A Phase 2 Randomized Trial of Apremilast in Patients with Atopic Dermatitis

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A phase 2, double-blind, placebo-controlled trial evaluated apremilast efficacy, safety, and pharmacodynamics in adults with moderate to severe atopic dermatitis. Patients were randomly assigned to receive placebo, apremilast 30 mg twice daily (APR30), or apremilast 40 mg twice daily (APR40) for 12 weeks. During weeks 12–24, all patients received APR30 or APR40. A biopsy substudy evaluated atopic dermatitis-related biomarkers. Among 185 randomly assigned intent-to-treat patients at week 12, a dose-response relationship was observed; APR40 (n = 63), but not APR30 (n = 58), led to statistically significant improvements (vs. placebo, n = 64) in Eczema Area and Severity Index (mean [standard deviation] percent change from baseline = −31.6% [44.6] vs. −11.0% [71.2], P < 0.04; primary endpoint). mRNA expression of T helper type 17/T helper type 22-related markers (IL-17A, IL-22, and S100A7/A8; P < 0.05) showed the highest reductions with APR40, with minimal changes in other immune axes. Safety with APR30 was largely consistent with apremilast’s known profile (common adverse events: nausea, diarrhea, headache, and nasopharyngitis). With APR40, adverse events were more frequent, and cellulitis occurred (n = 6). An independent safety monitoring committee discontinued the APR40 dosage. APR40 showed modest efficacy and decreased atopic dermatitis-related biomarkers in moderate to severe atopic dermatitis patients. Adverse events, including cellulitis, were more frequent with APR40, which was discontinued during the trial. Clinical Trial Registration Number: NCT02087943 (clinicaltrials.gov).

INTRODUCTION

Atopic dermatitis (AD) is a heterogeneous, chronic, inflammatory skin disorder with clinical features that include highly pruritic, eczematous lesions (Bieber, 2008; Eichenfield et al., 2014a, 2014b). Genetic and environmental factors are believed to underlie dysfunctional T-helper (Th) cell type 1, Th2, and Th17 innate and adaptive immune responses in patients with AD (Bieber, 2008; Brunner et al., 2017; Czarnowicki et al., 2014; Gittler et al., 2012; Gutman-Yassky and Krueger, 2017; Gutman-Yassky et al., 2011; Park et al., 2013). Some patients with AD exhibit elevated serum levels of total and allergen-specific IgE (extrinsic AD), whereas others have normal IgE levels and negative results for serum allergen-specific IgE (intrinsic AD) (Eichenfield et al., 2014b; Park et al., 2013; Park et al., 2008). Although total IgE levels may be more elevated in patients with greater AD disease severity, there is substantial variability in the general US population, making the clinical significance of this distinction unclear (Eichenfield et al., 2014b).

AD is treated primarily with topical therapies, mainly with intermittent, preventive application of topical corticosteroids and/or topical calcineurin inhibitors, paired with daily emollient use (McGregor et al., 2017). Intermittent corticosteroid use poses minimal risk of corticosteroid-associated adverse effects like skin atrophy, striae formation in sensitive or thin-skinned areas, and systemic effects (Hanifin et al., 2002). The rate of long-term adherence to topical therapy, however, is low (Snyder et al., 2015). Off-label use of other conventional systemic oral immunomodulatory agents such as cyclosporine, azathioprine, and methotrexate in adults with AD can be effective, but patients have reported adverse events (AEs) or ineffectiveness as reasons for discontinuation of treatment; use of these drugs poses well-known safety limitations and requires regular laboratory monitoring (Roekevisch et al., 2018; Sidbury et al., 2014). Thus, better systemic treatment options are needed, particularly for patients with AD who do not adequately respond to topical therapy. Dupilumab, a subcutaneous injectable biologic therapy that targets the IL-4 and IL-13 receptor (Beck et al., 2014), was approved by the US Food and Drug Administration for the treatment of adult patients with moderate to severe AD (Jensterle et al., 2015). The need for oral treatment options remains a priority in this disease state.

Apremilast, an orally available phosphodiesterase 4 (PDE4) inhibitor that is approved for the treatment of adults with moderate to severe psoriasis and active psoriatic arthritis (Celgene, 2017), regulates a number of the proinflammatory signals involved in AD, including IL-17, IL-22, IL-13, IL-31, IL-18, and tumor necrosis factor (TNF), which are produced by Th17 and Th1 cells (Simpson et al., 2016). In a phase 2, double-blind, placebo-controlled trial of 185 patients with moderate to severe atopic dermatitis, patients randomly assigned to receive placebo, a low dose of apremilast (APR30), or a high dose of apremilast (APR40) for 12 weeks showed modest efficacy and decreased atopic dermatitis-related biomarkers in moderate to severe atopic dermatitis patients. Adverse events, including cellulitis, were more frequent with APR40, which was discontinued during the trial. Clinical Trial Registration Number: NCT02087943 (clinicaltrials.gov).
IL-33, IL-5, and the alarmins S100A7, S100A8, and S100A12 (Adams et al., 2015; Gottlieb et al., 2013; Schafer et al., 2014). In patients with moderate to severe psoriasis receiving apremilast 30 mg twice daily for 16 weeks, 29%–41% achieved a 75% or greater reduction from baseline in Psoriasis Area and Severity Index score; continued treatment up to 52 weeks is marked by sustained Psoriasis Area and Severity Index response and an acceptable safety profile (Papp et al., 2012, 2013; Pau et al., 2015; Reich et al., 2017; Crowley et al., 2017). In small, single-center, open-label pilot studies, findings with apremilast have been mixed in patients with moderate to severe AD (Samrao et al., 2012; Volf et al., 2017), suggesting that systemic PDE4 inhibition may benefit patients with moderate to severe AD. The objective of this phase 2 study was to evaluate the efficacy, safety, and pharmacodynamics profile of apremilast for the treatment of adult patients with moderate to severe AD.

RESULTS

Patients

A total of 191 patients were enrolled and randomly assigned to treatment groups. However, because of the unanticipated death of an investigator at one of the study sites, the six patients enrolled at that site were excluded from the intent-to-treat population, because their data could not be confirmed by the investigator and were deemed invalid according to International Council for Harmonisation Good Clinical Practice guidelines. Consequently, 185 patients constituted the intent-to-treat population (placebo, n = 64; apremilast 40 mg twice daily, n = 63; apremilast 30 mg twice daily, n = 58). Of these, 146 (78.9%) completed week 12, with comparable completion rates among the placebo and apremilast treatment groups (78%–97%) (see Supplementary Figure S1 online). The most common reasons for discontinuation were lack of efficacy in the placebo and apremilast 30 mg twice daily arms and AEs in the apremilast 40 mg twice daily arm. A benefit-risk assessment by the sponsor’s independent data and safety monitoring board and an external data monitoring committee recommended that the apremilast 40 mg twice daily dose be discontinued and that patients in this arm be reassigned to receive apremilast 30 mg twice daily. Two patients taking apremilast 40 mg twice daily were reassigned to receive apremilast 30 mg twice daily on or after the week 20 visit.

Demographic and baseline clinical characteristics were generally comparable across treatment groups, with the exceptions that the placebo group had a smaller proportion of male patients, the apremilast 40 mg twice daily group had a smaller percentage of patients with a static physician’s global assessment—acute signs (sPGA-A) rating of severe, and the apremilast 30 mg twice daily group had greater prior use of systemic immunosuppressive therapy (Table 1). During the placebo-controlled period, use of permitted concomitant therapies for AD, which included low-potency topical corticosteroids and oral antihistamines, oral leukotriene antagonists, inhaled corticosteroids, skin emollients, moisturizers, sunscreen, and cosmetics, was slightly higher in the placebo group (24/64, 37.5%) and the apremilast 30 mg twice daily group (20/58, 34.5%) compared with the apremilast 40 mg twice daily group (16/63, 25.4%). In the placebo group, 6 of 64 (9.4%) and 5 of 64 (7.8%) patients were treated with betamethasone butyrate propionate and zinc oxide, respectively, whereas no patients in the apremilast 40 mg twice daily and apremilast 30 mg twice daily groups were treated with either dermatologic agent.

Clinical efficacy

At week 12, patients who received apremilast 40 mg twice daily showed significantly greater percent improvement from baseline in Eczema Area and Severity Index (EASI) score versus placebo (mean [standard deviation] = −31.6% [44.6] vs. −11.0% [71.2], P < 0.04; effect size [95% confidence interval [CI]] = −20.6 [−39.7 to −1.5]). Patients who received apremilast 30 mg twice daily showed a trend toward greater EASI improvement at week 12 (mean [standard deviation] = −26.0% [40.1]; effect size [95% CI] = −15.0 [−34.5 to 4.5]) versus placebo but did not reach statistical significance (Figure 1a). At week 24, with the observed data, mean (standard deviation) percent change in EASI score improved from baseline among patients initially randomly assigned to receive apremilast (apremilast 40 mg twice daily: −51.1% [42.2]; apremilast 30 mg twice daily: −49.6% [33.1]); placebo patients who switched to apremilast at week 12 showed week 24 EASI improvements consistent with apremilast-treated patients (placebo/apremilast 40 mg twice daily: −58.2% [30.8]; placebo/apremilast 30 mg twice daily: −49.4% [53.5]). A ≥50% reduction in EASI score at week 12 was achieved by 32.8% (21/64, placebo), 42.9% (27/63, apremilast 40 mg twice daily), and 31.0% (18/58, apremilast 30 mg twice daily) of patients (P not statistically significant for both apremilast dosages vs. placebo;
Apremilast 30 mg BID
Apremilast 40 mg BID

CI] to 18.2]; apremilast 30 mg twice daily effect size [95%
receive apremilast 30 mg twice daily (as-observed propor-
assigned to receive apremilast 40 mg twice daily and increased
3.4% (2/58, apremilast 30 mg twice daily) of patients (28/45
30 mg twice daily (as-observed proportions, 62.2%
attained through week 24 among patients initially randomly
30 mg twice daily was associated with a significantly greater
percent improvement (decrease) from baseline Dermatology
statistically significant for both apremilast dosages vs. placebo;
at week 12, apremilast 40 mg twice daily was associated with a significantly greater percent improvement (decrease) from baseline Dermatology Life Quality Index versus placebo (least-squares mean [standard error] = −27.3% [8.4] vs. 2.7% [8.4], P < 0.05); least-squares mean (standard error) improvement with apremilast 30 mg twice daily was −13.3% (8.7) (P not significant).

Subgroup analyses
At week 12, numerically greater improvements from baseline in EASI scores were observed with apremilast treatment versus placebo among patients with baseline IgE levels less than 360 μg/L (i.e., intrinsic AD) compared with baseline IgE levels of 360 μg/L or greater (i.e., extrinsic AD) and among patients with lower baseline eosinophil (EoS) level (<0.39 × 10⁹/L) versus higher baseline EoS level (≥0.39 × 10⁹/L); however, these changes did not achieve statistical signifi-
cance (P not significant for both apremilast dosages vs. placebo) (Figure 2a). A similar pattern was observed with sPGA-A response achievement among the subgroups (Figure 2b). Additional subgroup analyses of change from baseline in EASI score at week 12 showed a significant difference favoring apremilast 40 mg twice daily over placebo among patients in Japan versus those in North America; this difference did not reach statistical significance with the apremilast 30 mg twice daily dosage.

Pharmacodynamics results
Demographic and baseline clinical characteristics of the biopsy substudy patients are summarized in Supplementary Table S1 online; clinical efficacy findings based on EASI assessment at week 12 are summarized in Supplementary Table S2 online. In all groups at baseline, epidermal thickness (ET) and K16 protein expression were significantly greater in lesional skin than nonlesional skin (P < 0.01 and P < 0.001, respectively). A change from baseline in ET of −11.4% at week 12 was observed in lesions from patients treated with apremilast 40 mg twice daily that trended toward significance (P < 0.1 vs. baseline). In comparison, no sig-
nificant changes in ET were observed with apremilast 30 mg twice daily or placebo (both P-values not significant vs. baseline). K16 protein expression in the apremilast 40 mg twice daily group was significantly decreased (P < 0.001) at week 12, and the placebo and apremilast 30 mg twice daily groups showed nonsignificant changes. Only the apremilast 40 mg twice daily group had significantly more Ki67⁺ cells in baseline lesional versus nonlesional tissues. Ki67⁺ cell counts showed a statistically significant decline of −40.2% with apremilast 40 mg twice daily treatment at week 12 versus baseline (P < 0.001); no significant changes in Ki67 counts were noted with apremilast 30 mg twice daily or placebo. Changes from baseline at week 12 in ET, K16, and Ki67⁺ cells, based on immunohistochemistry studies and real-time polymerase chain reaction (RT-PCR) for K16 mRNA expression from a representative patient in the apremilast 40 mg twice daily group, are shown in Figure 3.
Heatmaps from gene array and RT-PCR assays of representative immune genes in pretreatment and posttreatment AD lesions are shown in Supplementary Figure S2a online and Figure 4. Gene array analysis showed that the apremilast 40 mg twice daily group had the highest baseline dysregulation in lesional skin; at week 12, the apremilast 40 mg twice daily group showed reductions in T helper (Th) 17/Th22 genes and related markers, including IL-22 and IL-19, that trended toward significance ($P < 0.1$ for both). Other general inflammatory (MMP12) and Th17/Th22 (IL-17, S100A12) markers were decreased by both apremilast 40 mg twice daily and placebo (S100A9, CXCL1-2, STAT3). When comparing treatment effects of apremilast versus placebo, apremilast 40 mg twice daily showed more substantial declines in expression of Th17/Th22-associated markers (S100A12, IL-19, IL-22), with no notable changes in other immune axes (Figure S2b). The apremilast 30 mg twice daily group did not show substantial changes from baseline at week 12.

RT-PCR mRNA changes mirrored gene array findings. At baseline, the apremilast 40 mg twice daily group had the highest dysregulation. At week 12, Th17 (IL-17A, IL-12B/IL-12/23p40) and Th17/Th22-associated markers (IL-22, S100A7/S100A8, S100A12) were significantly reduced only with apremilast 40 mg twice daily ($P < 0.05$ for all). Significant or major reductions from baseline were observed in Th2-associated cytokines IL-13, IL-31, and CCL17 in both the placebo and apremilast 40 mg twice daily groups. No significant changes from baseline were observed in the apremilast 30 mg twice daily group. Additional findings from the immunohistochemistry, gene array, and RT-PCR analyses are summarized in the Supplementary Materials, Supplementary Tables S1 and S3, and Supplementary Figure S3 online.
Safety

During weeks 0–12 and throughout the full 24-week apremilast exposure period, most AEs were mild to moderate in severity, and few AEs were serious or led to treatment withdrawal (Table 2). The incidence of AEs, AEs leading to treatment withdrawal, and serious AEs was higher in patients receiving apremilast 40 mg twice daily than in patients receiving apremilast 30 mg twice daily. Because of an unexpected elevated incidence of cellulitis (detailed in this section) among patients receiving apremilast 40 mg twice daily, the independent safety monitoring committees discontinued the apremilast 40 mg twice daily treatment arm on November 20, 2015. No patients were in the placebo-controlled phase at the time of this determination; nearly all had completed the 24-week visit, and two patients initially assigned to receive apremilast 40 mg twice daily were switched to apremilast 30 mg twice daily.

The most common AEs (≥5% of patients in any treatment group) during the placebo-controlled period included diarrhea, nausea, headache, nasopharyngitis, upper respiratory tract infection, abdominal discomfort, cellulitis, and dyspepsia. The incidence of drug-related AEs, serious AEs, or AEs leading to withdrawal did not increase with apremilast exposure through week 24 (Table 2).

A total of six serious AEs were reported for five patients during the study; four serious AEs were reported for three patients during the placebo-controlled period, and two occurred after week 12. During the placebo-controlled period, these included squamous cell carcinoma (n = 1, apremilast 30 mg twice daily), suicidal ideation (n = 1, apremilast 40 mg twice daily), and cellulitis and glomerulonephritis (n = 1, apremilast 40 mg twice daily). The two new serious AEs reported after week 12 included pneumonia (n = 1, apremilast 30 mg twice daily) and cellulitis (n = 1, apremilast 40 mg twice daily). Six patients receiving apremilast 40 mg twice daily experienced cellulitis (four cases during weeks 0–12, and two cases during weeks 12–24); all involved the lower extremities. Among four patients with nonserious cases of cellulitis, one patient had a history of peripheral neuropathy of the left foot corresponding to the same leg involved with cellulitis, and the other three patients with nonserious cases had no relevant medical history. Two cases of cellulitis were considered serious; one case occurred in a patient with a history of diabetes mellitus and was suspected to be potentially related to apremilast treatment. The second case, which occurred in a patient with a history of diabetes and streptococcal cellulitis, was not considered related to apremilast treatment; this patient discontinued because of complications from glomerulonephritis related to cellulitis. No other patients who developed cellulitis withdrew from the study; one case of nonserious cellulitis was considered by the investigator as suspected to be related to apremilast. No deaths occurred in the study.
Figure 4. mRNA levels of immune and epidermal markers in skin treated with apremilast or placebo. (a) Heatmap of mean mRNA expression levels of representative immune and barrier markers in pretreatment and posttreatment atopic dermatitis lesions. (b) Line graphs of representative immune marker mRNA changes with treatment. Immune genes are grouped by major inflammatory/regulatory pathways. Black asterisks denote significance in change between nonlesional and lesional skin, top blue asterisks denote significance in change from baseline, and bottom blue asterisks denote significance of treatment effect between apremilast 40 mg twice daily and placebo. Red or blue numbers denote sample number for nonlesional or lesional skin, respectively. *P < 0.1. **P < 0.05. ***P < 0.01. ****P < 0.001. APR30, apremilast 30 mg twice daily; APR40, apremilast 40 mg twice daily; LS, lesional NL, nonlesional.
DISCUSSION

In adult patients with moderate to severe AD, apremilast 40 mg twice daily showed modest but statistically significant improvement in EASI score (from baseline) at week 12; sPGA-A response was numerically better than placebo, but this was not statistically significant. Patients receiving apremilast 40 mg twice daily also reported significantly greater improvement in quality of life at week 12 versus placebo. Use of permitted concomitant dermatologic medications was slightly higher in the placebo and apremilast 30 mg twice daily groups than in the apremilast 40 mg twice daily group, and this may have attenuated differences between the placebo and apremilast 40 mg twice daily groups in efficacy or biomarker outcomes. However, the AEs observed with apremilast 40 mg twice daily conferred a benefit-to-risk profile that was not deemed appropriate for further investigation in AD.

The tissue biomarker data were consistent with clinical results, with the apremilast 40 mg twice daily group showing the greatest molecular and cellular improvements. These included reductions in epidermal hyperplasia (i.e., K16, Ki67, and ET) and inflammatory markers associated with Th17/Th22 pathways. In contrast, the apremilast 30 mg twice daily group did not show substantial biomarker changes compared with placebo. This likely reflects the expected lower dose effect on the measured biomarkers, which may have affected the ability to detect changes from baseline in this treatment group.

Clinical subgroup analyses suggest better response to apremilast treatment in patients with intrinsic AD compared with patients with extrinsic AD. Prior research has shown that intrinsic AD is associated with greater Th17 expression in lesional skin compared with extrinsic AD (Suarez-Farinas et al., 2013). Apremilast is known to modulate Th17 cytokines in psoriasis (Gottlieb et al., 2013) and appears to modulate the same pathway in AD patients based on the current findings. However, these results should be interpreted with caution because of the small sample size.

Pruritus is a central clinical feature of AD. In this study, improvements in pruritus with either dosage of apremilast

Table 2. Overview of adverse events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo Controlled Period, Weeks 0–121</th>
<th>Apremilast Exposure Period, Weeks 0 to ≤242</th>
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<tbody>
<tr>
<td></td>
<td>Placebo (n = 64)</td>
<td>Apremilast 30 mg Twice Daily (n = 58)</td>
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<tr>
<td>Any AE</td>
<td>30 (46.9)</td>
<td>36 (62.1)</td>
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<tr>
<td>Drug-related AE</td>
<td>8 (12.5)</td>
<td>26 (44.8)</td>
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<td>Severe AE</td>
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<td>0 (0.0)</td>
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<tr>
<td>Serious AE</td>
<td>0 (0.0)</td>
<td>1 (1.7)</td>
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<tr>
<td>AE leading to study drug interruption</td>
<td>3 (4.7)</td>
<td>0 (0.0)</td>
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<tr>
<td>AE leading to study drug withdrawal</td>
<td>1 (1.6)</td>
<td>2 (3.4)</td>
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<tr>
<td>AE leading to death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>AEs reported by ≥5% of patients in any treatment group, n (%)</td>
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<tr>
<td>Diarrhea</td>
<td>1 (1.6)</td>
<td>10 (17.2)</td>
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<tr>
<td>Nausea</td>
<td>1 (1.6)</td>
<td>9 (15.5)</td>
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<td>Headache</td>
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<td>4 (6.9)</td>
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<td>Nasopharyngitis</td>
<td>1 (1.6)</td>
<td>6 (10.3)</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>8 (12.5)</td>
<td>2 (3.4)</td>
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<tr>
<td>Abdominal discomfort</td>
<td>0 (0.0)</td>
<td>3 (5.2)</td>
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<tr>
<td>Cellulitis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<td>Vomiting</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Dyspepsia</td>
<td>1 (1.6)</td>
<td>3 (5.2)</td>
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<tr>
<td>AEs leading to drug withdrawal in patients during the apremilast exposure period, n (%)</td>
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<tr>
<td>Abdominal discomfort</td>
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<td>Diarrhea</td>
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<td>Headache</td>
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<td>Pneumonia</td>
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<td>Squamous cell carcinoma</td>
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<td>Suicidal ideation</td>
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<td>Glomerulonephritis</td>
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Abbreviations: AE, adverse event.

1Based on safety population.

2Includes all apremilast exposure data; patients could have started receiving apremilast at week 0 or week 12.
were not significantly different from placebo at week 12. By contrast, apremilast 30 mg twice daily significantly improved pruritus in phase 3 trials in moderate to severe psoriasis (Papp et al., 2015; Paul et al., 2015). It is unclear whether this divergence is due to a difference in the mechanism underlying pruritus in AD versus psoriasis or is because apremilast primarily modulates the Th17 pathway (Schafer et al., 2014), which may be a key disease driver of psoriasis but currently is not recognized as pathogenic in AD, although this axis is increased in AD, and particularly in certain disease subsets such as in Asian patients and those with early-onset pediatric AD (Bieber, 2008; Brunner et al., 2017; Esaki et al., 2016; Gutman-Yassky and Krueger, 2017; Gutman-Yassky et al., 2017; Noda et al., 2015; Tabarkiewicz et al., 2015). Our findings are somewhat surprising given the clinical efficacy of the topical PDE4 inhibitor crisaborole ointment (2%) (Pfizer, 2017; Paller et al., 2016). Differences in results from the trials with crisaborole versus apremilast might be attributable to route of administration, selected patient populations (i.e., children and adults vs. adults only), and baseline disease severity (i.e., mild to moderate vs. moderate to severe AD). More broadly, interpretation of the current findings may be limited to patients in North America. The small number of patients from Japan and lack of patients from other regions may limit meaningful conclusions about Japanese patients and patients from other racial groups.

The safety and tolerability of apremilast 30 mg twice daily observed in this study are largely consistent with the known safety profile of apremilast from phase 3 clinical trials in patients with psoriasis and psoriatic arthritis (Cutolo et al., 2016; Edwards et al., 2016; Kavanaugh et al., 2015; Papp et al., 2015; Paul et al., 2015). Most AEs were mild or moderate in severity, and few led to discontinuation of treatment; the most common AEs included diarrhea, nausea, headache, and nasopharyngitis. Overall, more AEs were observed with apremilast 40 mg twice daily than with apremilast 30 mg twice daily. There were six cases of cellulitis among patients receiving apremilast 40 mg twice daily; no cases of cellulitis were observed among patients receiving apremilast 30 mg twice daily or placebo. After a benefit-risk assessment by the independent safety monitoring committees, the apremilast 40 mg twice daily dosage was discontinued in November 2015, after most patients had completed the 24-week clinic visit; the remaining patients in this arm (n = 2) were switched to the apremilast 30 mg twice daily group. Cellulitis may be a phenomenon unique to patients with AD, because bacterial skin infections are often seen in patients with AD (Petry et al., 2012). In patients with psoriasis or psoriatic arthritis, apremilast 30 mg twice daily treatment was not associated with an increased incidence of infection or cellulitis (Crowley et al., 2017; Mease et al., 2017).

Treatment with apremilast 40 mg twice daily over 12 weeks showed modest efficacy in patients with moderate to severe AD. No significant differences were observed between apremilast 30 mg twice daily and placebo by week 12, although there were efficacy endpoints that were numerically improved at week 12 and continued to improve with continuous treatment through week 24. Biomarker analyses in tissues showed decreases in Th17/Th22-related markers with apremilast 40 mg twice daily versus placebo, with no substantial changes from baseline observed with apremilast 30 mg twice daily. The safety of apremilast 30 mg twice daily was generally similar to the known safety profile of apremilast in psoriasis and psoriatic arthritis patients, although more AEs, including cellulitis, were reported in patients treated with the 40 mg twice daily dosage.

MATERIALS AND METHODS

Patients

Adult patients (≥18 years of age) were eligible to participate if they had moderate to severe AD (i.e., AD-affected body surface area ≥10%, EASI score ≥12, and sPGA-A score ≥3 [moderate to severe]) not adequately controlled by a stable regimen (≥24 weeks) of topical corticosteroids or topical calcineurin inhibitors within 6 months of screening or if they were considered inappropriate candidates for topical therapy. Additional details of the inclusion/exclusion criteria are provided in the Supplementary Materials. All patients provided written informed consent before entering the study, and the protocol was approved by each site’s institutional review board or independent ethics committee.

Study design

This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (NCT02087943) conducted from January 2014 to February 2016 at 28 study centers in North America and Japan. Eligible patients were randomly assigned (1:1:1) to receive placebo, apremilast 30 mg twice daily, or apremilast 40 mg twice daily for 12 weeks (placebo-controlled period) with a permuted block method and were stratified by geographic region (North America and Japan) and, within region, by baseline EASI score (≤20 or >20) with an interactive web-response or interactive voice-response system. Apremilast was titrated in 10-mg increments over the first 8 days of treatment. At week 12, patients initially randomly assigned to receive placebo were reassigned randomly (1:1:1) to double-blind treatment with apremilast 30 mg twice daily or 40 mg twice daily through week 24 (with dose titration over the first 8 days); patients initially randomly assigned to receive apremilast continued to receive their assigned dosage. To maintain double-blind conditions for patients and clinical study personnel throughout the 24-week trial, assigned treatments were dispensed only by authorized personnel at each study site in coded, identically appearing blister cards containing the assigned treatment and dose. Patients who completed or discontinued early entered a 6-week posttreatment observational period. Concomitant medications that were permitted and not permitted are listed in the Supplementary Materials.

Assessments

Clinical efficacy was assessed at weeks 2, 4, 8, and 12 during the placebo-controlled phase; at weeks 16, 20, and 24 during the active-treatment phase; and at the end of the 6-week posttreatment observation period. The primary efficacy endpoint was the percent change from baseline in EASI score at week 12. The proportion of patients who achieved an sPGA-A response (score of 0 [cleared] or 1 [almost cleared] and ≥2-point reduction from baseline) at week 12 was a secondary endpoint, as was achievement of a 50% or greater improvement from baseline EASI score. Predefined exploratory endpoints included the percent change from baseline in average pruritus visual analog scale (cm) score (range: 0 [no itching] to 10 [worst itching imaginable]) (Kunz et al., 1997); percent change from
baseline in Dermatology Life Quality Index score (range: 0 [no effect on life] to 30 [extremely large effect on life]) at week 12; percent change from baseline in EASI score at week 24; and the proportion of patients who achieved an sPGA-A response at week 24. Post hoc analyses examined percent change from baseline in EASI score and sPGA-A response at week 12 among subgroups of patients defined by baseline IgE level less than 360 µg/L (intrinsic AD) versus 360 µg/L or greater (extrinsic AD), as well as among patients with low baseline EoS levels (<0.39 × 10^9/L) versus high baseline EoS levels (≥0.39 × 10^9/L), based on the median EoS level of the study population at baseline, 0.39 × 10^9/L. Safety was evaluated based on AE, vital signs, physical examinations, laboratory evaluations, and electrocardiograms.

**Pharmacodynamics assessments**

Blood samples were obtained at baseline; weeks 4, 12, 16, and 24; and the final study visit. IgE levels and EoS counts were determined; samples were also used to examine standard clinical chemistry and hematology parameters. For the biopsy substudy, pretreatment (week 0) lesional and nonlesional (>1 cm from active lesions) skin was obtained from 21 adult patients (see the Supplementary Materials and Supplementary Table S1 for further details). For immunohistochemistry, frozen optimum cutting temperature-embedded cryostat sections were labeled using purified mouse antihuman monoclonal antibodies (see the Supplementary Materials and Supplementary Table S3 for further details), as described previously (Suarez-Farinas et al., 2011; Tintle et al., 2011). Changes from baseline at week 12 in ET and two markers of epidermal proliferation, K16 and Ki67, were examined. ET and cell counts were quantified with ImageJ, version 1.42 (National Institutes of Health, Bethesda, MD). For gene expression analysis of key AD-related genes, RNA was extracted, followed by quantitative RT-PCR and Affymetrix Human U133Plus 2.0 gene arrays (Affymetrix, Santa Clara, CA) analyses, as previously described (Tintle et al., 2011) (see the Supplementary Materials and Supplementary Tables S4 and S5 online for further details).

**Statistical analysis**

Efficacy data were assessed in the intent-to-treat population, which included all randomized patients who received at least one dose of study medication according to the group to which they were randomly assigned; safety analyses included all patients who received at least one dose of study medication. A planned sample size of 189 patients would provide 80% power with a two-sided significance level of 0.05, allowing for 20% discontinuation by week 12. Comparisons for the primary endpoint (percent change from baseline in EASI score at week 12) were performed using an analysis of covariance model, with treatment and baseline stratification as factors; missing values were imputed using the last-observation-carried-forward methodology. The same analysis of covariance model was used for analyses of percent change from baseline in pruritus visual analog scale and change from baseline in Dermatology Life Quality Index score at week 12. For the sPGA-A and ≥50% improvement in EASI score analyses, treatment comparisons were performed using a Cochran-Mantel-Haenszel test, with missing values imputed using last-observation-carried-forward methodology. Percent change from baseline in EASI score at week 24 was analyzed with descriptive statistics and data as observed. Details of statistical analyses for the biopsy substudy are presented in the Supplementary Materials.

**CONFLICT OF INTEREST**

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**SUPPLEMENTAL MATERIAL**

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2018.10.043.

**REFERENCES**


Apremilast for Treatment of Atopic Dermatitis


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