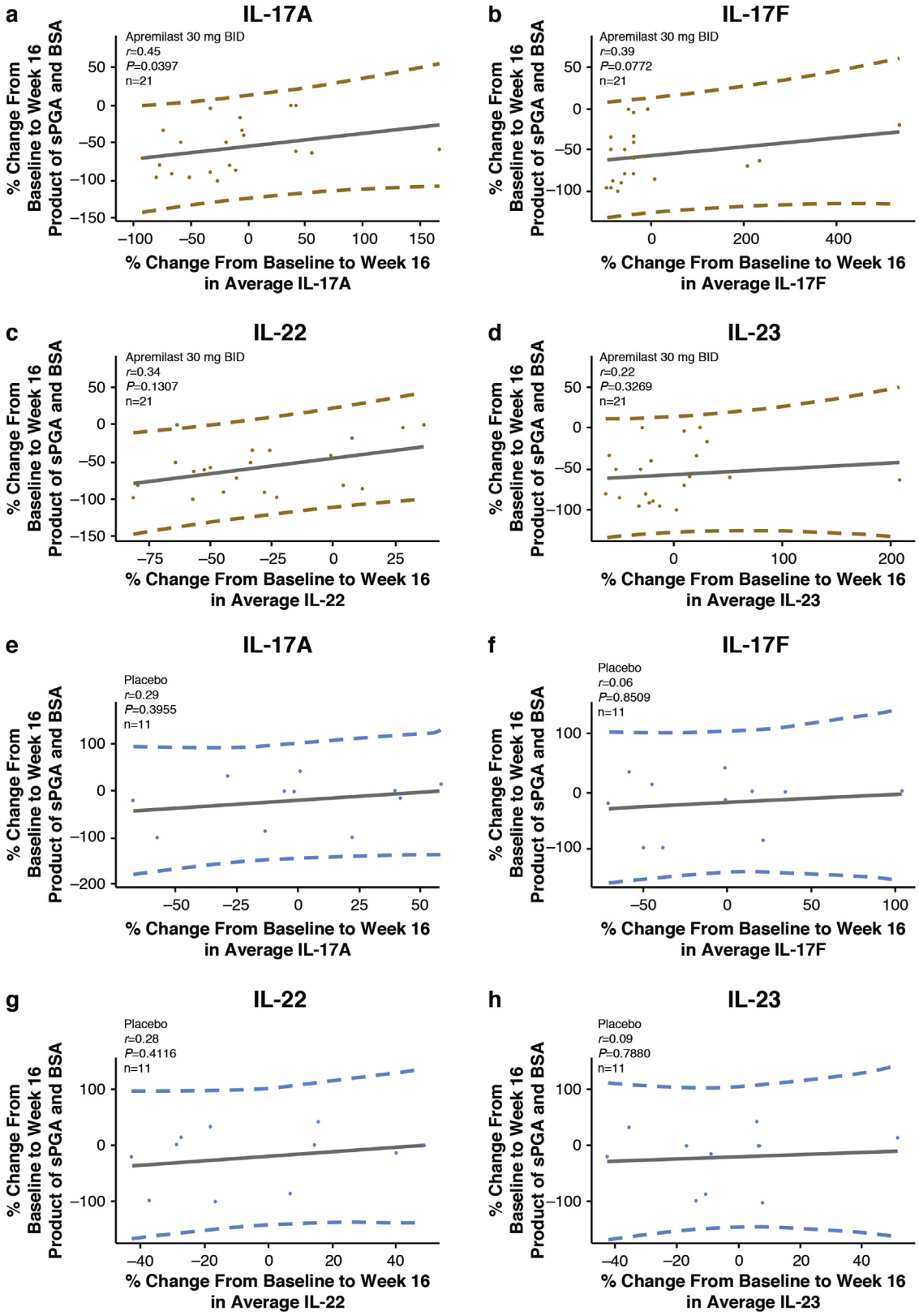

Fig. 3. Correlations Between Median Percentage Change From Baseline in PGAxBSA and Cytokine Levels at Week 16 With Apremilast 30 mg BID (a–d) and Placebo (e–h). Correlation coefficient (r) and *P* value are based on Spearman correlation analysis. BSA = psoriasis-involved body surface area; IL = interleukin; sPGA = static Physician's Global Assessment.

(*P* = 0.0772) and IL-22 (*P* = 0.1307) (Fig. 3**a, b,** and **c**). In the overall UNVEIL study population, subgroup analyses of the primary endpoint found a treatment effect favoring apremilast versus placebo across multiple demographic and disease characteristic subgroups (e.g., age, sex, race, baseline BMI, history of scalp psoriasis, nail psoriasis, or psoriatic arthritis); estimates were mostly similar among subgroups (i.e., overlapping 95% confidence intervals; data not shown).

Table 3
Association Between PGAxBSA Improvement and Plasma Biomarker Levels at Week 16[§].

Cytokine	Placebo n = 11		Apremilast 30 mg BID n = 22	
	r	*P* value	*r*	*P* value
Cytokines				
IL-17A	0.29	0.3955	0.45	0.0397
IL−17 F	0.06	0.8509	0.39	0.0772
IL-22	0.28	0.4116	0.34	0.1307
IL-23	0.09	0.7880	0.22	0.3269
Cardiometabolic biomarkers				
Leptin	0.09	0.7984	−0.27	0.2287
Adiponectin	−0.43	0.1843	−0.05	0.8359
Apolipoprotein-AI	0.34	0.3059	−0.20	0.3769
Apolipoprotein-AII	0.06	0.8509	0.0	0.9955
Apolipoprotein-B	−0.06	0.8614	−0.22	0.3312
Apolipoprotein-E	−0.38	0.2530	−0.29	0.1970
T-cell Populations				
Th17	−0.07	0.8298	0.22	0.3913
Regulatory T cells	−0.46	0.1501	0.09	0.7287
Total T cells	0.16	0.6462	−0.21	0.4128

Correlation coefficient (*r*) and *P* value are based on Spearman correlation analysis. IL = interleukin; Th17=T helper 17.

There were 2 patients who experienced a clinical improvement of ≥50% reduction in PGAxBSA without a corresponding decrease in IL-17A (Fig. 3**a**). In these 2 patients, there were large decreases in IL-22 (−56.5% and −49.6%). Similarly, there were 2 patients with ≥50% clinical improvement without a corresponding decrease in IL-22 (Fig. 3**c**). In these 2 patients there was a notable decrease in IL-23 (−50.0%, −62.8%). Therefore, it would appear that not all the cytokine changes occurred in parallel in all patients.

It should be noted that apremilast lacks AEs specific to biologic therapies that directly bind to and inhibit the activity of IL-17 (e.g., serious infections, such as tuberculosis, and worsening or *de novo* initiation of inflammatory bowel disease, such as Crohn's disease), [21,30] suggesting that the mechanism of action of apremilast does not exactly recapitulate the mechanism of action of biologics that target IL-17. It is also possible that differences in AE profiles between apremilast and biologics might reflect a magnitude of effect whereby apremilast reduces IL-17 levels less than the anti-IL-17 biologics and is thus less prone to these potential adverse outcomes.

In this study of patients with moderate plaque psoriasis, there were slightly greater reductions in plasma IL-17A, IL−17 F, and IL-22 observed in apremilast-treated patients at Week 4 versus Week 16. These differences were relatively minor and may be attributed to sampling noise due to the small sample size. No consistent loss of cytokine reduction was observed in the apremilast-treated patients with moderate to severe plaque psoriasis in the phase 3 ESTEEM 2 study or in the phase 2b Japanese PSOR-011 study.[24]

Preclinical studies have demonstrated the mechanism by which apremilast inhibits production of T-cell cytokines such as IL-17. [22] Through inhibition of PDE4 enzymatic activity, apremilast increases intracellular cyclic adenosine monophosphate (cAMP) levels and activates the protein kinase A pathway, resulting in phosphorylation of CREB and ATF-1, thereby increasing cAMP responsive element transcriptional activity and decreasing nuclear factor κB transcriptional activity. This results in downregulated production of multiple T-cell cytokines including IL-17 and TNF-α. [22] In addition to these direct effects on T cells, apremilast also has similar effects in myeloid cells, resulting in decreased expression of multiple genes of the Th1, Th17, and Th22 pathways. [23] The clinical pharmacodynamics observed in apremilast-treated psoriasis patients are consistent with this mechanism of action.

In this PD subanalsyis of UNVEIL, a phase IV randomized, placebo-controlled study of apremilast in systemic-naive patients with moderate plaque psoriasis, treatment with apremilast 30 mg BID significantly reduced plasma levels of key cytokines involved in the pathogenesis of psoriasis without significantly altering levels of IL-23, leptin, adiponectin, apolipoproteins, Th17, or regulatory T-cell populations. The significant association observed between reduction in IL-17A levels and improvement from baseline in PGAxBSA at Week 16 suggests that IL-17A cytokine inhibition is an important mechanism of the efficacy of apremilast.

Author disclosures

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Appendix A

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).

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BSA: week 16 results from the UNVEIL study. *J Drugs Dermatol.* 2017;16(8):801-8.

Appendix B. Supplementary data

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